ព្រះរាជាណាចក្រកម្ពុជា
ជាតិ សាសនា ព្រះមហាក្សត្រ



មគ្គុទ្ទេសក៍ព្យាបាលគ្លីនិក
CLINICAL PRACTICE GUIDELINES
ផ្នែក
FOR
វេជ្ជសាស្ត្រទូទៅ
MEDICINE

ភាគ ១

នាយកដ្ឋានសេវាសុខភាព
ឆ្នាំ ២០២៥

Kingdom of Cambodia
Nation Religion King



CLINICAL PRACTICE GUIDELINES

FOR

MEDICINE

Part 1

Department of Health Services

December 2025



Ministry of Health

CLINICAL PRACTICEGUIDELINES FOR MEDICINE

Part

1

December 2025

ព្រះរាជាណាចក្រកម្ពុជា
ជាតិ សាសនា ព្រះមហាក្សត្រ

ក្រសួងសុខាភិបាល
លេខ ០៣៦៤ សហវ/ន.ស.ស.ប្រ.ក

ប្រកាស
ស្តីពី
ការដាក់ឱ្យអនុវត្តមគ្គុទ្ទេសក៍ព្យាបាលគ្លីនិក ផ្នែកវេជ្ជសាស្ត្រទូទៅ

រដ្ឋមន្ត្រីក្រសួងសុខាភិបាល

- បានឃើញរដ្ឋធម្មនុញ្ញនៃព្រះរាជាណាចក្រកម្ពុជា
- បានឃើញព្រះរាជក្រឹត្យលេខ នស/រកត/០៨២៣/១៩៨១ ចុះថ្ងៃទី២២ ខែសីហា ឆ្នាំ២០២៣ ស្តីពីការតែងតាំងរាជរដ្ឋាភិបាលនៃព្រះរាជាណាចក្រកម្ពុជា
- បានឃើញព្រះរាជក្រឹត្យលេខ នស/រកត/០២២៤/២០៥ ចុះថ្ងៃទី២១ ខែកុម្ភៈ ឆ្នាំ២០២៤ ស្តីពីការបំពេញបន្ថែមសមាសភាពរាជរដ្ឋាភិបាលនៃព្រះរាជាណាចក្រកម្ពុជា
- បានឃើញព្រះរាជក្រឹត្យលេខ នស/រកត/០៩២៤/១១៦៩ ចុះថ្ងៃទី២០ ខែកញ្ញា ឆ្នាំ២០២៤ ស្តីពីការកែសម្រួល និងតែងតាំងសមាសភាពរាជរដ្ឋាភិបាលនៃព្រះរាជាណាចក្រកម្ពុជា
- បានឃើញព្រះរាជក្រឹត្យលេខ នស/រកត/១១២៤/១៤៧៧ ចុះថ្ងៃទី២០ ខែវិច្ឆិកា ឆ្នាំ២០២៤ ស្តីពីការកែសម្រួល និងតែងតាំងសមាសភាពរាជរដ្ឋាភិបាលនៃព្រះរាជាណាចក្រកម្ពុជា
- បានឃើញព្រះរាជក្រមលេខ នស/រកម/០៦១៨/០១២ ចុះថ្ងៃទី២៨ ខែមិថុនា ឆ្នាំ២០១៨ ដែលប្រកាសឱ្យប្រើច្បាប់ ស្តីពីការរៀបចំ និងការប្រព្រឹត្តទៅនៃគណៈរដ្ឋមន្ត្រី
- បានឃើញព្រះរាជក្រមលេខ នស/រកម/០១៩៦/០៦ ចុះថ្ងៃទី២៤ ខែមករា ឆ្នាំ១៩៩៦ ដែលប្រកាសឱ្យប្រើច្បាប់ស្តីពីការបង្កើតក្រសួងសុខាភិបាល
- បានឃើញព្រះរាជក្រមលេខ នស/រកម/១១១៦/០១៤ ចុះថ្ងៃទី១៦ ខែវិច្ឆិកា ឆ្នាំ២០១៦ ដែលប្រកាសឱ្យប្រើច្បាប់ ស្តីពីការគ្រប់គ្រងអ្នកប្រកបវិជ្ជាជីវៈសុខាភិបាល
- បានឃើញអនុក្រឹត្យលេខ២៣៩ អនក្រ.បក ចុះថ្ងៃទី០៣ ខែធ្នូ ឆ្នាំ២០២៥ ស្តីពីការរៀបចំ និងការប្រព្រឹត្តទៅរបស់ក្រសួងសុខាភិបាល
- យោងតាមការចាំបាច់របស់ក្រសួងសុខាភិបាល

អាសយដ្ឋាន៖ ដីឡូត៍លេខ៨០ វិថីសម្តេច ប៉ែន នុត (២៨៩) សង្កាត់បឹងកក់ទី២ ខណ្ឌទួលគោក រាជធានីភ្នំពេញ
ទូរស័ព្ទ៖(+៨៥៥) ២៣ ៨៨៥ ៩៧០
អ៊ីម៉ែល៖ info@moh.gov.kh
គេហទំព័រ៖ www.moh.gov.kh
តេឡេក្រាម៖ t.me/MOHCambodia

សម្រេច

ប្រការ១.-

ត្រូវបានដាក់ឱ្យអនុវត្តមគ្គុទ្ទេសក៍ព្យាបាលគ្លីនិក ផ្នែកវេជ្ជសាស្ត្រទូទៅ(Clinical Practice Guidelines For Medicine) ដែលជាឧបសម្ព័ន្ធនៃប្រកាសនេះ។

ប្រការ២.-

ប្រកាសនេះមានវិសាលភាពអនុវត្តចំពោះគ្រប់មូលដ្ឋានសុខាភិបាលសាធារណៈ និងឯកជនក្នុងព្រះរាជាណាចក្រកម្ពុជា។

ប្រការ៣.-

បទប្បញ្ញត្តិទាំងឡាយណាដែលផ្ទុយនឹងប្រកាសនេះ ត្រូវទុកជានិរាករណ៍។

ប្រការ៤.-

អគ្គលេខាធិការ អគ្គនាយកបច្ចេកទេសសុខាភិបាល អគ្គាធិការក្រសួងសុខាភិបាល គ្រប់ប្រធានអង្គភាពក្រោមឱវាទក្រសួងសុខាភិបាល ទាំងមូលដ្ឋានសុខាភិបាលសាធារណៈ និងឯកជន ត្រូវទទួលបន្ទុកអនុវត្តតាមប្រកាសនេះឱ្យមានប្រសិទ្ធភាព ចាប់ពីថ្ងៃចុះហត្ថលេខាតទៅ។

ថ្ងៃ ពុធ ១២ កើត ខែ បុស្ស ឆ្នាំម្សាញ់ សប្តស័ក ព.ស.២៥៦៩
ធ្វើនៅរាជធានីភ្នំពេញ ថ្ងៃទី ៣១ ខែ ធ្នូ ឆ្នាំ២០២៥

រដ្ឋមន្ត្រីក្រសួងសុខាភិបាល

សាស្ត្រាចារ្យ **ឈាង រ៉ា**

កន្លែងទទួលៈ
- ទីស្តីការគណៈរដ្ឋមន្ត្រី
- ក្រសួងសេដ្ឋកិច្ចនិងហិរញ្ញវត្ថុ
- ឧទ្ធរណ៍ឯកឧត្តមសាស្ត្រាចារ្យរដ្ឋមន្ត្រីក្រសួងសុខាភិបាល
- ដូចប្រការ៤
- រាជកិច្ច
- ឯកសារ កាលប្បវត្តិ

អារម្ភកថា

ក្រោមកិច្ចដឹកនាំរបស់រាជរដ្ឋាភិបាលនីតិកាលទី៧ នៃរដ្ឋសភា នៃ **ព្រះរាជាណាចក្រកម្ពុជា** ក្រសួងសុខាភិបាល យកចិត្តទុកដាក់ខ្ពស់ដល់សុខភាព និងសុខុមាលភាពប្រជាជនគ្រប់រូប និងប្តេជ្ញាចិត្តយ៉ាងមុឺងម៉ាត់លើកកម្ពស់ការផ្តល់សេវាសុខាភិបាលប្រកបដោយ គុណភាព សុវត្ថិភាព និងសមធម៌ ដោយផ្តោតលើអ្នកជំងឺ ជូនដល់ប្រជាជនកម្ពុជាគ្រប់រូប ស្របតាមផែនការយុទ្ធសាស្ត្រសុខាភិបាល ២០២៥-២០៣៤ ក៏ដូចជា ផែនទីបង្ហាញផ្លូវឆ្ពោះទៅការគ្របដណ្តប់សុខភាពជាសកលនៅកម្ពុជា ឆ្នាំ ២០២៤-២០៣៥ របស់រាជរដ្ឋាភិបាល។

មគ្គុទ្ទេសក៍ព្យាបាលគ្លីនិកផ្នែកវេជ្ជសាស្ត្រទូទៅ នេះជាមាគ៌ាណែនាំថ្នាក់ជាតិពាក់ព័ន្ធនឹងពិធីសារ នៃការគ្រប់គ្រងបញ្ហាសុខភាពជាអាទិភាពនៅកម្ពុជា ផ្តោតសំខាន់លើបែបបទនៃការធ្វើរោគវិនិច្ឆ័យ និងការថែទាំ ការព្យាបាល និងការបង្ការជំងឺ រាប់ទាំងការតាមដានបញ្ហាសុខភាព ឬជំងឺ។

មគ្គុទ្ទេសក៍ព្យាបាលគ្លីនិកវេជ្ជសាស្ត្រទូទៅនេះ ត្រូវបានរៀបចំចងក្រងជាលើកទី៣ នៅកម្ពុជា មានចំនួន ៣ភាគ៖ ភាគទី១ ភាគទី២ និងភាគទី៣ ដោយក្រុមការងារបច្ចេកទេសជំនាញ នៃក្រសួងសុខាភិបាល ដោយមានការចូលរួមពីដៃគូសំខាន់ៗ អ្នកជំនាញ ឯកទេសជំនាញពីផ្នែកពាក់ព័ន្ធទាំងឡាយ រួមទាំង គ្រូពេទ្យព្យាបាលបម្រើការងារនៅតាមមន្ទីរពេទ្យគ្រប់លំដាប់ថ្នាក់ មន្ត្រីដែលកំពុងបំពេញការងារនៅការិយាល័យសុខាភិបាលស្រុកប្រតិបត្តិ និងមន្ទីរសុខាភិបាលនៃរដ្ឋបាលរាជធានី ខេត្ត កម្មវិធីជាតិ សមាគមវិជ្ជាជីវៈសុខាភិបាលផ្សេងៗ ក៏ដូចជាអង្គការដៃគូពាក់ព័ន្ធ ។

មគ្គុទ្ទេសក៍ព្យាបាលគ្លីនិកនេះ ត្រូវបានរៀបចំឡើងសម្រាប់អ្នកវិជ្ជាជីវៈសុខាភិបាល និងអ្នកវិជ្ជាជីវៈពាក់ព័ន្ធ ជាពិសេសអ្នកផ្តល់សេវាសុខភាព រាប់បញ្ចូលទាំង វេជ្ជបណ្ឌិត និងអ្នកប្រកបវិជ្ជាជីវៈសុខាភិបាលផ្សេងទៀត នៅមូលដ្ឋានសុខាភិបាលសាធារណៈ និងឯកជន ក៏ដូចជាសិក្ខាកាម អ្នករៀបចំគោលនយោបាយ អ្នកពាក់ព័ន្ធនានា គណៈវិជ្ជាជីវៈ និងសមាគមវិជ្ជាជីវៈផ្សេងៗ។

ក្រសួងសុខាភិបាលសូមណែនាំដល់អ្នកវិជ្ជាជីវៈសុខាភិបាល និងអ្នកពាក់ព័ន្ធទាំងអស់ ត្រូវចូលរួមអនុវត្តតាមមគ្គុទ្ទេសក៍ព្យាបាលគ្លីនិកនេះ សម្រាប់ប្រតិបត្តិកិច្ចការរបស់ខ្លួន ក្នុងគោលបំណងពង្រឹងប្រសិទ្ធភាព ប្រសិទ្ធផល និងគុណភាព សុវត្ថិភាពក្នុងការថែទាំព្យាបាលអ្នកជំងឺ ក៏ដូចជាការកសាងសមត្ថភាពធនធានមនុស្សក្នុងវិស័យសុខាភិបាល ។

រាជធានីភ្នំពេញ ថ្ងៃ ..៣.១..... ខែធ្នូ ឆ្នាំ ២០២៥

រដ្ឋមន្ត្រីក្រសួងសុខាភិបាល

សាស្ត្រាចារ្យ ឈាង រ៉ា

FOREWORD

Under the leadership of the Royal Government of the 7th Legislature of the National Assembly of the Kingdom of Cambodia, the Ministry of Health pays high attention to the health and well-being of the entire population. The Ministry of Health is strongly committed to ensuring the provision of equitable, safe and quality patient-centered health services for the Cambodian population in line with the Health Strategic Plan 2025-2034 and the Royal Government Roadmap Towards Universal Health Coverage in Cambodia 2024-2035.

This Clinical Practice Guidelines (CPG) for General Medicine provides national guidance on the management protocols of priority health problems with a focus on diagnosis and care, including curative and preventive care, as well as follow-up of health problems.

The Guidelines, published for the third time in Cambodia in three parts, Part 1, Part 2 and Part 3; was developed by the Technical Working Group of the Ministry of Health with participation from various stakeholders and individuals, including experts from relevant fields ranging from clinicians working in hospitals at all levels to district health officers, Provincial Health Departments, national programs, health professional associations, as well as partner organizations.

The Guidelines is intended for use by health professionals and other relevant professionals, especially health care providers, including doctors and other health practitioners in both public and private health facilities as well as trainees, policymakers, relevant individuals, professional councils and professional associations.

The Ministry of Health guides all health professionals and relevant individuals to use this Guidelines in their professional practice with the aim of improving effectiveness, efficiency and quality in patient care and safety, as well as contributing to human resource capacity building.

Phnom Penh, 31 December, 2025

Minister of Health

Prof. CHHEANG RA

ACKNOWLEDGEMENT

The Ministry of Health wishes to extend its profound appreciation to Excellencies, Ladies and Gentlemen, Professors, Doctors, Experts, Officials of the Ministry at all levels, as well as partner organization officials and all individuals who have shared their experiences and inputs contributing to the development of this important Clinical Practice Guidelines.

We particularly thank H.E. Professor **Koy Vanny**, Secretary of State, Chair and all Vice-chairs and members of the Technical Working Group of Clinical Practice Guidelines for General Medicine, under the overall leadership and guidance of the Steering Committee for National Medical Care and Therapy of the Ministry of Health.

We would also like to express our deep gratitude to all partners involved, including the World Health Organization and other partners, for their technical and financial contributions to the formulation of the guidelines.

This Clinical Practice Guidelines for Medicine represent another significant and commendable achievement of the Ministry of Health of the Kingdom of Cambodia.

Phnom Penh, 31 December, 2025

Chair of the Steering Committee for National Medical Care and Therapy

H.E Prof. Yit Sunnara

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List of Abbreviation

ABG	Arterial Blood Gas
ACEI	Angiotensin-Converting Enzyme Inhibitor
ACLS	Advanced Cardiac Life Support
ACS	Acute Coronary Syndrome
ACT	Activated Clotting Time
ADA	American Diabetes Association
AF	Atrial Fibrillation
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute Respiratory Distress Syndrome
ASA	Aspirin
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUB	Abnormal Uterine Bleeding
AV	Arteriovenous
AVF	Arteriovenous Fistula
AVG	Arteriovenous Graft
AVPU	Alert, Verbal, Pain, Unresponsive
BD	Twice Daily
BID	Twice Daily (bis in die)
BIPAP	Bilevel Positive Airway Pressure
BLS	Basic Life Support
BMI	Body Mass Index
BP	Blood Pressure
BPH	Benign Prostatic Hyperplasia
BUSE	Blood Urea, Sugar, Electrolytes
CABG	Coronary Artery Bypass Graft
CAP	Community-Acquired Pneumonia
CBG	Capillary Blood Glucose
CCU	Coronary Care Unit
CDK	Chronic Kidney Disease
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPR	Cardiopulmonary Resuscitation
CRP	C-Reactive Protein
CT	Computed Tomography
CTPA	CT Pulmonary Angiography
CVA	Cerebrovascular Accident
CXR	Chest X-Ray
DAPT	Dual Antiplatelet Therapy
DKA	Diabetic Ketoacidosis
DLBCL	Diffuse Large B-cell Lymphoma
DM	Diabetes Mellitus

DRE	Digital Rectal Examination
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
ED	Emergency Department
EEG	Electroencephalogram
eGFR	Estimated Glomerular Filtration Rate
ENT	Ear, Nose, and Throat
ESR	Erythrocyte Sedimentation Rate
ESRD	End-Stage Renal Disease
FBC	Full Blood Count
FPG	Fasting Plasma Glucose
GCS	Glasgow Coma Scale
GI	Gastrointestinal
GIT	Gastrointestinal Tract
GORD	Gastro-Oesophageal Reflux Disease
GP	General Practitioner
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HCT	Hematocrit
HFrEF	Heart Failure with Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HHS	Hyperosmolar Hyperglycemic State
HR	Heart Rate
HTN	Hypertension
ICU	Intensive Care Unit
INR	International Normalized Ratio
IV	Intravenous
IVC	Inferior Vena Cava
IVDU	Intravenous Drug User
KIV	Keep In View
LFT	Liver Function Test
LMWH	Low Molecular Weight Heparin
LOC	Loss of Consciousness
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MAP	Mean Arterial Pressure
MI	Myocardial Infarction
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-Resistant Staphylococcus aureus
MS	Multiple Sclerosis
NA	Not Applicable
NG	Nasogastric
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NSTEMI	Non-ST Elevation Myocardial Infarction
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
OSA	Obstructive Sleep Apnea

OT	Occupational Therapy
$PaCO_2$	Partial Pressure of Carbon Dioxide
PaO_2	Partial Pressure of Oxygen
PCI	Percutaneous Coronary Intervention
PE	Pulmonary Embolism
PEF	Peak Expiratory Flow
PET	Positron Emission Tomography
PFT	Pulmonary Function Test
PPI	Proton Pump Inhibitor
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
RAAS	Renin-Angiotensin-Aldosterone System
RFT	Renal Function Test
RIG	Radiologically Inserted Gastrostomy
ROSC	Return of Spontaneous Circulation
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
RT	Radiotherapy
Rx	Prescription / Treatment
SABA	Short-Acting Beta Agonist
SaO_2	Arterial Oxygen Saturation
SARI	Severe Acute Respiratory Infection
SBP	Systolic Blood Pressure
SC	Subcutaneous
SIRS	Systemic Inflammatory Response Syndrome
SOB	Shortness of Breath
SpO_2	Peripheral Oxygen Saturation
STEMI	ST-Elevation Myocardial Infarction
SVD	Spontaneous Vaginal Delivery
SVT	Supraventricular Tachycardia
T2DM	Type 2 Diabetes Mellitus
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiography
TTP	Thrombotic Thrombocytopenic Purpura
UA	Unstable Angina
U&E	Urea and Electrolytes
URTI	Upper Respiratory Tract Infection
US	Ultrasound
UTI	Urinary Tract Infection
VBG	Venous Blood Gas
VF	Ventricular Fibrillation
VRE	Vancomycin-Resistant Enterococcus
VT	Ventricular Tachycardia
WBC	White Blood Cell

INTRODUCTION

I. BACKPROUND

The Ministry of Health of Kingdom of Cambodia is committed to improving the health and well-being of all Cambodian population through the provision of quality, safe, acceptable, equitable and affordable healthcare services. Implementing evidence-based, appropriate, and cost-effective health interventions within care packages at various levels of the health system, guided by contextually relevant best practices in clinical practice guidelines (CPGs), can significantly enhance population health.

Clinical Practice Guidelines (CPGs) are essential diagnostic and care tools in achieving UHC by ensuring that healthcare services are provided timely, effectively, safely, continuously and with patient-centeredness. The guidelines provide evidence-based and or up-to-health services at different levels of the health system. They ensure that health problems are appropriately diagnosed and clinical decisions are based on the best available evidence and experiences, leading to improved patient diagnosis and care outcomes as well as more efficient use of resources. By adhering to CPGs, healthcare providers can offer consistent, high-quality care that meets national and international standards.

The 1st Clinical Practice Guidelines (CPGs) for Medicine and Pediatrics were published in 2013. They are the only existing CPGs in Cambodia. Since then, many new developments have taken place, especially in the area of laboratory tests, medical imaging, diagnosis tools and treatment options. Regularly reviewing and updating the CPGs offer up-to-date and more evidence-based recommendations for health services and interventions tailored to Cambodia's current and future needs. Updating the clinical practice guidelines aims to enhance both quality and coverage by providing a solid evidence-based foundation for changes in services. This includes the diagnosing, treatments, and support necessary to deliver these services as defined in the essential packages of care under the CPA guidelines.

II. DEVELOPMENT PROCESS

This Clinical Practice Guidelines was formulated by "Technical Working Group of Clinical Practice Guidelines for General Medicine "of the Ministry of Health through face-to-face and online meeting of the working group and small group meeting and discussions with guidance and endorsements from the Steering Committee for National Medical Care and Therapy of the Ministry of Health mainly through its meeting .The development process of the guidelines was actively participated by various stake holders and individuals, including experts from related fields ranging from clinicians working in hospitals at all levels, district health officers, Provincial Health Department, national institutes, national programs, health professional associations as well as experts and officials partner organizations . Each health section follows standard format except in few cases. These guidelines contain three parts-Part I, Part II and Part III with each separate volume presented in its hard copy division and publication. The guideline covers 174 topics/diseases/conditions within 11 specialized chapters. The guideline do not cover the national programs topics/diseases/conditions such as HIV/AIDS, TB,

Malaria, Dengue, Schistosomiasis and vaccine preventable diseases. The list of the protocols/guidelines of these national programs are included in the annex B of the CPGs.

III. PURPOSE AND USERS

The main aim of these guidelines is to assist health care providers and practitioners make informed decisions on clinical diagnosing and treatment based on recommended protocols based on systematic review of evidence and an assessment of the benefits and harms of alternative care options. The guidelines is used for health professionals and relevant stakeholders in both public and private sectors, including doctors, related health professionals, trainees and medical students, policy makers, professional societies, in both public and private health facilities and institutions, including Provincial and district hospitals, private clinic, training and research institutions.

The main end users of the CPG are clinicians, managers and other health professionals practicing in patient care settings in both private and public sectors, particularly at referral hospitals and private clinics to support the delivery of consistently safe, quality and cost effective and equitable health care. They should be harmonized with the CPA guideline, IPC guideline, AMR guideline, Cambodian Hospital Accreditation Standards (CHAS) and Quality Enhancement Monitoring Tool (QEMT) and other MoH guidelines to motivate and facilitate their relevance and use. CPG can also be used by other relevant bodies and people such as in training and research institutions as well as by other organization or institutions as per the relevancy of their mandates.

CHAPTER I EMERGENCY

1. Assessment the patients in emergency room
2. Oxygen therapy and respiratory supports
3. Early warning score in hospital
4. Shock
5. Hemorrhagic shock
6. Stroke syndrome in emergency
7. Coma
8. Allergic reaction
9. General management of poisoning
10. Paracetamol poisoning
11. Methamphetamine poisoning
12. Organophosphate and Carbamate insecticides poisoning
13. Methanol and Ethylene glycol intoxication
14. Cardiopulmonary arrest; basic and advance cardiac life support
15. Acute metabolic complication of diabetes mellitus, Diabetes ketoacidosis
16. Acute metabolic complication of diabetes mellitus, Hyperosmolar hyperglycemia state
17. Traumatism in adult
18. Initial management of head trauma
19. Initial management of chest trauma
20. Acute abdominal syndrome
21. Hyperkalemia
22. Hypokalemia
23. Hypernatremia
24. Hyponatremia
25. Sepsis and septic shock, Empirical antibiotherapy
26. Severe acute respiratory infection (SARI) and influenza
27. Snake bites
28. Massive blood transfusion

ASSESSMENT THE PATIENTS IN EMERGENCY ROOM

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I. INTRODUCTION

Patients who present to the Emergency Room (ER) are typically unselected on arrival. A critical function of all ERs is to have reliable processes that can sort patients, in accordance with their clinical need. This process is termed "Patient Assessment" which is an important part of emergency patient evaluation. Even though it may seem time-consuming, it is necessary to properly and completely examine the patient to determine what care the patient requires. It is required not only to detect life-threatening conditions and correct them as quickly as possible but also detect problems that may become life-threatening if they go unnoticed.

II. TRIAGE

- Triage is a French verb meaning to sort.
- Most patients entering an emergency room (ER) are greeted by a triage nurse, who will perform a brief evaluation of the patient to determine a level of acuity or priority of care.

Priorities of Care and Triage Categories:

- Standardized triage categories are usually developed within each ER.
- Most common triage systems consist of five levels of acuity:
    - Triage Level I - Resuscitation
    - Triage Level II - Emergent.
    - Triage Level III - Urgent.
    - Triage Level IV - Less Urgent.
    - Triage Level V - Non-urgent.

Level I	Resuscitation	see patient immediately
Level II	Emergency	within 15 minutes
Level III	Urgency	within 30 minutes
Level IV	Less Urgency	within 60 minutes
Level V	Non Urgency	within 120 minutes

Figure 1: Emergency Department Triage and Acuity Scale colour scheme

Triage Level I - Resuscitation:

- Conditions requiring IMMEDIATE nursing and physician assessment.
- Any delay in treatment is potentially life - or limb - threatening.
- Includes conditions such as:
    - Airway compromise.

- Cardiac arrest.
- Severe shock.
- Cervical spine injury.
- Multisystem trauma.
- Altered level of consciousness (LOC) (unconsciousness).
- Eclampsia.

Triage Level II - Emergency:

- Conditions requiring nursing assessment and physician assessment within 15 MINUTES of arrival.
- Conditions include:
  - Head injuries
  - Severe trauma
  - Severe asthma
  - Lethargy or agitation
  - Severe allergic reaction
  - Chest pain
  - Back pain
  - GI bleed with unstable vital signs
  - Stroke with deficit
  - Abdominal pain in patients older than 50
  - Severe headache
  - Vomiting and diarrhea with dehydration
  - Any pain greater than 7 on a scale of 10

Triage Level III - Urgency:

- Conditions requiring nursing and physician assessment within 30 MINUTES of arrival.
- Conditions include:
  - Alert head injury with vomiting.
  - Mild to moderate asthma.
  - Moderate trauma.
  - Abuse or neglect.
  - GI bleed with stable vital signs.
  - History of seizure, alert on arrival.

Triage Level IV - Less Urgency:

- Conditions requiring nursing and physician assessment within 1 HOUR.
- Conditions include:
  - Alert head injury without vomiting.
  - Minor trauma.
  - Vomiting and diarrhea in patient older than age 2 without evidence of dehydration.
  - Minor allergic reaction.
  - Corneal foreign body.
  - Chronic back pain.

Triage Level V - Non-urgent:

- Conditions requiring nursing and physician assessment within 2 HOURS.
- Conditions include:
  - Minor trauma, not acute.

- Sore throat.
- Minor symptoms.
- Chronic abdominal pain.

III. ASSESSMENT

The primary and secondary assessment ensure that life-threatening conditions can be identified and treated early, in order of priority.

1. Primary Assessment:

- Primary assessment is meant to identify life-threatening conditions and treated early, in order of priority.
- It is an initial, rapid, A-B-C-D-E (airway, breathing, and circulation, neurologic disability and exposure). It should be performed in the first 5 minutes and repeated whenever a patient's condition changes or worsens.
- A problem discovered (A-B-C-D-E) must be addressed immediately before moving on to the next step.

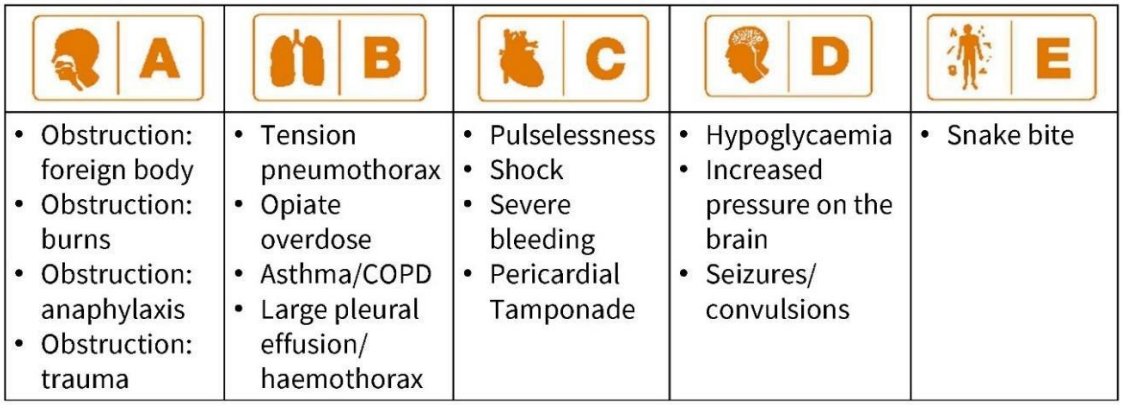


Figure 2: Acute Life-Threatening Conditions

A (Airway):

- Can the patient talk normally? If YES, the airway is open.
- If the patient cannot talk normally:
  - Look to see if the chest wall is moving and see if there is air movement from the mouth or nose.
  - Listen for abnormal sounds (such as stridor, grunting, or snoring) or a hoarse or raspy voice that indicates a partially obstructed airway. Stridor plus swelling and/or hives suggest a severe allergic reaction (anaphylaxis).
  - Look and listen for fluid (such as blood, vomit) in the airway.
  - Look for foreign body or abnormal swelling around the airway, and altered mental status.
  - Check if the patient is able to swallow saliva or is drooling.

B (Breathing):

- Look, listen, and feel to see if the patient is breathing.
- Assess if breathing is very fast, very slow, or very shallow.
- Look for signs of increased work of breathing (such as accessory muscle use, chest in drawing/retractions, nasal flaring) or abnormal chest wall movement.
- Listen for abnormal breath sounds such as wheezing or crackles.
- With severe wheezing, there may be limited/no breath sounds on examination because narrowing of the airways may be so severe that breathing cannot be heard.
- Listen to see if breath sounds are equal on both sides.

- Check for the absence of breath sounds and dull sounds with percussion on one side (large pleural effusion or hemothorax).
- If there are no breath sounds on one side, and hypotension, check for distended neck veins or a shifted trachea (tension pneumothorax).
- Check oxygen saturation with a pulse oximeter when available.

C (Circulation):

- Obtain a blood pressure (in both arms if chest trauma is suspected).
- Look and feel for signs of poor perfusion (cool, moist extremities, delayed capillary refill greater than 3 seconds, low blood pressure, tachypnoea, tachycardia, absent pulses).
- Look for both external AND internal bleeding, including bleeding: into chest; into abdomen; from stomach or intestine; from pelvic or femur fracture; from wounds.
- Look for hypotension, distended neck veins and muffled heart sounds that might indicate pericardial tamponade.

D (Disability):

- Assess level of consciousness using the AVPU scale:
    - A: The patient is aware of the examiner and can respond to the environment around them independently. The patient can also follow commands, open their eyes spontaneously, and track objects.
    - V: The patient's eyes do not open spontaneously. The patient's eyes open only in response to a verbal stimulus directed toward them. The patient can react to that verbal stimulus directly and in a meaningful way.
    - P: The patient's eyes do not open spontaneously. The patient will only respond to the application of painful stimuli by an examiner. The patient may move, moan, or cry out directly in response to the painful stimuli.
    - U: The patient does not respond spontaneously. The patient does not respond to verbal or painful stimuli.
- In trauma cases, check consciousness using the Glasgow Coma Scale (GCS).
- The AVPU scale correlates to distinct GSC ranges, as outlined below
    - GCS Score 15 - Alert
    - GCS 12 to 13 - Verbally Responsive
    - GCS 5 to 6 - Physically Responsive
    - GCS 3 - Unresponsive
- Always check glucose level in the confused or unconscious patient.
- Check for pupil size, whether the pupils are equal, and if pupils are reactive to light.
- Check movement and sensation in all four limbs.
- Look for abnormal repetitive movements or shaking on one or both sides of the body (seizure/convulsion).

E: Expose/environmental control

- Examine the entire body for hidden injuries, rashes, bites or other lesions.
- Rashes, such as hives, can indicate an allergic reaction
- Other rashes can indicate infection

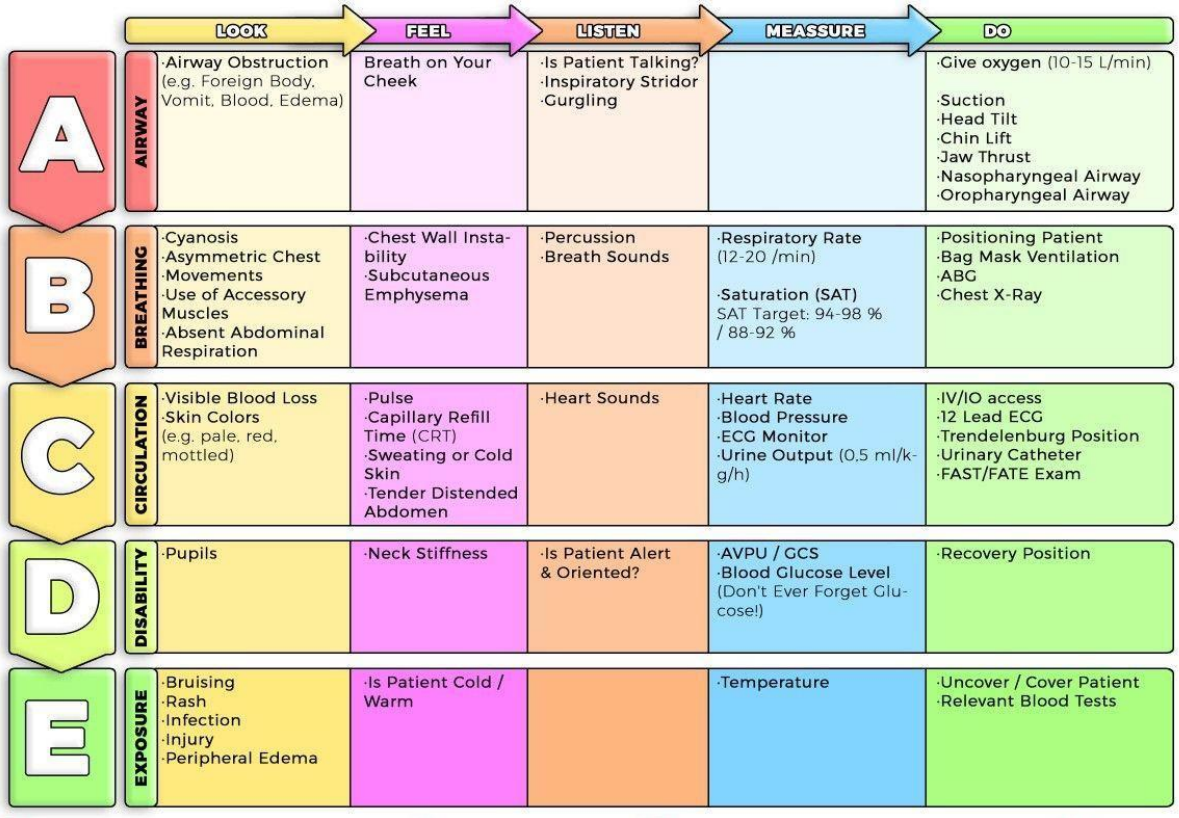


Figure 4: The ABCDE Approach

2. Secondary Assessment (F-G-H-I-J):

- Do not begin the secondary assessment until the primary assessment is complete and resuscitation procedures have been initiated as indicated.
- Continue to monitor ABCDE during the secondary assessment. If any life-threatening problems arise, return to the primary assessment and intervene as indicated.
- Prioritize and initiate interventions for injuries or conditions discovered in the secondary assessment after the entire head-to-toe examination is complete.
- Perform the secondary assessment using a systematic: the mnemonic F-G-H-I-J
- **F: Full set of vital signs/Five interventions/Facilitate family presence**
    - Full Set of Vital Signs
        - Obtain a full set of vital signs including blood pressure, heart rate, respiratory rate, and temperature.
        - Obtain blood pressure in both arms if chest trauma is suspected.
    - Five interventions
        - Pulse oximetry to measure the oxygen saturation.
        - Indwelling urinary catheter (do not insert if you note blood at the meatus, blood in the scrotum, or if you suspect a pelvic fracture).
        - Gastric tube (if there is evidence of facial fractures, insert the tube orally).
        - Laboratory studies frequently include type and crossmatching, hemoglobin and hematocrit, urine drug screen, blood alcohol, electrolytes, prothrombin time (PT) and partial thromboplastin time, and pregnancy test if applicable.
    - Facilitate family presence
        - It is important to assess the family's needs.

        - If any member of the family wishes to be present during the resuscitation, it is imperative to assign a staff member to that person to explain what is being done and offer support.
- **G: Get monitoring devices and Give comfort measures.**
    - Do not forget to give comfort measures to the family during the resuscitation process.
    - Follow the mnemonic L-M-N-O-P when obtaining resuscitation monitoring devices and supports.
        - L= Laboratory studies: ABG analysis, lactic acid level, type and crossmatch if indicated
        - M= Monitoring (Cardiac): arrhythmia may indicate a blunt cardiac injury
        - N= Nasogastric or orogastric tube: to relieve gastric distention, optimize lung inflation and prevent vomiting and aspiration. Avoid in patients with a suspected head injury or mid-face fractures.
        - O= Oxygenation and Ventilation: Assess SpO2 by pulse oximetry and plethysmography if any doubt, Monitoring ETCO2 via capnography
        - P= Pain assessment and management: using pain assessment scale then initiate pharmacologic and nonpharmacologic as indicated.
- **H: History and Head to Toe examination.**
    - Obtain prehospital information of the incident or illness. A helpful mnemonic M-I-S-T:
        - M: Mechanism of injury:
            - It is helpful to understand the mechanism of injury to anticipate probable injuries. It is particularly helpful in motor vehicle accidents to know such information as external and internal damage to the car and the period of time elapsed before the patient received medical attention.
        - I: Injuries sustained or suspected:
            - Ask prehospital personnel to list any injuries that they have identified.
        - S: Signs and symptoms before arrival
        - T: Treatment
            - What treatment did the patient receive before arriving at the hospital and what was his response to those interventions?
    - Obtain the patient's history. A helpful mnemonic is S-A-M-P-L-E.
        - **S-** Signs/symptoms associated with the injury or illness
        - **A-** Allergies and tetanus status
        - **M-** Medications currently used, especially anticoagulants
        - **P-** Past medical history (including hospitalizations and surgeries)
        - **L-** Last oral intake and output (last menstrual period if female of childbearing age)
        - **E-** Events and environmental factors related to the illness or injury?
    - Assess the patient from head to toe (Physical Examination)
- **I: Inspect posterior surfaces**
    - In the injured patient, obtain assistance to maintain cervical spine alignment and support injured extremities while log rolling the patient to the side.
    - Avoid rolling the patient onto an injured extremity or side if possible. If necessary, for adequate assessment of posterior surfaces, roll the patient to both sides.

- The log roll maneuver can result in spinal and pelvic movement. Carefully consider the risks and benefits of performing this maneuver, especially if the potential for spinal cord injury or pelvic fracture is significant.
- When spinal or pelvic injuries are suspected, radiographs are recommended before logrolling the patient.
- Inspect the posterior surfaces for wounds, deformities, or discolorations. Palpate all posterior surfaces for wounds, deformities, or muscle spasms.
- Remove the backboard or transferring device as indicated.

- **J: Just keep reevaluating**
  - Continue ongoing monitoring and evaluation of the patient. Reevaluation should include the primary survey, vital signs, level of pain and any injuries identified. A helpful mnemonic is V-I-P-P:
    - V = vital signs
    - I = injuries sustained and interventions
    - P = primary survey
    - P = level of pain

- **Physical examination**
  - **Head and Neck**
    - Observation face, head, neck & scalp
    - Palpation lymph node, parotid and salivary gland regions
    - Assess auditory acuity (crude test hearing loss)
      - If hearing loss, perform Weber & Rinne Tests 512 Hz fork (CN 8)
    - Ear: external and internal (otoscope)
    - Nose: observation, nares/mucosa (otoscope)
    - Oropharynx:
      - Inspect w/light from otoscope & tongue depressor(uvula), tonsils, tongue, mucosa
      - "Ahh" to help see back of throat
      - Inspect teeth & salivary gland ducts
      - Thyroid: Observation, palpation
  - **Eye Exam**, Including Ophthalmoscopy:
    - Observe external eye structures – lid, sclera, pupil
    - Visual acuity (hand-held card – CN2)
    - Visual fields (confrontation – CN 2)
    - Extra-ocular movements (CN 3, 4, 6)
    - Using Ophthalmoscope:
      - Examine external eye structures (lids, sclera, pupil, iris, conjunctiva)
      - Check pupillary response to light – direct and consensual (CN 2 & 3)
      - Red reflex
      - Retinal exam – identifying: Optic disc, arteries, veins, color of retina, and macular area.
  - **Pulmonary**
    - Observation and Inspection
      - General observation of breathing, note if using accessory muscles/general respiratory effort
      - Note shape of chest and spine
    - Palpation
      - Assess chest excursion
      - Assess tactile fremitus
    - Percussion

        - Percuss posterior lung fields, top to bottom, comparing side to side
        - Identify amount of diaphragmatic descent with inhalation
        - Percuss right antero-lateral chest (middle lobe) and anterior lobes (bilateral)
    - Auscultation
        - Listen w/diaphragm to posterior lung fields, top to bottom, comparing left w/right
        - Listen to right middle lobe area
        - Listen to anterior lung fields
        - Listen over trachea
- **Cardiovascular**:
    - Examiner stands on right side of patient's body
    - Patient lying w/head of table elevated ~ 30º
    - Observation & Palpation
        - Inspect precordium – visible PMI (Point of Maximal Impulse), other contours
        - Palpation of RV and LV (heaves, thrills); Determination of PMI
    - Auscultation
        - S1 and S2 in 4 valvular areas w/diaphragm; note rate, rhythm
        - Try to identify physiologic splitting S2
        - Assess for murmurs, characterize if present
        - Assess for extra heart sounds (S3, S4) w/bell over LV
    - Carotid artery
        - Palpation
        - Auscultation
    - Internal Jugular Vein
        - Measure jugular venous pressure
- **Abdomen**
    - Lay patient flat. Drape appropriately – allowing exposure of abdomen but not rest of body
    - Observe & inspect abdomen
        - Shape, scars, color, symmetry, protrusions
    - Auscultation
        - Listen w/diaphragm to 4 quadrants
        - Note quantity and quality of bowel sounds
        - Listen for bruits centrally & over renal arteries
    - Percussion
        - Percuss all quadrants
        - Percuss liver span
        - Percuss area of spleen, stomach
    - Palpation
        - Palpate all quadrants superficially
        - Palpate all deeply
        - Try to identify liver edge (w/inspiration)
        - Palpate region of spleen
        - Palpate area of aorta
- **Lower Extremities**
    - Assess femoral area
        - Palpation for nodes
        - Palpate femoral pulse
        - Auscultation femoral artery (for bruits)
    - Assess knees (non-mechanical exam)

        - Color, swelling
        - Palpate popliteal artery pulse
    - Assess ankles/feet:
        - Color
        - Temperature
        - Check cap refill
        - Check for edema
        - Pulses
            - Dorsalis pedis artery
            - Posterior tibial artery
- **Neurologic**
    - Higher Cognitive Function
        - Level of consciousness
        - Orientation to time, place, person and situation
        - Attention/Cognition – Counts backward from 100, subtracting 7 each time
        - Memory- 3 objects (Ex. cat, number 7 and table) repeat immediately and after 5 minutes
        - Abstract thinking- similarity and difference between orange and ball.
    - Mental Status Exam
        - Mood- as described by patient
        - Affect- observed by examiner could be congruent or incongruent to described mood
        - Speech- rate, tone, production
        - Thought process- linear, goal directed or circumstantial, tangential, disorganized
        - Thought content- delusions, suicidal or homicidal ideations/intent/plan
        - Insight- good, partial, poor
        - Judgment- what would you do if you found a sealed, addressed, stamped envelope on the ground?
    - Cranial Nerves – A few covered (above) in Eye and Head/Neck sections. Described 1 thru 12 here:
        - CN 1 – assess smell
        - CN 2 – visual acuity, visual fields
        - CN 2 & 3 pupillary response to light
        - CN 3, 4, & 6 – extra-ocular movements
        - CN 5 sensory & motor face; corneal reflex
        - (sensory 5, motor 7) – (Describe only)
        - CN7 – facial expression; smile, puff cheeks, close eyes against resistance
        - CN8 – hearing assessment
        - CN 9 & 10 – gag, palate rise
        - CN 11 – neck turn/shoulder shrug
        - CN12 – tongue movement
    - Motor testing (patient seated):
        - Muscle bulk of major groups (see below)
        - Tone of major groups (see below)
        - Strength of major groups – shoulders, elbows, wrists, hand, hips, knees, ankle
    - Sensory testing - in distal lower extremities:
        - Pain

        - Light touch
        - Proprioception
        - Vibration - 128 Hz tuning fork
    - Reflexes
        - Biceps
        - Brachioradialis
        - Triceps
        - Patellar
        - Achilles
        - Babinski assessment
    - Coordination (finger to nose, heel to shin, rapid alternating finger movements, hand supination →pronation)
    - Gait, Romberg

IV. ANAGEMENT

1. A = Airway management

If the patient is unconscious and not breathing normally and:

- NO TRAUMA: open the airway using the *head-tilt and chin-lift maneuver*.
    - Place one hand on the patient's forehead and the other under the chin.
    - Tilt the forehead back whilst lifting the chin forward to extend the neck.
- CONCERN FOR TRAUMA: maintain cervical spine immobilization and open the airway using the *jaw thrust maneuver*.
    - Identify the angle of the mandible
    - Place two fingers under the angle of the mandible (on both sides) and anchor your thumbs on the patient's cheeks
    - Lift the mandible forwards
- Place an oropharyngeal or nasopharyngeal airway to maintain the airway.
- If a foreign body is suspected: – If the object is visible, remove it– be careful not to push the object any deeper.
- If the patient is able to cough or make noises, keep the patient calm and encourage coughing.
- If the patient is choking (unable to cough, not making sounds) use age-appropriate chest thrusts/ abdominal thrusts/back blows.
- If the patient becomes unconscious while choking, follow relevant CPR protocols.
- If secretions or vomit are present, suction when available, or wipe clean. Consider placing patient in the recovery position if the rest of the ABCDE is normal and no trauma is suspected.
- If the patient has swelling, hives or stridor, consider severe allergic reaction (anaphylaxis), and give intramuscular adrenaline.

- Allow the patient to stay in a position of comfort and prepare for rapid handover/transfer to a center capable of advanced airway management, if needed.



Figure 5: Head-Tilt (Left) and Chin-Life Maneuver (Right)



Figure 6: Jaw-Thrust Maneuver



Figure 7: Nasopharyngeal Airway and Oropharyngeal Airway

2. **B = Breathing Management**

- If unconscious with abnormal breathing, start bag-valve-mask ventilation and follow relevant CPR protocols.
- If not breathing adequately (too slow for age or too shallow), begin bag-valve-mask ventilation with oxygen. If oxygen not immediately available, DO NOT DELAY ventilation. Start ventilation while oxygen is being prepared. Plan for rapid handover/transfer.
- If breathing fast or hypoxic, give Oxygen.
- If wheezing, give salbutamol.
- Repeat salbutamol as needed.
- If concern for severe allergic reaction (anaphylaxis), give intramuscular adrenaline.
- If concern for tension pneumothorax, perform needle decompression immediately and give IV fluids and oxygen. Plan for rapid handover/transfer.
- If concern for large pleural effusion or hemothorax, give oxygen and plan for rapid handover/transfer.
- If cause unknown, remember the possibility of trauma.



Figure 8: One-Hand bag mask ventilation technique

3. **C = Circulation Management**

- For cardiopulmonary arrest, follow relevant CPR protocols.
- If signs of poor perfusion, give IV fluids and oxygen and:
    - For external bleeding, apply direct pressure or use other technique to control.
    - If internal bleeding or pericardial tamponade are suspected, refer rapidly to a center with surgical capabilities.
- If cause unknown, remember the possibility of trauma: Bind pelvic fractures and splint femur fractures, or any fracture with compromised blood flow.

4. **D = Disability Management**

- If altered mental status and no evidence of trauma, place in recovery position.
- If glucose low (<3.5 mmol/L) or glucose test not available and patient has altered mental status, give glucose.
- For active seizures, give a benzodiazepine.
- If pregnant and having seizures, give magnesium sulphate.

- If pupils are small and breathing slow, consider opioid overdose and give naloxone.
- If pupils are not equal, consider increased pressure on the brain and raise head of bed 30 degrees if no concern for spinal injury.
- Plan for rapid transfer to an advanced provider or facility with neurosurgical care.

5. E = Exposure Management

- If snake bite is suspected, immobilize the limb, 20mn WBCT, give appropriate antivenom if available.
- Remove constricting clothing and all jewelry.
- Cover the patient as soon as possible to prevent hypothermia by using warm blankets, overhead warmers, and warmed I.V. fluids. Acutely ill patients have difficulty regulating body temperature.
- Remove any wet clothes and dry patient thoroughly.
- Respect the patient and protect modesty during exposure.
- If cause unknown, remember the possibility of trauma: Log roll if suspected spinal injury.

V. REFERENCES

1. Emergency care. (n.d.). Retrieved from https://books.google.com/books/about/EmergencyCare.html?id=LMWgBwAAQBAJ
2. Emergency primary assessment. (n.d.). Retrieved from https://elsevier.health/en-US/preview/emergency-primary-assessment
3. Emergency secondary assessment. (n.d.). Retrieved from https://elsevier.health/en-US/preview/emergency-secondary-assessment
4. Romanelli, D., & Farrell, M. W. (2023, April 3). AVPU scale. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK538431/
5. Wyatt, J. P., Illingworth, R. N., Graham, C. A., Hogg, K., Clancy, M. J., & Robertson, C. E. (2012b). General approach. In Oxford Handbook of Emergency Medicine (4 edn) (pp. 1–39). https://doi.org/10.1093/med/9780199589562.003.0001

OXYGEN THERAPY AND RESPIRATORY SUPPORTS

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I. DEFINITION

The administration of supplemental oxygen is necessary when a patient has low blood oxygen levels, termed hypoxemia. Untreated, acute hypoxemia can lead to tissue hypoxia (low level of oxygen at the cellular level), organ dysfunction and death. Delivery of oxygen to tissues also relies on adequate cardiac output and hemoglobin to carry oxygen to the tissues.

Oxygen therapy improves oxygen delivery to the tissues by increasing oxygen content in the blood. Oxygen content in the blood is frequently measured indirectly by pulse oximetry as oxygen saturation (SpO2).

- ***oxygen content in arterial blood*** (CaO_2) = 1.34 × (Hb) × SpO_2 + (0.003 × PaO_2)

Arterial oxygen partial pressure (PaO_2) measured in mmHg by arterial blood gas analyzer.

- ***Oxygen concentration*** (% O_2) from the oxygen source (i.e. wall outlet, bedside concentrator…) is the purity of oxygen produced by the device. It can range widely depending on the quality of the source but generally should range from 0.82–1.0 (82–100%).
- ***Fraction of inspired oxygen*** (% FiO_2) is the oxygen concentration that is inspired by the patient, usually a result of mixing the oxygen source and ambient air and can range from 0.21–1.0 (21–100%). This varies depending on the delivery device and the patient's respiratory drive.

Oxygen saturation (% SpO_2) and oxygen partial pressure (PaO_2) are the measured oxygen levels in blood, the former measured by pulse oximeter and the latter by blood gas analyzer.

II. INDICATIONS FOR OXYGEN THERAPY

- Respiratory distress
- Sepsis with hypoperfusion or shock
- Alteration of mental status
- Hypoxemia

The following conditions may require airway management in addition to oxygen.:

- obstructed or absent breathing,
- severe respiratory distress,
- central cyanosis,
- shock,
- coma and/or convulsions

Supplemental oxygen therapy should be provided immediately to achieve the following SpO2 targets:

- $SpO_2 \geq 90\%$ in adults and children
- $SpO_2 \geq 92–95\%$ in pregnant patients
- $SpO_2 \geq 94\%$ if child or adult with signs of multi-organ failure, including shock, alteration of mental status, severe anemia, and/or during resuscitation.
- Once stabilized, resume target $SpO_2 \geq 90\%$.

III. RESPIRATORY (VENTILATION) SUPPORT

Respiratory failure type 1 or hypoxic-respiratory-failure, as well as patients who have dyspnea and low SpO_2 need supplemental oxygen therapy. Most of the time, the standard oxygen delivery devices (nasal cannula, mask) or HFNC can help. When patients have also hypercapnia (respiratory failure type 2), then NIV is more helpful. In cases where the oxygenation disorder is

severe (e.g., in ARDS with PaO_2/FiO_2 <150), often, only invasive mechanical ventilation may help. Note that the NIV is the first-choice modality of ventilation support in Exacerbations of COPD and acute congestive heart failure.

A. Oxygen delivery devices

a. In adult

		O_2 flow	**FiO_2**
Non-invasive O_2 delivery devices	Nasal canular	1 - 5L/min	0.23 - 0.35
	Face mask	5 – 10L/min	0.30 – 0.50
	Venturi face mask	2 – 15L/min	0.24 – 0.6
	Face mask reservoir bag	10 – 15L/min	0.5 – 0.95
Advanced non-invasive O_2 delivery devices	High-flow nasal oxygen	10 – 60L/min	0.23 – 1.0
	BiPAP/CPAP oronasal	10 – 80L/min	0.21 – 1.0
	BiPAP/CPAP nasal		
	BiPAP/CPAP full face		
	BiPAP/CPAP Helmet		

b. In children

Nasal cannula is the preferred method of delivering oxygen to infants and children < 5 years of age with hypoxemia who require oxygen therapy.

Age of child	**Nasal canula size**	**Maximal oxygen flow rates**
Neonates	Neonatal	0.5 – 1L/min by nasal canula
Infants	Infant	1 – 2L/min by nasal canula
Pre-school aged	Child	1 – 4L/min by nasal canula
School-aged	Child to adult	1 - 5L/min by nasal canula

c. Humidification

When oxygen is delivered at standard flow rate (0.5–1 L/min for a neonate, 1–2 L/min for an infant, 1–4 L/min for an older child) through nasal prongs, humidification is not necessary. Higher flow rates without effective humidification may cause drying of nasal mucosa with associated bleeding, airway obstruction and may cause bronchoconstriction in some conditions (e.g. asthma, COPD).

Bubble humidifiers reduce the dryness of the oxygen supplied by bubbling the gas through water at room temperature. They must be filled with clean water at least once a day (distilled water or tap water that has been boiled and cooled). The water level in the humidifier should be checked twice daily and topped up as necessary. The humidifier equipment must be washed and disinfected regularly to prevent bacterial colonization.

B. Choosing the modality of respiratory support

- **Standard oxygen therapy:**

Simple mask and nasal cannula provided low FiO_2, can be used on patients with mild hypoxia. FiO_2 varies and depends on minute ventilation. Use cannula with O_2 flow < 5LPM; simple mask needs the O_2 flow 5-10LPM

Venturi-mask provides constant FiO2 as marked on the device, different color gives different FiO_2. Usually, the color red gives FiO_2=40% with O_2 flow 10-12LPM, the green one gives FiO_2 = 60% with oxygen flow 12-15 LPM.

Use a non-rebreathing mask with reservoir bag and the highest possible oxygen flow to the patient who is remarkable hypoxic (SpO_2 <90%), It may provide FiO_2 up to 80-95%

- **High Flow nasal canula (HFNC):**

The main use of HFNC is to provide relatively high FiO_2 to patients with severe non-hypercapnic-hypoxemic respiratory failure. Most devices can provide maximum FiO_2= 100%

and flow 60LPM. Sometimes HFNC can help hypoxic-respiratory-failure patient avoid intubation, but it is important to detect failure and move early to invasive mechanical ventilation if indicated.
The ROX score = $SpO_2/FiO_2 \div RR$,
may help to decide whether to continue HFNC or change.
score < 2.85 at 2h, or < 3.47 at 6h, or < 3.85 at h12 are predictors of failure
Score ≥ 4.88 after 2h, or 6h, or 12h predicts the success, and HFNC may continue.

- **Non-invasive ventilation (NIV):**

NIV with a mask delivering continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) can increase minute ventilation, reduce the work of breathing, recruit alveoli, and improve hemodynamics.

Contra-indication of NIV:

- Cardiac / respiratory arrest
- Medically unstable (hypotensive shock, uncontrolled cardiac ischemia, or arrhythmias)
- Severe upper gastrointestinal bleeding
- Unable to protect airway (impaired cough or swallowing)
- Excessive secretions
- Unable to apply mask due to facial surgery, trauma, burns, or facial deformity
- Agitated or uncooperative
- Undrained pneumothorax
- Multiorgan system failure

NIV helps to improve oxygenation (increase PaO_2) and ventilation (decrease $PaCO_2$).
Using ICU ventilator, in CPAP mode, CPAP = PEEP, in BiPAP mode EPAP=PEEP,
delta P = PS, PS + PEEP= IPAP. (EPAP: expiratory positive airway pressure, IPAP: inspiratory positive airway pressure)
Initial setting usually PEE=5 cmH_2O, PS=5-10 cmH_2O
Increase level of PEEP usually helps to increase PaO2, and increase the PS usually decreases $PaCO_2$.

- **Mechanical ventilation:**

Endotracheal intubation and controlled mechanical ventilation should be pursued aggressively when ventilatory support is needed and NIV is not expected to improve outcomes, such as for acute exacerbations of asthma and diseases that do not respond rapidly to medical therapy (e.g., pneumonia and ARDS).
Endotracheal intubation is an aggressive procedure that should be done by trained personals. Some anesthetic drugs (hypnotic, opioids, myorelaxant) often used during intubation and for neuro sedation. The intubation tube-cuff pressure should be between 20 - 30cmH2O.
Modern ventilators have many settings and choices to adapt with patient conditions. The most frequent initial setting in emergency is:

- Mode: V-ACV (volume target-assist-control-ventilation)
- Vt: 6-8ml/kg (Ideal body weight), ~ 400ml for adult 60-70kg actual body weight.
- PEEP: 5 cmH2O
- FiO_2: start 100%, then reduce progressively as condition improved
- Frequence: 12-18/min (varies to PCO_2, increase Frequence if PCO_2 high)
- Plateau pressure: < 30 cmH2O
- Trigger: -2 cmH_2O, or – 2L/min

Most often, after putting on mechanical ventilation in ER, the patient was transferred to operation room or ICU where the team adapt the ventilation setting and follow up accordingly. The control of mechanical ventilation is guided by arterial blood gas analysis or $PetCO_2$ and SpO_2 measures, the surveillance of respiratory mechanic and clinical response.
The main objectives of mechanical ventilation are:

(1) normalization of oxygenation and ventilation
(2) Avoid or limit the complications of ventilation. And
(3) wean patients from ventilator as soon as possible

IV. OXYGEN SUPPLY

At the facility level, there are many considerations required to estimate oxygen demand, including:

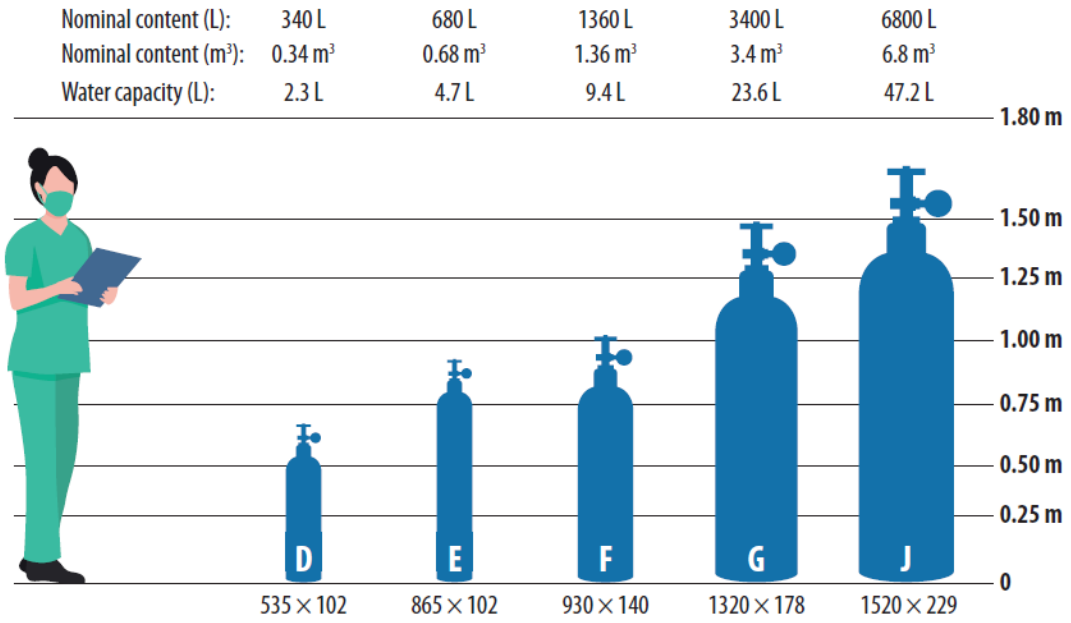
- Oxygen source type:
  - pressure swing adsorption (PSA),
  - vacuum pressure swing adsorption (VPSA) plants,
  - bulk liquid tank,
  - bedside oxygen concentrators,
  - distribution manifolds with high-pressure cylinders, or
  - a combination of sources.
- Distribution system: Oxygen may travel from the source to the patient's bedside in two main ways: pipe network or bedside high-pressure gas cylinders (or bedside concentrators). Accessories for monitoring and regulation of the medical gas should be included (e.g. pressure regulators and flowmeters).
- Delivery equipment and devices: This refers to biomedical equipment connected to the network (e.g. patient ventilators, or direct interfaces such as nasal cannula).

Oxygen concentrator

There are multiple devices available and approved, with different power efficiencies and a range of minimum and maximum oxygen output between a minimum of 0.125 L/min to a maximum of 10 L/min. Few portable oxygen concentrators can deliver more than 10 L/min, and many oxygen concentrators may claim a wide range of flows but only with low oxygen concentrations.

Oxygen cylinders

Many hospitals use oxygen cylinders, the pressure is in Bar. A full compressed cylinder is 120-130 Bar. A cylinder size J, has 47.2L water capacity, full compressed to 120 bar have oxygen = $47.2 \times 120 = 5664$L. A pressure release manometer is needed to reduce the outlet pressure to a constant pressure usually from 3.5-5 Bar to run the ventilator. Some model ventilators (e.g., Hamilton T1) can be connected also to low pressure O_2 flow outlets.



Note: dimensions: height × diameter mm

Source: Adapted from WHO-UNICEF technical specifications and guidance for oxygen therapy devices.

Cylinder size

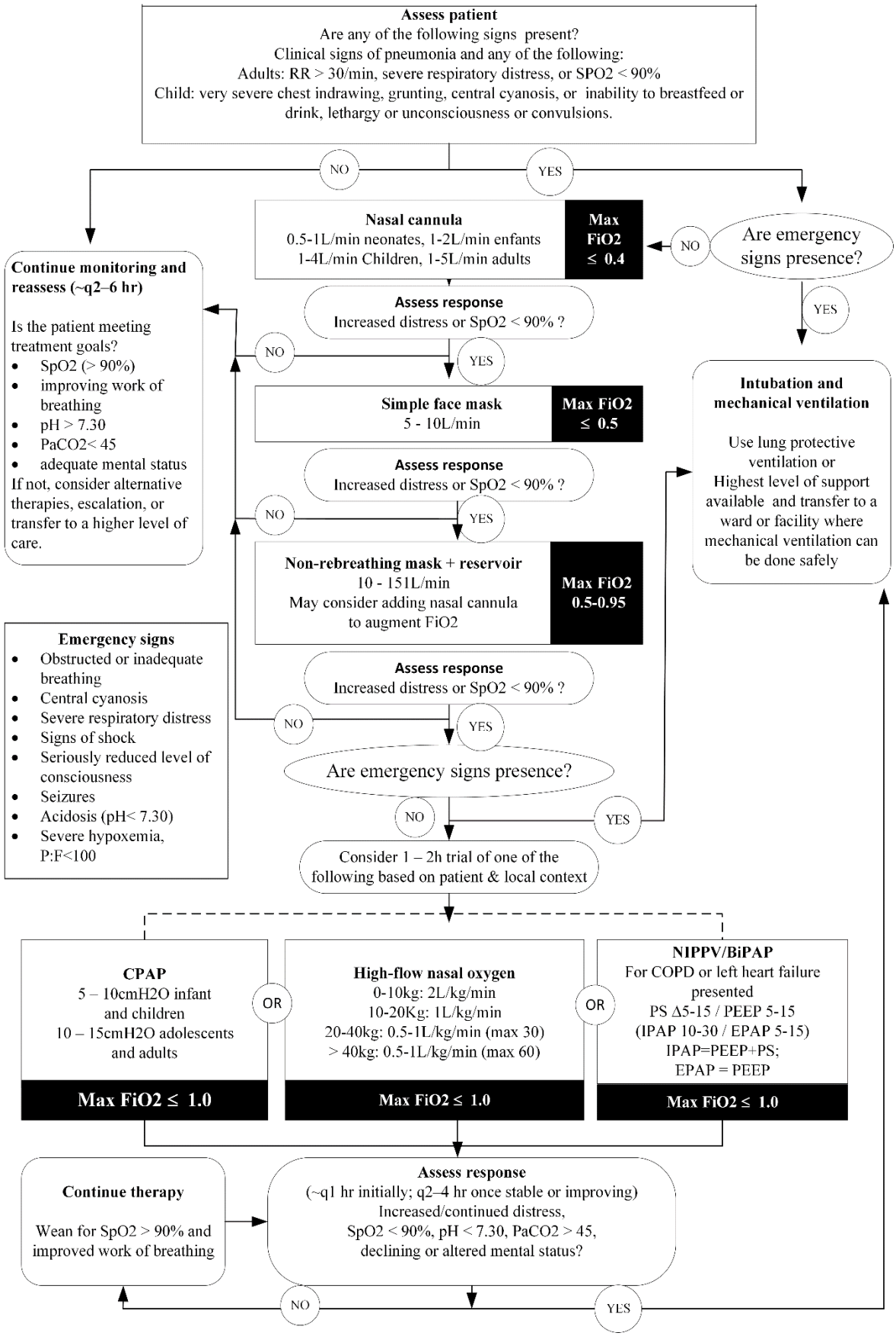
	D	E	F	G	J
Nominal content/oxygen capacity (L)	340	680	1360	3400	6800
Water capacity (L)	2.3	4.7	9.4	23.6	47.2
Dimensions (height × diameter) (mm)	535 × 102	865 × 102	930 × 140	1320 × 178	1520 × 229
Approximate full weight (kg)	3.9	6.5	17	39	78
Valve outlet connection (and specification)	Pin index (ISO 407)	Pin index (ISO 407)	Bullnose (BS 341)	Bullnose (BS 341)	Pin index side spindle (ISO 407)
Nominal service pressure (kPa/bar/psi)	13 700 kPa (137 bar/1987 psi)	13 700 kPa (137 bar/1987 psi)	13 700 kPa (137 bar/1987 psi)	13 700 kPa (137 bar/1987 psi)	13 700 kPa (137 bar/1987 psi)
Health facility use	Emergency and ambulance transport	Emergency and ambulance transport	Stand-alone	Stand-alone	Manifold connection and stand-alone

Notes: BS – British Standard; ISO – International Organization for Standardization; psi – pounds per square inch absolute.

Source: BOC Healthcare (https://www.bochealthcare.co.uk/en/images/cylinder_data_med309965_2011_tcm409-54065.pdf, accessed 12 June 2019).

V. ALGORITHM

a. Algorithm to escalate respiratory support in patient with pneumonia (schema 1)
b. Titration oxygen therapy in adult_ (schema 2)
c. Titration of oxygen therapy in children_ (Schema 3)
d. Titration of oxygen therapy in neonates_ (Schema 4)


Assess patient
Are any of the following signs present?
Clinical signs of pneumonia and any of the following:
Adults: RR > 30/min, severe respiratory distress, or SPO2 < 90%
Child: very severe chest indrawing, grunting, central cyanosis, or inability to breastfeed or drink, lethargy or unconsciousness or convulsions.
NO
YES
Are emergency signs presence?
NO
YES
Nasal cannula
0.5-1L/min neonates, 1-2L/min enfants
1-4L/min Children, 1-5L/min adults
Max FiO2 ≤ 0.4
Assess response
Increased distress or SpO2 < 90% ?
NO
YES
Simple face mask
5 - 10L/min
Max FiO2 ≤ 0.5
Assess response
Increased distress or SpO2 < 90% ?
NO
YES
Non-rebreathing mask + reservoir
10 - 151L/min
May consider adding nasal cannula to augment FiO2
Max FiO2 0.5-0.95
Assess response
Increased distress or SpO2 < 90% ?
NO
YES
Are emergency signs presence?
NO
YES
Consider 1 – 2h trial of one of the following based on patient & local context
Continue monitoring and reassess (~q2–6 hr)
Is the patient meeting treatment goals?
SpO2 (> 90%)
improving work of breathing
pH > 7.30
PaCO2< 45
adequate mental status
If not, consider alternative therapies, escalation, or transfer to a higher level of care.
Emergency signs
Obstructed or inadequate breathing
Central cyanosis
Severe respiratory distress
Signs of shock
Seriously reduced level of consciousness
Seizures
Acidosis (pH< 7.30)
Severe hypoxemia, P:F<100
Intubation and mechanical ventilation
Use lung protective ventilation or
Highest level of support available and transfer to a ward or facility where mechanical ventilation can be done safely
CPAP
5 – 10cmH2O infant and children
10 – 15cmH2O adolescents and adults
Max FiO2 ≤ 1.0
OR
High-flow nasal oxygen
0-10kg: 2L/kg/min
10-20Kg: 1L/kg/min
20-40kg: 0.5-1L/kg/min (max 30)
> 40kg: 0.5-1L/kg/min (max 60)
Max FiO2 ≤ 1.0
OR
NIPPV/BiPAP
For COPD or left heart failure presented
PS Δ5-15 / PEEP 5-15
(IPAP 10-30 / EPAP 5-15)
IPAP=PEEP+PS;
EPAP = PEEP
Max FiO2 ≤ 1.0
Continue therapy
Wean for SpO2 > 90% and improved work of breathing
Assess response
(~q1 hr initially; q2–4 hr once stable or improving)
Increased/continued distress,
SpO2 < 90%, pH < 7.30, PaCO2 > 45,
declining or altered mental status?
NO
YES

Titrate oxygen in adult



- **Start oxygen at 1-5L/min**
- Use nasal prongs
- Assess response

FiO_2 0.23-0.4

If continued distress or SpO2< 90%
(or < 94% if emergency signs)





- **Use venturi mask or (face mask)**
- Titrate oxygen 2-15L/min by color or 5-10L/min for face mask
- Assess response

FiO2 0.24-0.6 (FiO_2 0.3-0.5)

If continued distress or SpO2< 90%
(or < 94% if emergency signs)



- **Use face mask with reservoir**
- Start oxygen 10-15L/min
- Titrate to ensure bag inflates

FiO_2 0.5-0.85

If continued distress or SpO2< 90%
(or < 94% if emergency signs)

Transfer to higher level care and consider:

HFNO:
30 – 60L/min (may also adjust FiO2)
CPAP:
10-15cmH2O
BiPAP:
PS Δ5–15 / PEEP 5-15
i.e. IPAP 10-30 /EPAP 5-15
IPAP=PEEP+PS; EPAP=PEEP

Heated humidification should be used

FiO_2 0.21-1.0



Oronasal BiPAP/CPAP



HFNO

If continued respiratory distress or SpO2< 90% on 15L/min consider intubation and mechanical ventilation.
Wean O2 flow and avoid SpO2 100% to avoid ill effects of hyperoxia and excess O2 consumption.

Titrate oxygen in children



- **Start oxygen at 1-5L/min**
- Use nasal prongs
- Assess response

FiO_2 0.23-0.4

If continued distress or SpO2< 90%
(or < 94% if emergency signs)



- **Use face mask**
- Increase Oxygen to 5-10L/min
- Assess response

FiO_2 0.3-0.5

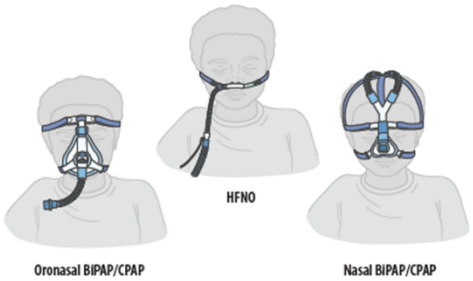
If continued distress or SpO2< 90%
(or < 94% if emergency signs)



- **Use face mask with reservoir**
- Start oxygen 10-15L/min
- Titrate to ensure bag inflates

FiO_2 0.5-0.85

If continued distress or SpO2< 90%
(or < 94% if emergency signs)



Transfer to higher level care and consider:

HFNO:
10-20kg 1L/kg/min
20-40kg 0.5-1L/kg/min (max 30)
> 40kg 0.5-1L/kg/min (max 60)

CPAP:
5-10cmH2O

BiPAP:
PS Δ5–15 / PEEP 5-15
Ie. IPAP 10-30 /EPAP 5-15
IPAP=PEEP+PS; EPAP=PEEP

Heated humidification should be used

FiO_2 0.21-1.0

If continued respiratory distress or SpO2< 90% on 15L/min consider intubation and mechanical ventilation.
Wean O2 flow and avoid SpO2 100% to avoid ill effects of hyperoxia and excess O2 consumption.

Titrate oxygen in neonates



- **Start nasal cannula oxygen at**
- 1-5L/min neonates
- 1-2L/min infants

If continued distress or SpO2< 90%
(or < 94% if emergency signs)

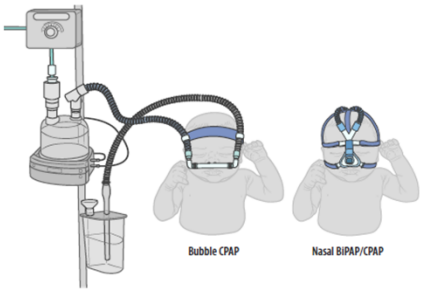


- Consider **face mask with reservoir** only if HFNO, CPAP,bCPAP, BiPAP unavaialble
- Start oxygen at 10-15L/min and titrate to ensure bag inflates

Flow rate higher than 4L will dry mucous membranes and humidification should be used

If continued distress or SpO2< 90%
(or < 94% if emergency signs)





Find higher level of care and consider one of the following if adequate O2 supply:

HFNO:
0-10kg 2L/kg/min
10-20kg 1L/kg/min

CPAP:
5-10cmH2O
Bubble CPAP:
Start flow at 5L/min, immerse expiratory limb (cm depth in H2O equals CPAP pressure; look for bubbles; titrate to 10L/min if needed to generate bubbles

BiPAP:
PS Δ5–15 / PEEP 5-15
i.e. IPAP 10-30 /EPAP 5-15
IPAP=PEEP+PS; EPAP=PEEP

If continued respiratory distress or SpO2< 90% on 15L/min consider intubation and mechanical ventilation.
Wean O2 flow and avoid SpO2 100% to avoid ill effects of hyperoxia and excess O2 consumption.

VI. SAFETY MEASURES FOR USING CYLINDERS

- Check cylinder pressure: Before use, verify that the cylinder has sufficient oxygen by checking the pressure gauge.
- Open valve slowly: When opening the cylinder valve, do so slowly to prevent rapid gas release.
- Use correct flow rate: Set the oxygen flow rate according to the patient's needs and medical prescription.
- Monitor patient: Continuously monitor the patient's oxygen saturation levels and adjust the flow rate as needed.
- Secure oxygen delivery device: Ensure the oxygen delivery device (nasal cannula, mask, etc.) is securely fitted to the patient.
- Close valve when finished: Close the cylinder valve when the oxygen is no longer needed.

VII. MONITORING AND ADJUSTMENT OF OXYGEN THERAPY

- **Assess response**

Re-evaluate patient every hour initially, then every 2-4h once the condition is stable or improving. Check for:

- Increased/continued distress?
- $SpO_2 < 90\%$, $pH < 7.30$, $PaCO_2 > 45$,
- declining or altered mental status?

- **Titration and SpO_2 goal**
  - $SpO_2 \geq 90\%$ in adults and children
  - $SpO_2 \geq 92–95\%$ in pregnant patients
  - $SpO_2 \geq 94\%$ if child or adult with signs of multi-organ failure
  - Avoid $SpO_2 > 96\%$ to avoid ill effects of hyperoxia and to conserve O2 supply.

VIII. SPECIAL CASES

A. Chronic Obstructive pulmonary disease (COPD),

- Acute exacerbation of COPD

medical therapy including bronchodilators, corticosteroids, and antibiotics when indicated.

For patients presenting to the emergency department, provide supplemental oxygen if the patient is hypoxemic, and perform an assessment to determine the optimal treatment setting and whether noninvasive ventilation is indicated (due to increased work of breathing or impaired gas exchange).

- Titrate oxygen to a target saturation of 88%-92% to improve hypoxemia and prevent worsening partial pressure of carbon dioxide (PCO_2) levels.
- Carbon dioxide retention can occur, especially if higher saturations are achieved.
- Perform arterial blood gas (ABG) measurements 30-60 minutes after starting oxygen.
- Venturi masks (high-flow devices) are more accurate than nasal cannula but less likely to be tolerated.
- Use pulse oximetry or ABG to track or adjust supplemental oxygen and monitor for carbon dioxide retention and/or worsening acidosis

- Post exacerbation long term use of oxygen

At least 2months after exacerbation, Check if patient need long term supplemental oxygen. Perform 2 times ABG check in 3 weeks apart.

Prescribe oxygen at least 15h/day for long time in patients with stable chronic obstructive pulmonary disease who have “severe chronic resting hypoxemia”, defined as any one of the following:

- arterial oxygen partial pressure (PaO_2) ≤ 55 mm Hg
- oxygen saturation by pulse oximetry (SpO_2) ≤ 88%
- PaO_2: 56-59 mm Hg, SpO_2= 89% or arterial oxygen saturation (SaO_2) ≤ 88%, if evidence of peripheral edema, right heart failure, P pulmonale on electrocardiogram (ECG), polycythemia (hematocrit ≥ 55%), or pulmonary hypertension.

Long term oxygen therapy (at home) should be initiated at a flow rate of 1 L/minute and titrated up by 1 L/minute increments until oxygen saturation measured by pulse oximetry (SpO_2) is > 90%. Consider arterial blood gas testing after initial titration to SpO_2 > 90% to confirm target resting arterial oxygen partial pressure (PaO_2) ≥ 60 mm Hg has been achieved (If available).

Oxygen flow should be sufficient to achieve PaO_2 > 60 mm Hg or 90% SpO_2 without causing hypercapnia or acidosis (Strong recommendation).

B. Patient with Central nervous System lesion (stroke, brain injury)

- Patient with ischemic stroke

Patients with adequate ventilation should have their oxygen saturation monitored. Patients who are hypoxic should receive supplemental oxygen to maintain oxygen saturation >94%. Supplemental oxygen should not routinely be given to nonhypoxic patients with acute ischemic stroke.

- Brain injury (traumatic)
  - Pre-hospital: Patients who are not intubated should receive supplemental oxygen as necessary to maintain an SpO_2 >90% to 93%
  - In Emergency department: Endotracheal intubation should be performed at this time for all patients with a GCS score <9, inability to protect the airway, inability to maintain SpO_2 >90 % despite the use of supplemental oxygen, or clinical signs of cerebral herniation. Adequate oxygenation (PaO_2 >60 mmHg) continues to be a priority.
  - Recent study found that, the lowest mean PaO_2 observed to maintain $PbtO_2$ (Oxygen partial pressure in brain tissue) above the ischemic threshold (20mmHg) was 94 mmHg. The authors' results suggest that the minimal PaO_2 target to ensure adequate cerebral oxygenation during the first few days after TBI should be higher than that suggested in the Brain Trauma Foundation guidelines

IX. OXYGEN TOXICITY AND COMPLICATIONS

- Oxygen toxicity — Oxygen toxicity is considered to be a harmful effect of inspired oxygen at pressures greater than atmospheric pressure (i.e., >0.21 inspired fraction of oxygen at sea level).
- Oxygen toxicity can be caused by hyperoxia and hyperoxemia and is generally responsible for parenchymal lung injury, the retinopathy of prematurity and bronchopulmonary dysplasia in infants.
- In general, patients at greatest risk of oxygen toxicity are those who are receiving mechanical ventilation for respiratory failure with a fraction of inspired oxygen (FiO_2) greater than 0.6 for prolonged durations (e.g., >24 hours).
- Efficient oxygen usage should be:
  - ***Target Saturation Range***: Oxygen should be prescribed according to a target saturation range. For most acutely ill patients, the goal is to achieve normal or near-normal oxygen saturation.
  - ***Monitoring***: Continuous monitoring of oxygen saturation using pulse oximetry is essential. This helps ensure that the patient remains within the target range and allows for adjustments as needed.

- ***Controlled Administration***: For patients with conditions like COPD, controlled or low-dose oxygen therapy is recommended to avoid complications such as hypercapnia.

X- REFERENCES

1. Clinical care for severe acute respiratory infection: toolkit, update 2022. COVID-19 adaptation. WHO/2019-nCoV/SARI_toolkit/2022.1
2. Atul Malhotra, MD Richard M Schwartzstein, MD "Adverse effects of supplemental oxygen." UpToDate, Update Feb 6, 2024, Accessed on August 5, 2024. URL: https://www.uptodate.com/contents/adverse-effects-of-supplemental-oxygen
3. Dellazizzo L, Demers SP, Charbonney E, Williams V, Serri K, Albert M, Giguère JF, Laroche M, Williamson D, Bernard F. Minimal PaO2 threshold after traumatic brain injury and clinical utility of a novel brain oxygenation ratio. J Neurosurg. 2018 Nov 2;131(5):1639-1647. doi: 10.3171/2018.5.JNS18651. PMID: 30485198

EARLY WARNING SCORE IN HOSPITAL

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I- INTRODUCTION

Patients seldom deteriorate abruptly, even though clinicians may recognize the deterioration suddenly.

In early stages, some signs may be subtle, and clinicians may not fully appreciate the severity of the clinical picture.

The physiologic deterioration precedes many cardiopulmonary arrests by hours, suggesting that early intervention could prevent the need for resuscitation, admission to the ICU, and other sentinel events.

II- EARLY RECOGNITION OF PATIENT WHO DETERIORATES IN HOSPITAL

The NEWS-2 score

Assessment of vital signs correctly frequently plus observation of patient general condition may ensure good patient care. Based on the degree of change from normal range of the vital signs, the score NEWS (National Early Warning Score) categorizes the patient group who need more frequent assessment and escalation of management before they become urgent or critically ill. The NEWS provides the basis for a unified and systematic approach to the first assessment and triage of acutely ill patients, and a simple track-and-trigger system for monitoring clinical progress for all patients in hospitals.

The NEWS is based on a simple aggregate scoring system in which a score is allocated to physiological measurements, already recorded in routine practice, when patients present to, or are being monitored in hospital.

The NEWS-1 issue in 2012, was reviewed and updated in 2017 as NEWS-2

Six simple physiological parameters form the basis of the scoring system:

1. respiration rate
2. oxygen saturation
3. systolic blood pressure
4. pulse rate
5. level of consciousness or new confusion*
6. temperature.

**The patient has new-onset confusion, disorientation and/or agitation, where previously their mental state was normal* – this may be subtle. The patient may respond to questions coherently, but there is some confusion, disorientation and/or agitation. This would score 3 or 4 on the GCS (rather than the normal 5 for verbal response), and scores 3 on the NEWS system.

A score is allocated to each parameter as they are measured, with the magnitude of the score reflecting how extremely the parameter varies from the norm. The score is then aggregated. The score is uplifted by 2 points for people requiring supplemental oxygen to maintain their recommended oxygen saturation.

NATIONAL EARLY WARNING SCORE 2 (NEWS-2)

Physiological parameter	SCORE						
	3	2	1	0	1	2	3
Respiratory rate (/ minute)	≤ 8		9 - 11	12 -20		21-24	≥ 75
SpO2 scale 1 (%)	≤ 91	92-93	94 - 95	≥ 96			
SpO2 scale 2 (%) [COPD]	≤ 83	84-85	86 - 87	88 -92 ≥ 93 on air	93-94 on oxygen	95–96 on oxygen	≥ 97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤ 90	91-100	101 - 110	111 - 219			≥ 220
Pulse (/ minute)	≤ 40		41 - 50	51 - 90	91-110	111-130	≥ 131
Consciousness				Alert			CVPU
Temperature (°C)	≤ 35.0		35.1–36.0	36.1 – 38.0	38.1–39.0	≥ 39.1	

- The chart has a dedicated section (SpO2 Scale 2) for use in patients with hypercapnic respiratory failure (usually due to COPD) who have clinically recommended oxygen saturation of 88–92%. (for general patient use scale-1 to score SpO2, use scale 2 only after discussed with doctor)
- Sepsis should be considered in any patient with a known infection, signs or symptoms of infection, or in patients at high risk of infection, and a NEW score of 5 or more.
- In identifying patients with sepsis (sepsis-3) outside of ICU, qSOFA_ (three criteria: altered mental status, systolic blood pressure ≤100 mmHg, and respiratory rate ≥22 breaths per minute. When any 2 were positive) have been proposed. Compared with NEWS-2, qSOFA is more specific but it is less sensitive than NEWS-2. So, when both are positive, it is more certain that patient has sepsis.
- Clinical response to the NEWS should be recorded. This will provide a continuous record of actions taken in response to variations in the NEWS and act as a prompt for escalating care if necessary.

The grade of risk of deterioration following NEWS-2 Score and type of response:

New Score	Clinical Risk	Response
Aggregate score 0 – 4	Low	Ward-based response
Red score, Score of 3 in any individual parameter	Low-medium	Urgent ward-based response
Aggregate score 5 - 6	Medium	Key threshold for urgent response. With team of competent, consider escalation of care to ICU
Aggregate score 7 or more	High	Urgent or emergency response, include critical Care skill

The increase of NEWS score range, implied the scaleup of patient assessment frequency and additional measure

New score	Frequency of monitoring	Clinical response
0	Minimum 12 hourly	• Continue routine NEWS monitoring
Total 1-4	Minimum 4-6 hourly	• Inform registered nurse (RN), who must assess the patient • RN decides whether increase frequency of monitoring and /or escalation of care is required
3 in single parameter	Minimum 1 hourly	• RN to inform medical team caring for the patient, who will review and decide whether escalation of care in necessary
Total 5 or more Urgent response threshold	Minimum 1 hourly	• RN to immediately inform the medical team caring for the patient • RN to request urgent assessment by a clinician or team with core competencies in the care of acutely ill patients • Provide clinical care in an environment with monitoring facilities
Total 7 or more Emergency response threshold	Continuous monitoring of vital signs	• RN to immediately inform the medical team caring for the patient_ this should be at least at specialist registrar level • Emergency assessment by a team with Critical care competencies including practitioners with airway management skills. • Consider transfer of care to a level 2 or 3 clinical care facility, ie. Higher-dependency unit or ICU • Clinical care in an environment with monitoring facilities

Note:

- A ward-based response typically involves a prompt assessment by a ward nurse to decide on changes to the frequency of monitoring or escalation of clinical care.
- An urgent-based response involves an urgent review by a ward-based doctor to determine the cause and decide on changes to monitoring or escalation of clinical care
- To adapt to our situations, a Registered nurse (RN) should be the head of the nurse-shift.

III- EARLY RECOGNITION AND MANAGE THE PATIENTS WHO DETERIORATED IN HOSPITALS

(The care that should be provided to all critically ill patients in all hospitals in the world)

A. The concept of Essential Emergency and Critical Care (EECC)

In hospitals, sometimes patients' conditions may deteriorate and become life threatening while the medical team only manages or transfers the patient to ICU lately. Not as people expected, many factors contributed to this situation: No correct vital signs checked, no vital signs Interval Policy, Understaffed Hospital, Undertrained providers, critical illness not recognized, No Senior Staff Available.

The early stage of critical condition, mostly response well with the simple measures and techniques of management while late management in ICU is often costly, complex, less effective or fails to help.

Critical illness is often reversible. Identification is time-critical. Early identification of critically ill patients is key.
Prompt, time-critical care interventions are crucial to reversing the course of critical illness and saving patient lives.

Essential Emergency and Critical Care (EECC) was established around 2020, with its initial framework and guidelines developed through a Delphi process—a structured approach to building consensus among healthcare experts worldwide. Over 270 specialists from various regions and backgrounds collaborated on the design of EECC, focusing on practical, low-cost interventions that could be feasibly implemented in all hospitals, including those in low-resource settings. This initiative was partially driven by the need for effective care models during the COVID-19 pandemic, which highlighted critical care gaps globally.

The framework builds on WHO's Basic Emergency Care principles and aims to provide consistent, essential care that can stabilize critically ill patients, regardless of their specific diagnosis or the availability of specialized intensive care resources. This model is being gradually implemented worldwide, especially in areas where access to advanced critical care is limited, to address preventable mortality among critically ill patients.

B. The process of EECC

The purpose of EECC is to identify critical illness and provide the timely, lifesaving care patients need to reverse their course of illness.
Evaluating the 8 vital signs of EECC is core to this process
Providers must be able to determine normal vital signs. Knowing the normal enables providers to then recognize when vital signs are critically deranged.
When patient vital signs are in danger zone, the clinical management starts to stabilize the condition by using adapted basic life support techniques. If conditions are a common problem like post-partum bleeding, anaphylaxis reaction, poisoning, healthcare providers may start the initial measures and follow the EECC protocol.

C. The EECC vital signs

There are 8 vital signs in EECC. Traditional
5 vital signs include:

1) heart rate,
2) blood pressure,
3) respiratory rate,
4) oxygen saturation, and
5) temperature.

EECC includes additional 2 vital assessments:
(6) level of consciousness

Level of consciousness can be assessed by GCS or AVPU scale.

(7) assessment for abnormal airway sounds.

Snoring, gurgling, or stridor predict airway obstruction and compromised oxygenation.

The additional one from overall patient condition and intuition of health worker

(8) The overall condition of the patient's health (heath worker, patient, or guardian concern that condition has worsened). Health worker intuition_ when a health worker is concerned that a patient is critically ill, then they ARE critically ill, even if all vital signs are ok

All hospital patients should have their (8) vital signs assessed at initial presentation and at a minimum every 24 hours thereafter. EECC recommends that vital signs be reassessed for changes in condition and setting, for example when:

- When bedside providers, patients, or guardians become concerned the patient's condition has worsened
- During and after surgery or anesthesia
- During and after transport/transfer of a patient at risk of critical illness
- Following treatment or action for re-evaluation

Even before vital assessments, providers must start to determine if the patient is experiencing a life-threatening process. This is done by assessing:

- If the patient is awake (level of consciousness), which can be assessed using AVPU
- If the patient is talking (airway) and their breathing is calm, easy and quiet, (breathing).
- If the patient is unconscious, providers must quickly determine if there is a palpable pulse (circulation)

Airway, breathing and circulation can be remembered by "ABC".

From data of vital signs measured, classify the degree of derangement, identify danger signs and prompt intervention using VSDT (Vital signs Direct therapy) table.

Danger signs of Arway:

- When GCS < 8 or Unresponsive
- Abnormal airway sound

Danger signs of breathing:

- Respiratory rate <8 or >30 bpm or
- Need supplemental oxygen > 10L/min or FiO2= 80-100% or
- Saturation (SpO2) < 90%

Danger signs of Circulation:

- Heart rate <40 or >130 bpm or
- Systolic blood pressure <90 mmHg

Vital Signs Direct Treatment (VSDT)

		Danger	Ab-normal	Normal	Ab-normal	Danger	Treatment if danger signs
A Airway	**GCS**	**3 – 8**	**9 – 14**	**15**			PROTECT AIRWAY Lateral position Chin tilt / jaw thrust Oro-pharyngeal airway suction
	Airway sound			**Normal airway sound**		**Abnormal airway sound**	
B Breath-ing	**RR**/min	**< 8**	**8 – 11**	**12 – 18**	**19 – 30**	**> 30**	HYPOXIA? Sit patient up (if no shock) Increase Oxygen
	FiO2			**Air**	**< 80% or ≤10L/min**	**80-100% or > 10l/min**	
	SpO2 (%)	**< 90%**	**90 - 94**	**95 - 100**			
C Circula -tion	**HR**/min	**< 40**	**40 – 59**	**60 – 100**	**101 – 130**	**> 130**	SHOCK? Tip bed head-down IV RL/NS 500ml in 30min Recheck & repeat as long as sign persists If > 2L given in 2h: call doctor
	SBP (mmHg)	**< 90**	**90 - 99**	**100 - 180**	**> 180**		

Bedside nurse or treatment team should prompt the management without delay or wait for doctor to come.

If a health provider or patient's family remarks that the patient condition is getting worst (= danger sign), whatever vital signs measured, it should prompt to check the patient again or ask doctor to review.

Clinical practice and procedures in VSDT (Should be able to practice by nurse):

- Protect airway _ see basic life support techniques
- Recovery position_ see basic life support techniques
- Chin tilt / jaw thrust_ see basic life support techniques
- Oro-pharyngeal airway suction_ SOP in Emergency & ICU nursing
- Position the patient according to pathology (sit-up, lateral, elevation head of the bed, bed head down.) _ see basic life support techniques.
- Use oxygen correctly_ see guideline on oxygen use
- IV-line placement, and fluid (Ringer lactate) bolus up to 2L in 2h

Continuous Monitoring: Regularly reassess vital signs to ensure the patient's condition is improving

Doctor reviews and take additional measures or transfer the patient

- Procedure for post-partum hemorrhage
- Procedure for coma
- Procedure for poisoning
- Procedure for anaphylaxis

The content of the EECC program includes:

- 40 Clinical Processes: These are specific actions and treatments, such as triage, monitoring, patient positioning, oxygen therapy, and intravenous fluids.
- 67 Hospital Readiness Requirements: These ensure that hospitals are equipped to provide the necessary care.

- COVID-19 Specific Additions: Additional guidelines tailored to the care of critically ill patients with COVID-19.

Implementing EECC can help reduce preventable deaths and improve patient outcomes. Most of the clinical practices skills needed are included in basic life support, however healthcare providers should be able to regularly refresh their skill, and additional skill can be gained by EECC online training or Institutional organized training.

IV- EFERENCES

1. Royal College of Physicians. National Early Warning Score (NEWS) 2: Standardizing the assessment of acute-illness severity in the NHS. Updated report of a working party. London: RCP, 2017.
2. Schell, C.O., Gerdin Wärnberg, M., Hvarfner, A. et al. The global need for essential emergency and critical care. Crit Care 22, 284 (2018). https://doi.org/10.1186/s13054-018-2219-2
3. Schell CO, Khalid K, Wharton- Smith A, et al. Essential Emergency and Critical Care: a consensus among global clinical experts. BMJ Global Health 2021;6:e006585. doi:10.1136/ bmjgh-2021-006585

SHOCK

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I. DEFINITION

Shock is a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells. Circulatory shock leads to cellular and tissue hypoxia resulting in cellular death and dysfunction of vital organs. There is circulatory failure manifested as hypotension (= reduced tissue perfusion); however, it is crucial to recognize that a patient in shock can present hypertensive, normotensive, or hypotensive.

II. EPIDEMIOLOGY

Shock affects about one-third of patients admitted to the intensive care unit (ICU). Distributive shock is the most common type of shock, followed by hypovolemic and cardiogenic shock. Obstructive shock is relatively less common. The most common type of distributive shock is septic shock and has a mortality rate between 40 to 50%.

III. TIOLOGY

Four types of shock are recognized: hypovolemic, distributive, cardiogenic and obstructive.

1. Hypovolemic Shock

Hemorrhagic	Non-hemorrhagic
- Trauma - Gastrointestinal bleeding (eg, varices, peptic ulcer) - Intraoperative and postoperative bleeding, retroperitoneal bleeding (eg, ruptured aortic aneurysm), - Ruptured ectopic pregnancy - Postpartum hemorrhage - Uterine or vaginal hemorrhage (eg, infection, tumors, lacerations)	- Gastrointestinal losses (eg, diarrhea, vomiting, external drainage) - Skin losses (eg, heat stroke, burns, dermatologic conditions) - Renal losses (eg, excessive drug-induced or osmotic diuresis, salt-wasting nephropathies, hypoaldosteronism) - Third space losses into the extravascular space or body cavities (eg, postoperative and trauma, intestinal obstruction, crush injury, pancreatitis, cirrhosis)

2. Distributive Shock

Septic	Non-septic
Gram positive (Pneumococcus, Staphylococcus, Streptococcus, Enterococcus, Listeria) Gram negative (Klebsiella, Pseudomonas, Escherichia, Haemophilus, Legionella,	- Inflammatory shock (systemic inflammatory response syndrome) – Burns, trauma, pancreatitis, post cardiac arrest, viscus perforation, amniotic fluid embolism, fat embolism - Neurogenic shock – Traumatic brain injury, spinal cord injury (quadriparesis with bradycardia or paraplegia with tachycardia), neuraxial anesthesia

Neisseria, Moraxella, Rickettsia, Francisella [tularemia]) Fungal (Candida, Aspergillus) Viral (influenza, cytomegalovirus, Ebola, varicella) Parasitic (Plasmodium, Ascaris, Babesia) Mycobacterium (Mycobacterium tuberculosis, Mycobacterium abscesses)	- Anaphylactic shock – IgE-mediated (eg, foods, medications, insect bites or stings), IgE-independent (eg, iron dextran), nonimmunologic (eg, exercise or heat-induced), idiopathic Other – Liver failure, transfusion reactions, vasoplegia (eg, vasodilatory agents, cardiopulmonary bypass), toxic shock syndrome, toxicologic (eg, heavy metals), beriberi

3. Cardiogenic Shock

Cardiomyopathic	▪ Myocardial infarction ▪ Severe right ventricle infarction ▪ Acute exacerbation of severe heart failure ▪ Stunned myocardium from prolonged ischemia (eg, Cardiac arrest, hypotension) ▪ Advanced septic shock ▪ Myocarditis ▪ Myocardial contusion ▪ Drug-induced (eg, beta blockers)
Arrhythmogenic	▪ Tachyarrhythmia - Atrial tachycardias (fibrillation, flutter, reentrant tachycardia), ventricular tachycardia and fibrillation ▪ Bradyarrhythmia – Complete heart block, Mobitz type II second degree heart block
Mechanical	▪ Severe valvular insufficiency, acute valvular rupture, critical valvular stenosis, acute or severe ventricular septal wall defect, ruptured ventricular wall aneurysm, atrial myxoma

4. Obstructive Shock

Obstructive shock is due to extracardiac cause of cardiac pump failure and often associated with poor right ventricular failure. It is divided into 2 categories:

- Pulmonary vascular
  - Pulmonary embolus
  - Severe pulmonary hypertension
  - Acute obstruction of pulmonic or tricuspid valve
- Mechanical
  - Tension pneumothorax / hemothorax (trauma, iatrogenic)
  - Pericardial tamponade (trauma, viral/bacterial infection, autoimmune…)
  - Constrictive pericarditis

IV. PATHOPHYSIOLOGY

Cellular hypoxia causes cell membrane ion pump dysfunction, intracellular edema, leakage of intracellular contents into the extracellular space, and inadequate regulation of intracellular pH. These processes progress to the systemic level, resulting in acidosis, and

endothelial dysfunction, as well as further stimulation of inflammatory or anti-inflammatory cascades. Compounding this process is further reduction in tissue perfusion from complex humoral and microcirculatory processes that impair regional blood flow.
Serum lactate levels have traditionally been used as surrogates for hypoperfusion and tissue hypoxia. Elevations in serum lactate level are useful risk-stratification tools in undifferentiated shock. Four types of shock are recognized:

- Distributive: is characterized by severe peripheral vasodilatation with decreased systemic vascular resistance and altered oxygen extraction (vasodilatory shock). For example, severe sepsis or anaphylaxis.
- Cardiogenic: is due to intracardiac causes of cardiac pump failure that result in reduced cardiac output (CO) such as due to acute myocardial infarction, end-stage cardiomyopathy, advanced valvular heart disease, myocarditis, or cardiac arrhythmias).
- Hypovolemic: is due to reduced intravascular volume from internal or external fluid loss (ie, reduced preload), which, in turn, reduces CO.
- Obstructive: is due to extracardiac causes of cardiac pump failure and often associated with poor right ventricular output (pulmonary embolism, cardiac tamponade, or tension pneumothorax).

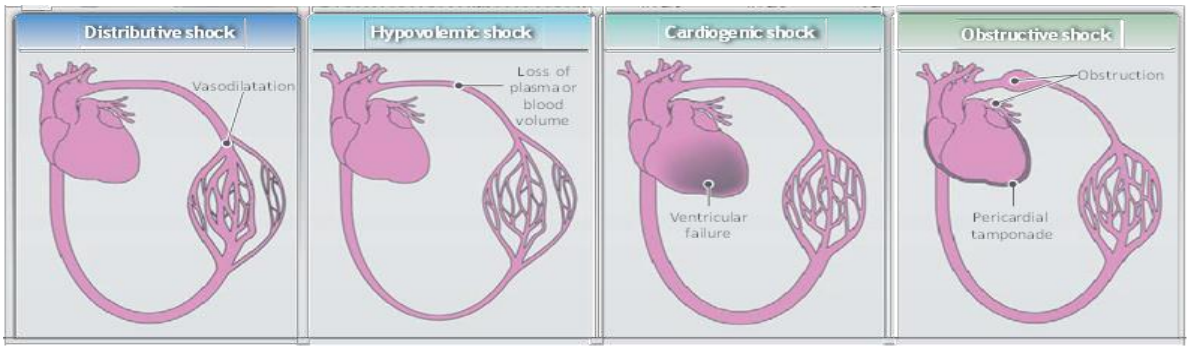


Figure 1: Schematic Representations of the four main types of shock (From NEJM.org)

V. DIAGNOSIS

A diagnosis of shock is based upon a constellation of clinical suspicion, biochemical, and hemodynamic features.

a. Clinical Manifestation

The clinical findings associated with shock vary according to the etiology and stage of presentation (pre-shock, shock, end-organ dysfunction). A diagnosis of shock is based on clinical, hemodynamic, and biochemical signs, which can broadly be summarized into three components:

1. Hypotension:
   - Absolute (eg, systolic blood pressure <90 mmHg; mean arterial pressure <65 mmHg, associated tachycardia (except for patients under beta blockers)
   - Relative (eg, a drop in systolic blood pressure >40 mmHg)
2. Clinical signs of tissue hypoperfusion which are apparent through the three “windows” of the body:
   - Cutaneous (skin that is cold and clammy, with vasoconstriction and cyanosis, findings that are most evident in low-flow states)
   - Renal (urine output of <0.5 ml/kg/h)
   - Neurologic (altered mental state, which typically includes obtundation, disorientation, and confusion).

3. Hyperlactatemia (>1.5 mmol/L)

A focused history should be obtained from the patient (if feasible) and/or patient's relatives (information regarding risk factors, medications, and trend of baseline vital signs including blood pressure, valuable clues regarding the patient's risk for shock and potential etiology). Clinical features and symptoms can vary according to the type and stage of shock. Also, features pertaining to the underlying cause of the shock can be present.

- Patients with hypovolemic shock can have general features as mentioned above as well as evidence of orthostatic hypotension, pallor, flattened jugular venous pulsations, may have sequelae of chronic liver disease (in case of variceal bleeding).
- Patients with septic shock may present with symptoms suggestive of the source of infection (example-skin manifestations of primary infection such as erysipelas, cellulitis, necrotizing soft-tissue infections)
- Patients with anaphylactic shock can have hypotension, flushing, urticaria, tachypnea, hoarseness of voice, oral and facial edema, hives, wheeze, inspiratory stridor, and history of exposure to common allergens such as medications or food items the patient is allergic to or insect stings.
- Tension pneumothorax should be suspected in a patient with undifferentiated shock who has tachypnea, unilateral pleuritic chest pain, absent or diminished breath sounds, tracheal deviation to the normal side, distended neck veins and also has pertinent risk factors for tension pneumothorax such as recent trauma, mechanical ventilation, underlying cystic lung disease.
- In a patient with undifferentiated shock, diagnostic clues to pericardial tamponade as the etiology include dyspnea, the Beck triad (elevated jugular venous pressure, muffled heart sounds, hypotension), pulsus paradoxus, and known risk factors such as trauma, the recent history of pericardial effusion, and thoracic procedures.
- Cardiogenic shock should be considered as the etiology if the patient with undifferentiated shock had chest pain suggestive of cardiac origin, narrow pulse pressure, elevated jugular venous pulsations or lung crackles, and significant arrhythmias on EKG.

Point-of-Care Ultrasound (POCUS) is effective at identifying the cause of shock and identifying appropriate next steps.

b. Investigation

Laboratory evaluation:

- Complete blood count and differential
- A complete metabolic panel, including renal and liver function tests
- Serum lactate
- Blood gas analysis (arterial or venous)
- Coagulation studies and D-dimer level
- Cardiac enzymes (Troponin-I or -T) and natriuretic peptides (NT-proBNP) [cardiogenic shock]. C-Reactive protein (CRP), procalcitonin, urine analysis, blood culture and/or urine culture (before administration of antibiotics) and other microbiology exploration [Septic shock]

Imaging:

- EKG
- Chest radiography
- Point-of care (POC) ultrasound (if available with trained personnel)
- Directed at etiology of shock

VI. DIFFERENTIAL DIAGNOSIS

Each class of shock (distributive, cardiogenic, hypovolemic, obstructive) is distinguished from the other by a collection of clinical features supported by etiology found, laboratory, imaging, and hemodynamic findings.

1. Hypovolemic shock
- Reduced preload in context of a suspected or known cause.
- Hypovolemia displaying signs of reduced skin turgor, dry mucous membranes, a collapsible IVC on imaging.

2. Distributive shock
- Hypotension without clinical and hemodynamic signs of reduced preload (eg, normal skin turgor, normal inferior vena cava on imaging) or fluid overload.
- A preserved or hyperdynamic left ventricle is typically observed on echocardiography.

a. Septic Shock

i. Definition

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

Septic Shock is defined as sepsis that has circulatory, cellular, and metabolic abnormalities. Clinically, this includes patients who fulfill the criteria for sepsis who, despite adequate fluid resuscitation, require vasopressors to maintain a mean arterial pressure (MAP) ≥ 65mmHg and have a lactate > 2mmol/L (>18mg/dL).

ii. Evaluation

Patients who have sepsis have organ dysfunction that can be identified by using the Sequential Organ Failure Assessment (SOFA):

Variable	SOFA Score				
	0	1	2	3	4
Respiratory	PaO_2/FiO_2>400	PaO_2/FiO_2= 301 to 400	$PaO_2/FiO_2 \leq$ 300	PaO_2/FiO_2= 101 to 200 with ventilatory support	$PaO_2/FiO_2 \leq$ 100 with ventilatory support
Cardiovascular (dose: mcg/kg/min)	MAP≥70mmHg	MAP < 70mmHg	Dopamine ≤ 5 or Any, Dobutamine	Dopamine > 5, Epinephrine ≤ 0.1, norepinephrine ≤ 0.1	Dopamine > 15, Epinephrine > 0.1, norepinephrine > 0.1
Liver (Bilirubin, mg/dl)	<1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	> 12
Renal (Creatinine, mg/dl)	<1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9	>5.0
Coagulation (Platelet x 10^3/mm3)	≥150	<150	<100	<50	<20
Neurologic (GCS)	15	13 - 14	10 - 12	6 - 9	<6

Maximum SOFA Score	Mortality
0 to 6	< 2%
7 to 9	0 – 10%
10 to 12	10 – 30%
13 to 14	40 – 60%
15	75 – 90%
16 to 24	> 90%

b. Anaphylactic shock

- Clinical = Diagnostic
- Most common (90%) Cutaneous: Urticaria, erythema, pruritus, angioedema, flushing
- Danger sign:
  - Respiratory: stridor, wheezing, dyspnea, increased work of breathing, persistent cough, cyanosis
  - Cardiovascular: Hypotension, dysrhythmias, collapse, chest pain
  - Gastrointestinal: Nausea, Vomiting

c. Neurogenic Shock

- Clinical: Hypotension without tachycardia, bradycardia, warm and dry skin

3. Cardiogenic shock

- Hypotension in association with pulmonary edema,
- Large dilated ventricles and poor left ventricle function, or valvular or septal abnormalities on echocardiography.

4. Obstructive shock

- Hypotension associated with distended neck veins but usually without clinical signs of fluids overload or reduced preload.
- Bedside ultrasonography or echocardiography is useful in this setting to detect pericardial tamponade and pneumothorax.
- Clinical:
  - Pulsus paradoxus (a drop on systolic BP greater than 10 mmHg on inspiration)
  - Muffled heart tones (cardiac tamponade)
  - Elevated JVD (depending on volume status)
  - Unilateral absence of breath sounds (tension pneumothorax)
  - Tracheal deviation (tension pneumothorax)

VII. ANAGEMENT

Shock is a time-sensitive condition. All patients with shock must be early recognized and managed well without delay. The management of shock comprises of the following principles that include:

- Recognition of the pattern of shock
- Selecting appropriate treatment (resuscitation)
- Specific therapy for the underlying problem
- Monitoring clinical response.

1. Objectives

The objectives of intervention:

- Restore adequate tissue perfusion
- Prevent worsening or to help recover organ dysfunction (include coagulation disorders) and organ failure.
- Once identified, the cause must be corrected rapidly.

2. Critical Sign

- Anuria and acute renal failure
- Acidemia further depresses CO (pH <7.2)
- Hypotension becomes severe and irresponsive to therapy
- Hyperlactatemia often worsens
- Restlessness evolves into obtundation and coma.

3. Mortality risk factor

- Patient-related factors (age, comorbidities, immune status…)
- Shock-related factors (types, duration and severity, underlying causes, MOD…)
- Response to treatment (delayed appropriate treatment or failure to respond to initial treatment)

4. Outpatient Management

All patients with shock cannot be managed in the outpatient setting.

5. First-line treatment

Initial management (= ABC)

- **A**irway:
  - Assess the signs of airway obstruction: “see-saw” respiration, central cyanosis, no breath sounds.
  - Opening the airway using: Head-tilt chin-lift, Jaw-thrust maneuver, insertion of an oropharyngeal or nasopharyngeal airway. Tracheal intubation may be required if those maneuver fails.
- **B**reathing:
  - All patients should receive supplemental oxygen.
  - For patients with respiratory distress or who are hemodynamically unstable, noninvasive or invasive mechanical ventilation are typically needed.
  - Goal: Arterial oxygen saturation should be restored to >94% and ventilation controlled to maintain a $PaCO_2$ of 35 to 40 mm Hg.
- **C**irculation:
  - IV access through large-bore peripheral venous lines.
  - Central venous access is the preferred route for the long-term administration of vasopressor therapy and in assessing volume status (preload) and monitoring $ScvO_2$.
  - Passive leg raising above the level of the heart with the patient supine (useful in hypovolemic shock but not in cardiogenic shock).
  - Internal bleeding: surgical consultation.
  - External hemorrhage: direct compression, wound packing and extremity tourniquets.
  - Isotonic Crystalloid solutions:
    - 0.9% NaCl, Ringer lactate (use RL for all cases except brain injury that use 0.9% NaCl)
    - 20 to 40 mL/kg given rapidly (over 10 to 20 minutes)

- Hemorrhagic shock: new concept in early intervention is to stop the bleeding source and early transfusion to minimize crystalloid or colloids use.

6. Treatment Adjustment

A. Hypovolemic Shock

Supportive Treatment	Etiologic Treatment

▪ O2: 6 - 10L/min (High flow oxygen mask) - Intubation-Ventilation?
▪ 2 larges caliber IV access (14 - 16 G)
▪ Passive leg raising above the level of the heart with the patient supine.
▪ Anti-shock pant
▪ Fluid therapy
  ▪ Crystalloids (RL, SSI)
  ▪ Colloids: Gelatins (Gelofusine), Dextrans, Albumin
▪ If no response to fluids (SBP < 80 mmHg and MAP < 60 mmHg): Norepinephrine starts 5 mcg/min IV
▪ Blood products:
  ▪ Packed red blood cell (PRBC)
  ▪ Objectives, Hemoglobin:
  ▪ > 7g/dl most case
  ▪ 10g/dl: heart failure or coronary artery disease; traumatic brain injury
  ▪ Platelet transfusion: 1 unit of apheresis platelets, or 6 units of random donor platelets if platelet <50,000/microL
  ▪ Fresh frozen plasma (FFP) if PT < 40% or INR > 2
	Contemporary of the symptomatic treatment:
	▪ Surgical procedure: goal to achieve hemostasis in aortic aneurysm rupture; gastrointestinal bleeding; open penetrating wound
	▪ Medical procedure: Sclerosis of varices Embolization endovascular

Notes: ▪ The presence or likelihood of severe, ongoing hemorrhage, Massive Transfusion Protocol (MTP) in a 1:1:1 ratio of plasma to platelets to pRBCs is generally used.	

B. Distributive Shock

i. Septic shock

Supportive Treatment	Etiologic Treatment

▪ Oxygen therapy (6-10L/min) - Intubation - Ventilation
▪ 2 larges peripheral IV, Central venous catheter (CVC) if needed
▪ Measure serum lactate
▪ Fluid therapy:
	▪ BLOOD CULTURE prior to antibiotic use
	▪ Empiric antibiotic therapy:
	  ▪ IV - dual therapy
	  ▪ Choice according to clinical context, suspected infectious source

▪ Crystalloids: 30 ml/kg (usually 500 to 1000ml) ▪ Red blood cells if Hb < 8g/dl ▪ Norepinephrine: Goal MAP > 65 mmHg, dose 5-30 mcg/min IV ▪ If no response: Acute adrenal insufficiency ▪ Hydrocortisone: 200 to 300mg IV or 3 to 4 injections (during 5 days then titrated)	▪ Nosocomial pneumonia: ▪ Carbapenem + Vancomycin ▪ Urinary or biliary infections: ▪ C3G or Quinolones + Aminosides ▪ Soft tissue infections ▪ C3G + Flagyl + Aminosides ▪ Fulminant purpuras: ▪ Carbapenem +/- Vancomycin ▪ Source control: close-space infection drained or debrided (eg, empyema, abscess)

ii. Neurogenic shock
- Maintain ABC
- Maintain Spinal Immobilization
- Hypotension: Norepinephrine, Dopamine (Goal MAP >65mmHg)
- Bradycardia: Atropine 0.5mg IV (Every 5mn, Total dose: 3mg)
- Methylprednisolone IV (1-2mg/kg IV within 8 hours)

iii. aphylactic shock (See Algorithm 2)

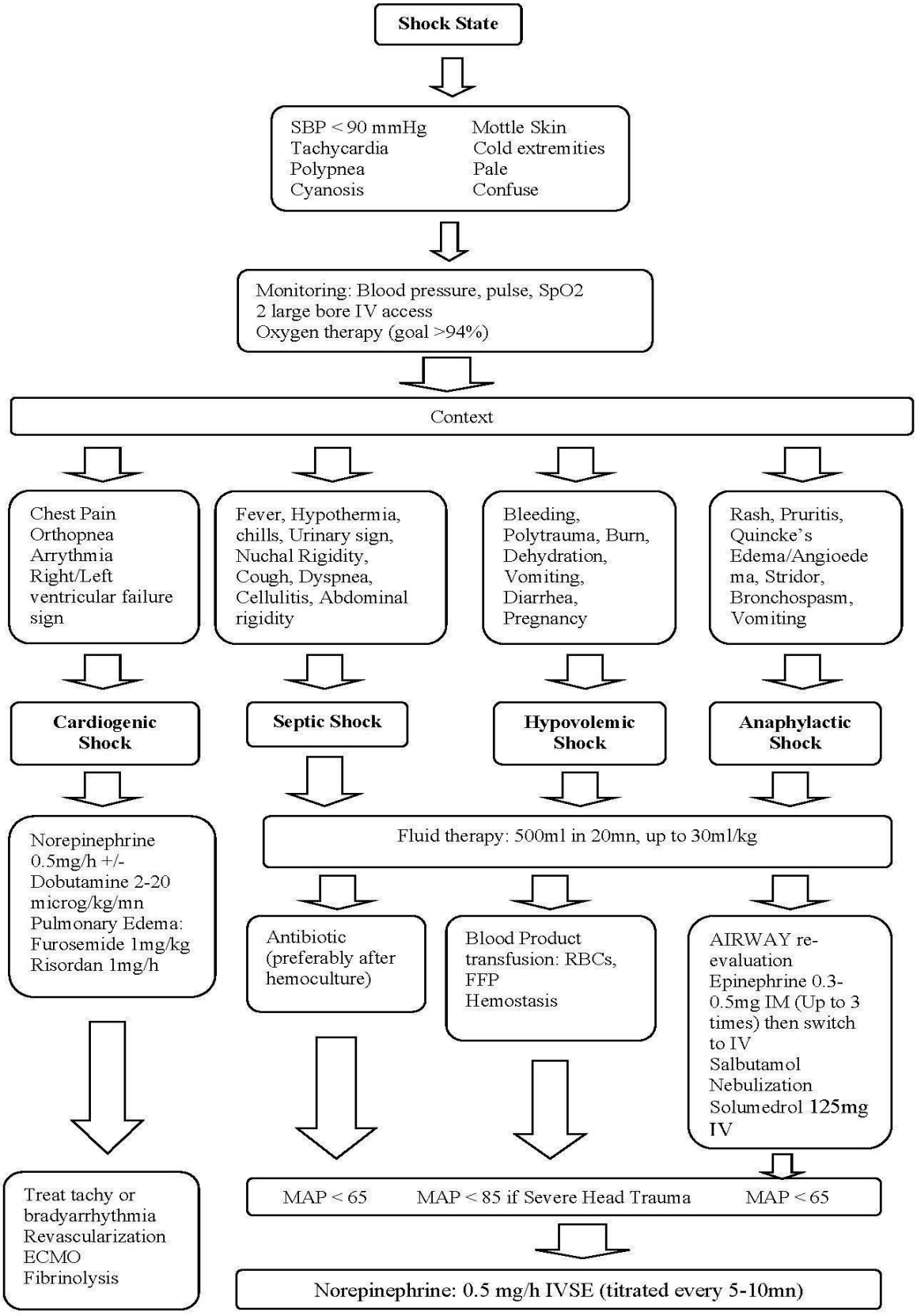
C. Cardiogenic Shock

Supportive Treatment	Etiologic Treatment
▪ Oxygen - CPAP or BIPAP – Intubation – Ventilation ▪ Small Fluid Challenge: 250-500ml ▪ Vasopressor (Recommendation in order, combination possible): ▪ Norepinephrine: 5-30 mcg/min IV ▪ Dobutamine: 2-20 mcg/kg/min IV ▪ Dopamine: 5-20 mcg/kg/min IV ▪ Epinephrine: 1-40 mcg/min IV ▪ Diuretics (in case of fluid overload): Furosemide ▪ Treat electrolyte imbalance (eg, hyper or hypo-kalemia, hyperglycemia…) ▪ Treat unstable arrhythmia	▪ Cardiomyopathic: ▪ Myocardial infarction: Immediate revascularization Percutaneous coronary intervention, IABP, fibrinolysis ▪ Severe right ventricle infarction ▪ Acute exacerbation of severe heart failure: Diuretic, Nitroglycerine ▪ Advanced septic shock ▪ Myocarditis ▪ Arrhythmic: Tachyarrhythmia or Bradyarrhythmia ▪ Mechanical: Surgical repairment ▪ Severe valvular insufficiency ▪ Acute valvular rupture ▪ Critical valvular stenosis

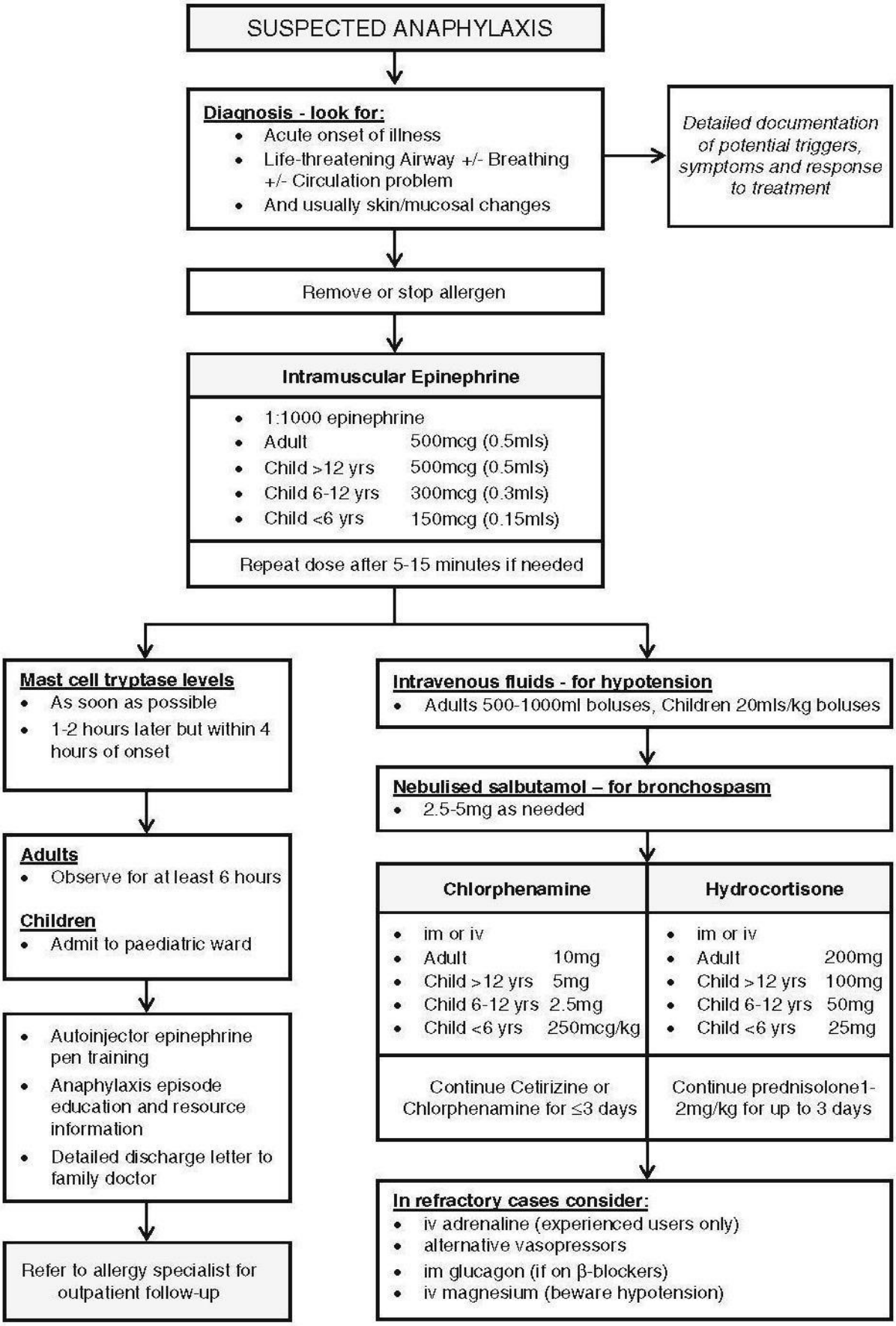
D. Obstructive Shock

- The goal is to remove the obstruction as quickly as possible.
- A cardiac tamponade requires a pericardiocentesis in which a provider inserts a needle or catheter into the pericardium to remove the accumulated fluid.
- In a tension pneumothorax, a provider inserts a large bore needle (i.e., 14-gauge) or chest tube into the pulmonary space causing immediate evacuation of air, therefore re-expanding the lung.
- A pulmonary embolism large enough to cause shock is treated with a thrombolytic or removed during a surgical embolectomy or fragmented and aspirated through percutaneous mechanical thrombectomy.

7. Algorithm



Algorithm 1: Management of shock



Algorithm 2: Management of anaphylaxis

VIII. SPECIAL CASES

Patients often present with combined forms of shock. Examples include:

- Patients with shock from sepsis or pancreatitis have distributive shock (due to the effects of inflammatory and anti-inflammatory cascades on vascular permeability and peripheral vasodilation); however, they also often have a hypovolemic component (due to decreased oral intake, insensible losses, vomiting, diarrhea) and a cardiogenic component (due to inflammation-related myocardial depression).
- Patients with underlying cardiomyopathy may present with hypovolemic shock (from over-diuresis) and cardiogenic shock (from inadequate compensatory tachycardia and/or stroke volume).
- Patients with severe traumatic injury may have hemorrhagic shock from blood loss as well as distributive shock from SIRS or, less commonly, fat embolism.
- Patients with trauma to the spinal cord can have distributive shock from injury-related autonomic dysfunction and cardiogenic shock from myocardial depression.
- Patients with a ruptured left ventricular free wall aneurysm can have cardiogenic shock from primary pump failure, obstructive shock from cardiac tamponade when blood loss is contained by the pericardial sac, and hemorrhagic shock when blood loss is not contained by the pericardial sac.
- Patients with septic shock may transition from a distributive (low systemic vascular resistance) shock state to multifactorial shock state after massive volume resuscitation that results in abdominal compartment syndrome and/or acute right heart syndrome.

IX. EVOLUTION AND PROGNOSIS

Effects of shock are reversible in the early stages and a delay in diagnosis and/or timely initiation of treatment can lead to irreversible changes including multiorgan failure (MOF) and death. Even with treatment, mortality from cardiogenic shock after MI (60 to 65%) and septic shock (30 to 40%) is high. Prognosis depends on the cause, preexisting or complicating illness, time between onset and diagnosis, and promptness and adequacy of therapy.

X. COMPLICATIONS

As global tissue hypoxia progresses, shock ensues, followed by the multiorgan dysfunction syndrome (MODS), which is manifested by:

- Acute renal failure (ARF)
- Respiratory failure: Acute respiratory distress syndrome (ARDS)
- Myocardial depression
- Liver failure
- Disseminated intravascular coagulation (DIC)
- Anoxic encephalopathy.

Once MODS progresses, in some cases, death is inevitable despite proper eradication of the inciting cause.

XI. REVENTION AND RECOMMENDATION

For medical professionals:

- Recognize the patients from early stage of shock (pre-shock, shock)
- Rapidly identify the etiology
- Early apply the appropriate interventions and therapy to correct the cause of shock and prevent MOF and death.

For general population:

- Alert any serious case without delay (SAMU, hospital, etc.)!!! (Time is life)

- Get regular vaccinations against viral infections that may cause sepsis.
- Avoid any contact with the responsible allergen (anaphylactic shock)
- Practice good hygiene.
- Care for and clean any open or gaping wounds.
- Follow medical advice on managing bacterial infections.
- Treat fungal and parasitic infections as soon as symptoms appear.
- Control diabetes, if relevant.
- Avoid smoking.

XII. EFERENCES

1. Vincent, J. L., & De Backer, D. (2013). Circulatory shock. New England Journal of Medicine, 369(18), 1726-1734.
2. TAN, S. Etats de choc. Clinical practice guideline for MEDECINE. April 2013. Ministry of Health. p35-47
3. Peter, J. V., & Pulicken, M. (2016). Hypotension and Shock. Clinical Pathways in Emergency Medicine: Volume I, 179-190.
4. Haseer Koya H, Paul M. Shock. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK531492/
5. Nick, B. A, Gaillard J. P (2020). Approach to Nontraumatic Shock. 9th Edition Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 57-63.
6. Somand, D.M, Ward K. R (2020). Approach to Traumatic Shock. 9th Edition Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 63-68.
7. Bhatt S.P, (2018). Therapeutic Approach to The Hypotensive Patient. 8th Edition Tintinalli's Emergency Medicine Manual. 60-63
8. AlBadwawi, M. (2018). Shock. Cevik AA, Quek LS, Noureldin A, Cakal ED (eds) iEmergency Medicine for Medical Students and Interns – 2018. Retrieved Dec 04, 2023. From https://iem-student.org/shock/
9. Stolz, L. A, Shah, A., Rapid Ultrasound for Shock and Hypotension (RUSH). https://www.acep.org/sonoguide/advanced/rush - 2021. Retrieved Dec 08, 2023
10. Campbell, R. L., & Kelso, J. M. (2018). Anaphylaxis: emergency treatment. UpToDate, Waltham, MA. (Accessed Jun 24, 2023)
11. Perrin, K. O., & MacLeod, C. E. Understanding the Essentials of Critical Care Nursing. 3rd ed. 2018. 330 Hudson Street, NY, NY 10013. 188-207
12. Gaieski, D. F., & Mikkelsen, M. E. (2022). UPTODATE. Definition, classification, etiology, and pathophysiology of shock in adults. UpToDate, Waltham, MA. (Accessed Jun 24, 2023)

HEMORRHAGIC SHOCK

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I. DEFINITION

Hemorrhagic shock refers to a state of hypoperfusion due to significant rapid blood loss. Significant and rapid blood loss results in decreased circulating blood volume and therefore inadequate tissue perfusion. This results in severe, life-threatening systemic hypoxia and cellular dysfunction. Without support, hemorrhage may result in hemodynamic instability, end-organ hypoperfusion, and eventually death.

Shock is a physiologic continuum, there are 3 stages of shock:

- ***Compensated shock*** (Pre-shock): Patient's physiologic reserve prevents significant alteration in vital signs. Potentially, with timely and appropriate management, deterioration can be prevented, and signs of impending deterioration can be reversed (eg, normalization of heart rate and serum lactate levels).
- ***Decompensated shock*** (Shock): Loss of circulating volume overcomes patient's physiologic reserve, resulting in significant alteration in vital signs. The signs and symptoms of organ dysfunction appear (tachycardia, dyspnea, restlessness, diaphoresis, metabolic acidosis, hypotension, oliguria, and cool, clammy skin)
- ***End-organ dysfunction*** – Progressive shock leads to irreversible organ damage, multiorgan failure (MOF), and death. During this stage, anuria and acute kidney failure develop, acidemia further depresses CO, hypotension becomes severe and recalcitrant to therapy, hyperlactatemia often worsens, and restlessness evolves into obtundation and coma. Death is common in this phase of shock.

II. EPIDEMIOLOGY

Hemorrhagic shock in Southeast Asia is a critical public health issue, often resulting from trauma, gastrointestinal bleeding, or ruptured aneurysms.

Incidence and Mortality

High Incidence: Southeast Asia has a high incidence of hemorrhagic shock due to road traffic accidents, natural disasters, and violence.

Mortality Rates: Mortality rates vary by country, but hemorrhagic shock remains a leading cause of death in trauma cases.

III. ETIOLOGY

- Trauma- penetrating and blunt:
    - Abdominal:
        - Splenic injury
        - Liver injury
    - Chest:
        - Hemothorax
        - Aorta or great vessel injury

- Pelvis:
  - Pelvic fracture with vascular injury
- Vascular malformations:
  - May lead to thoracic, intraperitoneal, or retroperitoneal bleeding
  - Aneurysms:
    - Abdominal aortic aneurysm most common
    - Mycotic aneurysm secondary to endocarditis
  - Aortogastric fistula
  - Arteriovenous malformations
- Abortion: Complete, partial, or inevitable
- Ectopic pregnancy
- Epistaxis
- Fractures (especially pelvis and long bones)
- GI bleeding
- Hemoptysis
- Malignancies
- Placenta previa or abruption
- Postpartum hemorrhage
- Retroperitoneal bleeds
- Splenic rupture
- Vascular injuries

IV. PHYSIOPATHOLOGY

In hemorrhagic shock, blood loss exceeds the body's ability to compensate and provide adequate tissue perfusion and oxygenation.

Cellular hypoxia occurs as a result of reduced tissue perfusion/oxygen delivery and/or increased oxygen consumption or from inadequate oxygen utilization. Cellular hypoxia, in turn, causes cell membrane ion pump dysfunction, intracellular edema, leakage of intracellular contents into the extracellular space, and inadequate regulation of intracellular pH. These biochemical processes, when unchecked, progress to the systemic level, resulting in acidosis and endothelial dysfunction, as well as further stimulation of inflammatory and anti-inflammatory cascades.

Compounding this process is a further reduction in tissue perfusion from complex humoral and microcirculatory processes that impair regional blood flow.

Serum lactate levels, when elevated, have traditionally been used as surrogates for hypoperfusion and tissue hypoxia (note that epinephrine-mediated aerobic glycolysis in skeletal muscle contributes to hyperlactatemia as well).

A posttraumatic coagulopathy (trauma-induced coagulopathy) may be resulted from dilutional loss of coagulation factors during hemorrhage and fluid resuscitation, increased chemical mediators like activated protein C, disordered fibrinolysis, and posttraumatic platelet and endothelial dysfunction.

Note: Total blood volume (TBV) is about 7% of ideal body weight = 70ml/kg IBW.

Male (heigh 158.5-168.5cm) whose IBW ~ 60kg, will have TBV= 60 x 70= 4200ml

V. DIAGNOSIS

Signs and Symptoms

- Class I hemorrhage: Loss of up to 15% of blood volume (up to 630 ml in 60-kg adult).

- HR <100
- SBP normal
- Respiratory rate (RR) 14-20
- Increased or normal pulse pressure
- Slight anxiety

- Class II hemorrhage: Loss of 15-30% of blood volume (630-1260 ml):
  - Tachycardia: HR >100
  - SBP normal, or minimally decreased
  - Tachypnea: RR 20-30
  - Narrowed pulse pressure
  - Mild anxiety
  - Small decrease in urine output
- Class III hemorrhage: Loss of 30-40% of blood volume (1260-1680 ml):
  - Marked tachycardia: HR >120
  - Hypotension: SBP decreased
  - Marked tachypnea: RR 30-40
  - Marked narrowing of pulse pressure
  - Significant change in mental status: Confusion
  - Delayed capillary refill
  - Marked decrease in urine output
- Class IV hemorrhage: Loss of >40% of blood volume (>1680 ml):
  - HR >140
  - Marked hypotension: SBP decreased
  - RR >35
  - Very narrow pulse pressure
  - Depressed mental status: Confusion, lethargy, loss of consciousness
  - Negligible urine output
  - Cold and pale skin

  Note: Female patient with heigh of 156.4-166.4cm, has IBW~55kg their total blood volume is 3850ml. Hemorrhage class I, II, III, IV correspond to the volume loss of < 577ml, 577-1155ml, 1155-1540ml, > 1540ml)

History
Thorough health and past medical history:

- Underlying disease, risk factors, age
- Medications
- Trauma

Physical Exam
(complete physical exam usually perform after stabilization of A.B.C.)

- Complete physical exam to determine shock class and assess for hemorrhage source
- Vital signs including HR, RR, BP
- Temperature
- Mental status (anxiety, confusion, lethargy, obtundation, coma)
- Pulse character, capillary refill, and skin perfusion
- Pulse pressure

- Abdominal exam
- Pelvic/rectal exam for bleeding as indicated

Essential Workup

- Thorough history and physical exam
- IV access for resuscitation
- Blood type and crossmatch

Diagnostic Tests and Interpretation

- Ultrasound FAST.
- CBC
- Blood type and crossmatch
- Coagulation studies:
    - PT, PTT
    - International normalized ratio (INR)
- Other measures of tissue hypoperfusion:
    - Base deficit/excess:
    - Can assist in determining class of hemorrhage
    - Arterial blood gas
    - Serum lactate level
    - Serum electrolytes
- Pregnancy test/β-hCG

Imaging

- CXR:
    - Hemothorax:
        - Blunt chest injuries
        - Thoracic arteriovenous malformation
    - Pelvic x-ray for possible occult fracture
    - Focused abdominal sonography for trauma (FAST exam):
        - Abdominal trauma
        - Possible abdominal aortic aneurysm
        - Nontraumatic intraperitoneal hemorrhage
        - Fluid in Morrison pouch implies significant hemorrhage or ascites
        - Negative findings do not rule out intraperitoneal hemorrhage
    - Endovaginal Ultrasound:
        - Positive pregnancy test
        - Fluid in the cul-de-sac
        - Ectopic pregnancy
    - Abdominal CT scan (once patient stable):
        - Detects both intraperitoneal and retroperitoneal hemorrhage
        - Abdominal aortic aneurysm

Diagnostic Procedures/Other

- Insert Foley catheter:
    - Monitor urine output
- Nasogastric tube:
    - For undifferentiated hypovolemic shock to rule out GI hemorrhage
- Diagnostic peritoneal lavage:

- For unstable trauma patients when US fails to show intraperitoneal hemorrhage
- Endoscopy:
  - In the setting of upper or lower GI bleeding
- Angiography:
  - Pelvic fracture
  - Retroperitoneal hemorrhage
  - Lower GI bleeding
  - Embolization therapy for bleeding from arterial sources can be performed

VI. DIFFERENTIAL DIAGNOSIS

- Cardiac tamponade
- Tension pneumothorax
- Cardiogenic shock
- Sepsis
- Adrenal insufficiency
- Neurogenic shock

VII. MANAGEMENT

a. Objective

Treatment should be initiated as soon as shock state is recognized while simultaneously identifying the underlying bleeding source.
The goal is to restore tissue and organ perfusion and to control the source of hemorrhage to normalize hemodynamic, coagulation, and perfusion parameters.

b. Critical signs

Early recognition and initiate treatment of shock is the key to prevent mortality.
Reliance solely on SBP as indicator of shock state can result in delayed recognition
Massive blood loss may only result in minimal decrease in Hb or Hct initially
A high index of suspicion is necessary for prompt, accurate diagnosis. Probable mechanisms of hemorrhagic shock must be thoroughly and rapidly examined and treated.

- A narrowed pulse pressure is typically present, and often missed owing to a normal systolic value.
- Anxiety or violent behavior may be a sign of shock and can easily be confused for intoxication or isolated brain injury.
- Decreased mental status should be considered an ominous sign of impending decompensation.
- Hypothermia and / or acidosis a key component of the lethal triad (hypothermia, coagulopathy, acidosis), is an independent predictor of mortality in hemorrhaging patients.
- Acute bleeding in previously normal individual, a hemoglobin < 11 g/dL is associated with a mortality rate of nearly 40%
- Patients with a base deficit (BD) greater than 6 are at higher risk of mortality and the need for massive transfusion.

- an international normalized ratio (INR) > 1.5 reliably predicts the need for massive transfusion

c. Mortality risk factors
- Very young and very old people
- Underlying illness or injury
- cardiac arrest (ROSC)
- Craniotomy
- thoracotomy

d. Outpatient management

Pre-Hospital

- Minimize further blood loss and provide limited fluid resuscitation and other life-saving measures while rapidly transporting the patient to a facility for definitive care.
- Immediate interventions during rapid transport may include:
  - Bleeding site identification and control (strategies may include direct pressure, tourniquets, hemostatic dressing, and tranexamic acid if possible; use of a pelvic binder for suspected pelvic fracture)
  - Restrictive fluid resuscitation with crystalloid solutions to a target mean arterial pressure of 50-60 mm Hg in patients without clinical evidence of a traumatic brain injury (TBI); in patients with severe TBI (Glasgow Coma Scale ≤ 8), maintain a mean arterial pressure of ≥ 80 mm Hg.
  - Hypothermia prevention (such as the removal of wet clothing, increasing the ambient air temperature, and the warming of IV fluids).
  - Endotracheal intubation or other airway management if indicated in trauma patients.

e. First line treatment
- Every patient who is at risk for hemorrhage should be evaluated by quickly proceeding through the primary survey (A. B. C.), immediate life threats are recognized and treated before a head-to-toe exam and precise diagnosis is made.
- Focused Assessment with Sonography in Trauma [FAST] for patients with thoracoabdominal injuries (if feasible) should be the first investigation exam.
- Coagulopathy resulting from hemorrhage or resuscitation efforts must be minimized to reduce additional bleeding risk.

Initial Stabilization/Therapy

- Airway and breathing:
  - Intubation as indicated by patient's respiratory and mental status
  - 100% oxygen via face mask should be administered
- Circulation:
  - 2 large-bore peripheral IV lines (16G or larger)
  - Central venous line or venous cutdown (saphenous) may be necessary
  - Intra-osseous route may be considered
  - Fluid resuscitation with warmed, isotonic crystalloid fluid - total volume based on patient response to initial fluid bolus (bolus: 1-2L for adult, 20ml/kg

pediatric). Target: MAP of 50-60 mm Hg in absence of TBI, and 80-90 mm Hg in cases of severe TBI.
    - Approach is to balance goal of perfusion and risk of rebleeding and may vary with patient:
        - In blunt trauma, BP maintenance may take precedence to reduce risk of traumatic brain injury
        - In penetrating trauma with hemorrhage, delayed aggressive fluid resuscitation until definitive control may reduce bleeding risk

- Early transfusion with whole blood or balanced blood products for class Ill or IV shock:
    - Type-specific and cross-matched blood preferred when time permits, often 1 hr
    - Type-specific blood is usually available within 10-15 min
    - Type O blood can be used in immediate, life-threatening situations (type O Rh-negative blood only for women of child-bearing age)
    - Massive transfusion protocols for patients requiring >4u pRBC in 1 hr, or > 10 U pRBC / 24 hr

Ed Treatment/Procedures

- Place patient on continuous monitor
- NPO status, strict bed rest
- Control hemorrhage (direct pressure, pelvic fixation/stabilization, etc.)
- Central venous access may be indicated for CVP monitoring, but placement of such lines should not interfere with resuscitation
- Continually reassess patient for clinical response/deterioration:
    - Vital signs, mental status, and urine output
    - Follow serial blood gas, lactate level, and hemoglobin/hematocrit measurements
    - Maintain urine output at 50 ml/h
- Response to initial fluid resuscitation is the key to determining subsequent therapy:
    - Rapid response to fluid indicates minimal (<20%) blood loss
    - Transient response indicates ongoing hemorrhage or inadequate resuscitation; continue fluid and blood administration and obtain necessary studies and consultations
    - Minimal or no response to volume resuscitation indicates ongoing severe blood loss; immediate angiography or surgical intervention is warranted
- Use fluids warmed (~39°C) by microwave ovens, fluid warmers
- Transfuse whole blood, RBCs, platelets, and other blood products as indicated
- Consider autotransfusion devices with tube thoracostomy treatment of large hemothoraces.
- Monitor closely for coagulopathy particularly with massive transfusion
- Specialty consultation and additional procedures (surgery) as indicated by cause and source of hemorrhagic shock

f. Treatment adjustment

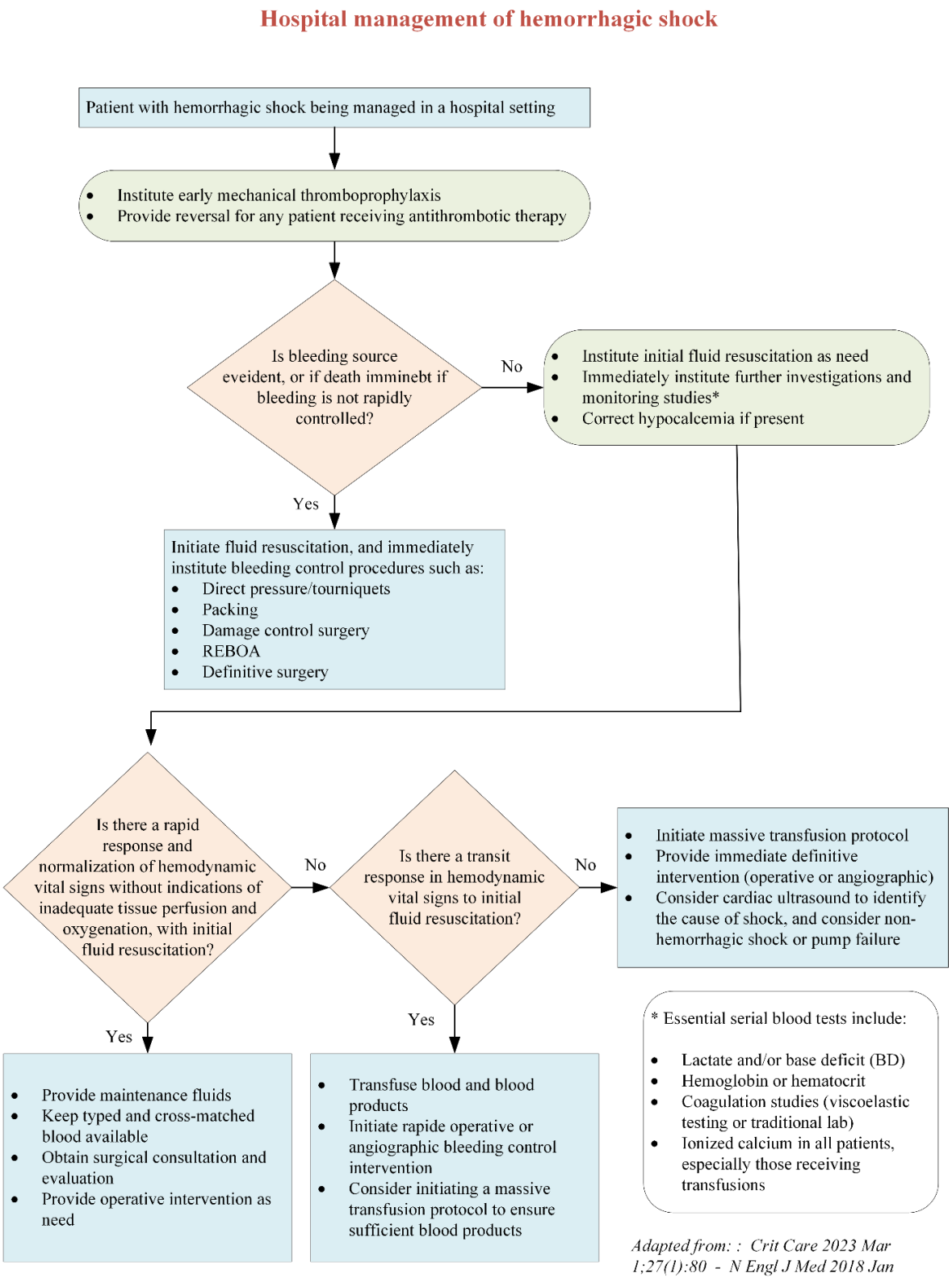
- Antifibrinolytic agents: Tranexamic acid should be given as soon as possible (within 3h of injury) to hemorrhaged patients. Dose: 1g bolus over 10min followed by an infusion of 1g over 8h. Do not use through the transfusion line.
- Initiate damage control surgery in patients with
  - the lethal triad of hypothermia, acidosis, and coagulopathy.
  - combined abdominal vascular and pancreatic injuries,
  - severe injuries and signs of ongoing bleeding or
  - coagulopathy, and in those in whom definitive repair is not immediately feasible.

Provide definitive surgical management in all other patients with traumatic hemorrhage.

- Vasopressors have a limited role and may be used for selected patients in hemorrhagic shock.
- The Assessment of Blood Consumption (ABC) score includes four variables:
  - penetrating mechanism,
  - SBP ≤90 mm Hg in emergency department
  - emergency department heart rate ≥120 beats/minute, and
  - positive fluid on abdominal ultrasonography (FAST)

Give 1 point to each positive item. Sum the points to get ABC score.
Score ≥ 2, patient is likely to require massive transfusion (≥ 10 units pRBCs) [sensitivity: 75-90%, specificity: 67-88%]

g. Algorithm



REBOA: resuscitative endovascular ballon occlusion of the aorta

Adapted from: : Crit Care 2023 Mar 1;27(1):80 - N Engl J Med 2018 Jan 25;378(4):370?379 - Henry S. ATLS Student Course Manual. 10th ed. Chicago, IL: American College of Surgeons; 2024

VIII. SPECIAL CASES

1. Pediatric Considerations

- Children often have greater physiologic reserve than adults and can preserve normal vital signs longer
- Systemic responses to blood loss in the pediatric patient include:
  - Volume loss <25%: Weak, thready pulse and tachycardia; lethargy, irritability, and confusion; cool, clammy skin; decreased urine output/increased urine specific gravity
  - Volume loss 25--40%: Tachycardia; marked change in consciousness; dulled response to pain; cyanotic, cold extremities with decreased capillary refill; minimal urine output
  - Volume loss >40%: Hypotension, tachycardia, or bradycardia; comatose; pale, cold skin; no urine output

2. Geriatric Considerations

- Underlying disease, overall deconditioning, and medications may alter responses to hemorrhage and blood loss.

3. Postpartum hemorrhage

- In patients with major hemorrhage (blood loss > 1,000 mL and continued bleeding and/or signs of clinical shock), infuse a maximum of 3.5 L of clear fluids (initially 2 L of warmed isotonic crystalloid) while awaiting compatible blood.
- Isotonic crystalloids are preferred over colloids for fluid resuscitation
- Blood Transfusion
  - A blood transfusion is indicated in patients with continued bleeding or signs of clinical shock and major postpartum hemorrhage.

  For patients with major postpartum hemorrhage:
  - In the absence of timely laboratory results, a massive transfusion protocol with a fixed ratio of 1:1:1 of packed red blood cells (RBC) to fresh frozen plasma to platelets can be used.
  - If immediate transfusion is indicated, give emergency type O, RhD-negative blood in the form of red cell concentrate and switch to type-specific red cells as soon as possible.
  - Consider transfusion of platelets when the platelet count is $< 75 \times 10^9$/L based on laboratory monitoring
  - If hemostatic results are unavailable and bleeding continues, infuse fresh frozen plasma 12-15 mL/kg after 4 units of red blood cells until hemostatic test results are available
  - Consider early fresh frozen plasma if hemostatic results are unavailable and coagulopathy, such as placental abruption or amniotic fluid embolism, is suspected or detection of postpartum hemorrhage has been delayed.
  - If prothrombin time/activated partial thromboplastin time is > 1.5 times normal and hemorrhage is ongoing, fresh frozen plasma > 15 mg/kg may be needed to correct coagulopathy.
  - Maintain plasma fibrinogen level > 2 g/L during ongoing postpartum hemorrhage

- Medication:
    - Oxytocin 10 units intramuscularly or 10-40 units IV in 0.5-1 L normal saline as a continuous infusion [20-40 milliunit/min] (or another uterotonic if IV oxytocin is not available)
    - Avoid undiluted rapid IV infusion as it may cause hypotension.
    - Adverse effects include nausea and vomiting.
    - If oxytocin is not available or for bleeding refractory to oxytocin, alternative uterotonics may be considered. Options include:
        - Ergot alkaloids
            - Methylergonovine (Methergine): 0.2 mg intramuscularly every 2-4 hours.
            - Ergonovine (ergometrine)
            - Ergometrine/oxytocin
        - Misoprostol (Cytotec) [oral/sublingual/rectal]

IX. EVOLUTION AND PROGNOSIS

- The prognosis of hemorrhagic shock depends on several factors, including the severity of the blood loss, timeliness of medical intervention, and underlying health conditions of the patient
- Without intervention, severe hemorrhagic shock presents a classic trimodal distribution of deaths:
    - Death occurs within minutes of hemorrhage (immediate exsanguination),
    - Death after 1 to several hours (progressive decompensation),
    - Death occurs days to weeks later (sepsis and organ failure).
- Among survivors, hemorrhagic shock is associated with poor functional outcomes and significantly increased long-term mortality.
- Elevated serum lactate and/or base deficit (BD) at admission is associated with increased mortality and worse outcomes in trauma patients.
- Patients in end-stage/refractory shock will have irreversible cellular damage, resulting in multiple organ failure and most likely death.

X. COMPLICATIONS

- Major hemorrhage may lead to a "lethal triad" of coagulopathy, metabolic acidosis, and hypothermia.
- Without life-saving interventions, complications of hemorrhagic shock and continued bleeding may include cardiac failure, acute kidney injury, lung damage, and poor cerebral perfusion.
- Shock-related hypoperfusion and end-organ damage in the kidneys, liver, intestine, and skeletal muscle may lead to multiorgan failure in survivors.
- Patients with multiple-trauma are at high risk for hospital-acquired venous thromboembolism (VTE),
- Complications of rapid transfusions of blood products and large amounts of fluids.

XI. RECOMMENDATIONS

- Initial therapy until blood products are available needs to be differentiated to be effective in terms of hemodynamic stabilization and coagulation. Treatment of acidosis and hypothermia can further reduce bleeding complications.
- Early imaging (ultrasonography or contrast-enhanced CT) should be used for detection of free fluid in patients with suspected torso trauma.
- CT assessment should be provided for hemodynamically stable patients.
- Low initial Hb should be considered an indicator for severe bleeding associated with coagulopathy.
- Repeated Hb measurements should be used as a laboratory marker for bleeding, as an initial Hb value in the normal range may mask bleeding.
- Serum lactate and/or base deficit measurements are sensitive tests to estimate and monitor the extent of bleeding and shock.
- Repeated monitoring of coagulation, using a traditional laboratory determination (prothrombin time [PT], activated partial thromboplastin time [APTT], platelet counts, and fibrinogen) and/or a viscoelastic method, should be provided.
- Target systolic blood pressure is 80-90 mm Hg until major bleeding has been stopped in the initial phase following trauma without brain injury.
- In patients with severe traumatic brain injury (TBI) (GCS ≤8), mean arterial pressure ≥80 mm Hg should be maintained.
- Fluid therapy using isotonic crystalloid solutions should be initiated in the hypotensive patient with bleeding trauma.
- Excessive use of 0.9 % NaCl solution should be avoided.
- Hypotonic solutions such as lactated Ringer's solution should be avoided in patients with severe head trauma.
- Use of colloids should be restricted due to adverse effects on hemostasis.
- Target Hb is 7-9 g/dL.
- In initial management of patients with expected massive hemorrhage, one of the following strategies should be used: Plasma (FFP or pathogen-inactivated plasma) should be provided at a plasma-to-RBC ratio of at least 1:2 as needed, with fibrinogen concentrate and RBC according to Hb level.
- Tranexamic acid should be administered as early as possible to the trauma patient who is bleeding or is at risk of significant hemorrhage, at a loading dose of 1 g infused over 10 minutes, followed by an IV infusion of 1 g over 8 hours.
- Tranexamic acid should be administered to the bleeding patient with trauma within 3 hours after injury.
- Protocols for treatment of bleeding patients should consider administration of the first dose of tranexamic acid en route to the hospital.
- If a plasma-based coagulation resuscitation strategy is used, plasma (FFP or pathogen-inactivated plasma) should be administered to maintain PT and APTT < 1.5 times normal control values.
- Plasma transfusion should be avoided in patients without substantial bleeding.
- Platelets should be administered to maintain a platelet count above 50×10^9/L.

- Platelet count above 100×10^9/L should be maintained in patients with ongoing bleeding and/or TBI.
- Initial dose is 4-8 single platelet units or 1 apheresis pack

In general, few indications exist to transfer a patient who is in shock to a specialized facility. Ideally, all hospitals and physicians should be prepared to initially treat and stabilize the patient with exsanguinating hemorrhage. After control of the bleeding and reversal of acute shock, patients may be transferred to facilities that can treat additional injuries.
The patient should be transferred by an advanced life support unit with the capability of blood transfusion in route.

XII. REFERENCES

1. Lilly, Craig M.; Irwin, Richard S.; Boyle, Walter A.; Kelly, William F.. Irwin and Rippe's Intensive Care Medicine (p. 1650). Wolters Kluwer Health. Kindle Edition.
2. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care. 2016 Apr 12. 20 (1):100. [QxMD MEDLINE Link].
3. DynaMed. Hemorrhagic Shock. EBSCO Information Services. Accessed December 22, 2024. https://www.dynamed.com/condition/hemorrhagic-shock
4. UpTodate. Initial management of moderate to severe hemorrhage in the adult trauma patient, Wolters Kluwer. Accessed December 20, 2024
5. https://www.uptodate.com/contents/initial-management-of-moderate-to-severe-hemorrhage-in-the-adult-trauma-patient
6. Hemorrhagic Shock [Internet]. In: Schaider JJJ, Barkin RMR, Hayden SRS, Wolfe RER, Barkin AZA, Shayne PP, Rosen PP, editors. 5-Minute Emergency Consult. Lippincott Williams & Wilkins; 2020. [cited 2024 December 26]. Available from: https://www.unboundmedicine.com/ucentral/view/5-Minute_Emergency_Consult/307461/all/Hemorrhagic Shock.
7. DynaMed. Postpartum Hemorrhage. EBSCO Information Services. Accessed December 28, 2024. https://www.dynamed.com/condition/postpartum-hemorrhage

STROKE SYNDROME IN EMERGENCY

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I. DEFINITION

Stroke is defined as any disease process (non-traumatic) that interrupts blood flow to the brain.

II. EPIDEMIOLOGY

Approximately 80 percent of strokes are due to ischemic cerebral infarction and 20 percent to brain hemorrhage.

III. ETIOLOGY

There are two main subtypes of stroke: (1) Ischemic stroke, (2) Hemorrhagic stroke. Ischemic stroke may be caused by: Thrombosis, Emboli or Systemic hypoperfusion. Hemorrhagic stroke sub-divided into:

- Intra cerebral hemorrhage, usually due to chronic hypertension, and vascular disease (amyloidosis), or complications from cocaine or methamphetamines use.
- Subarachnoid hemorrhage, most frequently caused by rupture of cerebral arterial-venous malformations or cerebral aneurysm.

The transient ischemic attack (TIA): A transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

IV. PHYSIOPATHOLOGY

In ischemic stroke, the lower or absence perfusion to a brain territory due to emboli, thrombosis or systemic hypotension may produce an ischemic zone that evolve to necrosis. The center of the ischemic zone, called “ischemic penumbra” usually stays longer and may survive if the reperfusion was achieved early (before 4.5h). The signs and symptoms of ischemic stroke is related to the damaged zone.

In Hemorrhagic stroke, the hematoma may compress underneath brain causes its dysfunction. The hematoma may extend triggering ICP elevation, blood in the ventricle may block CSF absorption and induce hydrocephalus. In subarachnoid bleeding, the coagulation process of hematoma may trigger cerebral vasospasm and secondary brain ischemic. In the process of intracranial problems (hematoma, cerebral edema, hydrocephalus) the ICP tend to increase, the acute treatment of hypertension may vary also the cerebral perfusion pressure (CPP) that tend to decrease. CPP = MAP - ICP

V. DIAGNOSIS

The diagnosis of stroke in the ED rests on the bedrock of a focused, accurate history and physical examination.

A. Clinic signs & symptoms.

Signs & symptoms of stroke varied to the location of the lesion (anterior cerebral artery circulation, posterior cerebral artery circulation, middle cerebral artery circulation, watershed infarction).

a. Ischemic stroke

The mnemonic BE FAST, is the suspect signs of stroke.

-B: Sudden **B**alance impairment
-E: Sudden vision loss in one **E**ye / one field
-F: **F**acial droop (have patient show teeth or smile)
-A: **A**rm drift (patient closes eyes and extends both arms straight out, with palm up for 10")
-S: Abnormal **S**peech
-T: **T**ime to call emergency

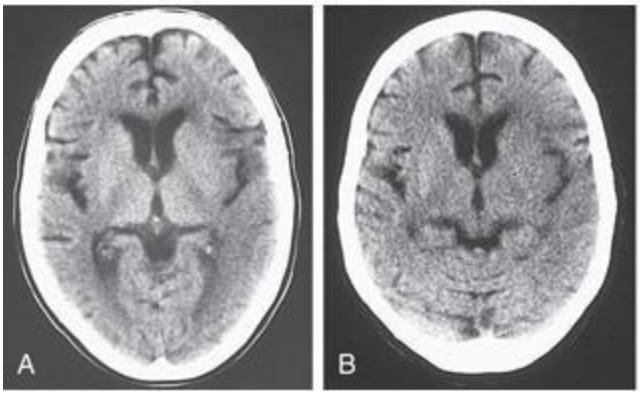
Clinically, the differentiation of an ischemic from hemorrhagic stroke is not accurate. It is necessary to obtain an emergency non–contrast-enhanced CT for all suspected acute stroke upon arrival. The utility of the first brain CT is primarily to exclude intracranial bleeding, abscess, tumor, and other stroke mimics, as well as to detect current contraindications to thrombolytics.

Physical examination

Assessment of airway, breathing, and circulation is the top priority.
Next, the goals of examination are to confirm the diagnosis of stroke, exclude stroke mimics and identify co-morbidities.

B. Investigation

Non-contrast-enhanced brain CT imaging



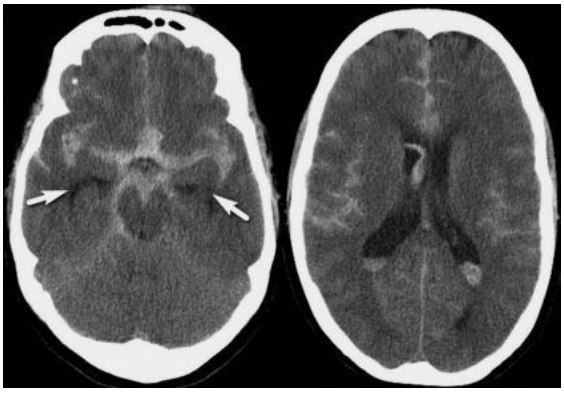
A. Normal computed tomography (CT) scan of brain 2 hours after onset of aphasia and left hemiparesis.

B, Repeat CT scan at 5 hours after stroke onset shows early CT changes, including basal ganglia hypodensity, loss of the insular ribbon, and slight effacement of the sulci on the left.

Pictures from: textbook of Critical care 8th Edition, Jean-Louis Vincent

b. Hemorrhagic stroke

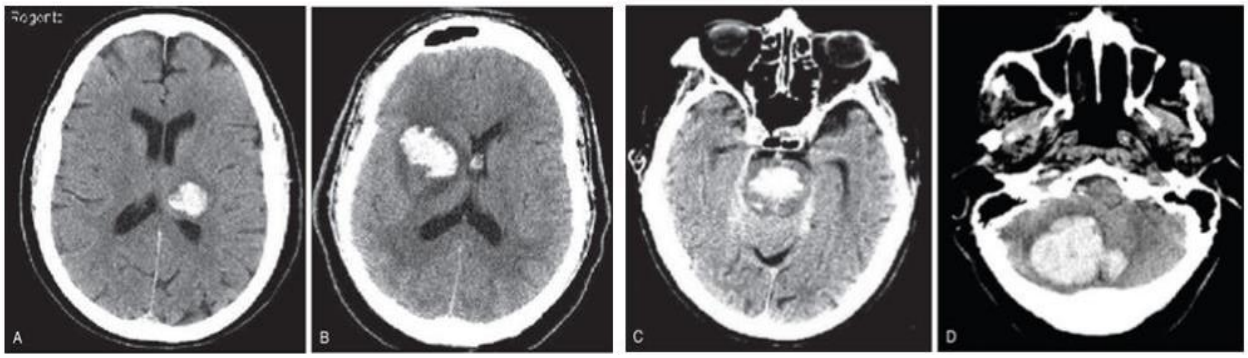
Subarachnoid hemorrhage (SAH) classically presents with sudden onset of a headache at its most severe. It occurs 20% of the time during activity associated with elevated blood pressures, such as sexual intercourse, weightlifting, defecation, or coughing.
Vomiting, photophobia, nuchal irritation, low-grade fever, and altered mental status all may occur. Focal findings can occur depending on the location of the aneurysm.



Shown is the non-contrast head CT of a large SAH from a ruptured berry aneurysm, resulting in blood in all major cisterns, interhemispheric and Sylvian fissures, and both ventricles. Mild obstructive hydrocephalus is also present, as visible by the slightly dilated temporal horns (white arrows).

Pictures from: textbook of Critical care 8th Edition, Jean-Louis Vincent

Intracerebral hemorrhage (ICH), is intraparenchymal hemorrhage from previously weakened arterioles. The frequent etiology is chronic arterial hypertension, amyloidosis, iatrogenic anticoagulation, vascular malformations and cocaine use.



CT Scans Showing Common Locations of Spontaneous Hypertensive Intracranial Hemorrhage. **A**, Thalamus, **B**, caudate/putamen, **C**, pons, and **D**, cerebellum.

Pictures from: textbook of Critical care 8th Edition, Jean-Louis Vincent

VI. DIFFERENTIAL DIAGNOSIS

Stroke mimics conditions:

- Seizures/ post tical paralysis (Todd's paralysis)

- Syncope
- Meningitis / encephalitis
- Complicated migraine
- Brain neoplasm or abscess
- Epidural / subdural hematoma
- Subarachnoid hemorrhage
- Hypoglycemia
- Hyponatremia
- Hypertension encephalopathy
- Hyperosmotic coma
- Wernicke's encephalopathy
- Labyrinthitis
- Drug toxicity (Lithium, phenytoin, carbamazepine)
- Bell's palsy
- Ménière's disease
- Demyelinating disease (multiple sclerosis)
- Conversion disorder

VII. MANAGEMENT

1. Objectives

The management of ischemic stroke is time-dependent, different steps need to be done quickly. Find out whether any specific treatment is feasible.

- Eliminate the problems that mimic stroke symptom.
- Differentiate ischemic from hemorrhagic stroke.
- Re-perfusion therapy, if feasible. (Thrombolysis, mechanical thrombectomy)
- Prevent the expansion of the brain damage, by saving the "ischemic penumbra" and prevent or treat the early complications (re-bleeding, vasospasm, cerebral edema, intracranial hypertension).
- Maintain cerebral perfusion pressure (CPP). In selected patients, surgery or microinvasive procedures is indicated to remove hematoma, drain the hydrocephalus, or to prevent re-bleeding (clipping, stenting, coiling).

2. Severity grading

In Acute phase of stroke (ischemic or hemorrhagic), NIHSS is used to grade the severity of stroke and help decide on treatment modality. After treatment, the severity of handicap was commonly measured by modified Rankin Score.

The National Institutes of Health stroke scale (NIHSS) for Ischemic stroke
It is composed of 11 items. A score of 0 indicates normal function and the higher score indicates impairment with maximum score of 42. Score of more than 25 indicate a severe stroke. (For details, see reference 1).

At the time of presentation, the severity of subarachnoid hemorrhage (SAH) is scored by Hunt & Hess scale or The WFNS scale.

Hunt & Hess Clinical classification of subarachnoid hemorrhage

Grade	Neurologic Status
I	Asymptomatic or mild headache and neck stiffness
II	Moderate to severe headache and neck stiffness + cranial nerve palsy
III	Mild focal deficit, lethargy, or confusion
IV	Stupor, moderate to severe hemiparesis
V	Deep coma, extensor posturing

The World federation of neurosurgical surgeon (WFNS).

Grade 1	GCS: 15	Risk of death or severe disability 13%
Grade 2	GCS: 13-14, and no motor deficit	Risk of death or severe disability 20%
Grade 3	GCS: 13-14, with motor deficit	Risk of death or severe disability 42%
Grade 4	GCS: 7-12, w/wo motor deficit	Risk of death or severe disability 51%
Grade 5	GCS: 3-6, w/wo motor deficit	Risk of death or severe disability 68%

Fisher Grade of Subarachnoid Hemorrhage on initial CT scan

1. No blood detected
2. Diffuse or vertical layers < 1mm thick
3. Localized subarachnoid clot and/or vertical layer ≥ 1mm thick.
4. Intraparenchymal or intraventricular clot with diffuse or no SAH

Modified Fisher CT Rating Scale

1. Minimal or diffuse thin SAH without IVH
2. Minimal or thin SAH with IVH
3. Thick cisternal clot without IVH
4. Thick cisternal clot with IVH

CT: computed tomography; IVH: intraventricular hemorrhage; SAH: subarachnoid hemorrhage

Intracerebral hemorrhage (ICH) score

Age 80+ years	Yes = 1, No = 0
GCS at presentation	(3-4) = 2; (5-12) =1; (13-15) = 0
ICH volume 30+ ml	Yes = 1, No = 0
Intraventricular blood	Yes = 1, No = 0
Infratentorial origin of ICH	Yes = 1, No = 0
Score = sum of points.	

30d mortality: Score 0 = 0%; 1 =13%; 2 = 26%; 3 = 72%; 4 = 97%; 5-6 = 100%

3. Risk factors for mortality
    - Larger size of brain damage or hematoma
    - Factors contributed to elevation of intracranial pressure (cerebral edema, extending hematoma, cerebral herniation)
    - Systemic factors contributed to secondary exacerbation (hypotension, hypoxia, hypercapnia, fever, agitation, hyponatremia, cerebral vasospasm, re-bleeding)

4. Out-patient management

    Only after assessment and treatment in acute phase, that patients who survived with variable handicaps may have outpatient management. The treatment focus on rehabilitation, most importantly during the first 3 months, and the Secondary prevention of cardiovascular disease.

5. First-line treatment

    The management of Stroke syndrome consisted of early stabilization (SpO2> 94%, PaCO2: 35-40mmHg, SBP > 90mmHg, treat hypoglycemia, keep glycemia 140-180mg/dl for hyperglycemic patient. Once the patient's condition is stabilized, immediately send the patient for a non-contrast head CT

a) Supportive treatment

Supportive therapy for patients with Intracerebral vascular diseases (ICVD) should begin upon hospitalization.
Head of the bed elevated to 30 - 45 degree
Keep the patient nothing-per-os (for the first few days).
Treatment of elevated blood pressure in the first 24 hours of an ischemic stroke is reserved for those with malignant hypertension (> 220 mmHg systolic, 120 mmHg diastolic) or other end-organ failure (e.g., congestive heart failure, renal failure, and hypertensive encephalopathy). The blood pressure typically autoregulates spontaneously with bed rest in the first few days after ischemic stroke; if it remains substantially elevated, it should be carefully lowered daily up to 20% of the mean arterial pressure. Subcutaneous heparin or low-molecular-weight heparin therapy should be considered for immobilized patients with ICVD to reduce the risk of deep venous thrombosis. In

hemorrhagic stroke, use instead the intermittent pneumatic compression device for the first few days.
For patients with evidence of elevated ICP, get head of bed elevation to 30°, analgesia, and sedation is needed.
Indwelling urinary catheters and unneeded IV lines should be avoided, because they can serve as portals of entry for infections.
Elevated temperature should be treated with antipyretics. Looking for causes.
Aspiration pneumonia can be avoided by delaying oral feedings until safe swallowing is demonstrated. Early mobilization and rehabilitation should be attempted.

b) Specific treatment for different type of stroke

A. Ischemic stroke:
Hypertension management in acute ischemic stroke depend on the thrombolysis.
• Is not a candidate for thrombolysis, then permissive hypertension is in order
(No intervention unless SBP >220mmHg or DBP >120 mmHg.)
• Is a candidate for thrombolytics, then the target blood pressures are SBP ≤185 mmHg and DBP≤ 110mmHg
If blood pressure control is needed, use a titratable IV antihypertensive,
Labetalol, starting dose is 10 to 20 mg over 1 to 2 min; continuous infusion at 2 mg/min, (titrated to effect) with a target MAP reduction of 10% to 25%.
Take extreme caution to avoid overcorrection.

Reperfusion therapy:
(1) Intravenous Thrombolysis, (2) Mechanical thrombectomy

a. Intravenous Thrombolysis

Thrombolytic therapy for patients with ICVD is directed at reversing the neurological deficits and preventing progression. The total dose of IV tissue plasminogen activator (tPA) for stroke is 0.9 mg/ kg, given as a 60-minute IV infusion, with 10% of the total dose given as an initial bolus.

Indication & contra-indication of r-TPA (recombinant tissue plasminogen activator) Alteplase®

Alteplase is Contraindicated in:
- Active internal bleeding
- History of cerebrovascular accident (for MI and PE only)
- Recent (within 3 mo) intracranial or intraspinal injury or trauma
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Known bleeding diathesis
- Severe uncontrolled hypertension (systolic BP >185 mmHg or diastolic BP >110 mmHg specifically for stroke indication)

- Evidence or suspicion of intracranial hemorrhage on pretreatment evaluation (for stroke indication only)
- Recent (within 3 months) stroke (for stroke indication only)
- History of intracranial hemorrhage (for stroke indication only)
- Seizure at the onset of stroke (for stroke indication only)
- Current use of oral anticoagulants or an INR >1.7 or a prothrombin time >15 sec (for stroke indication only)
- Administration of heparin 48h before the onset of stroke with an elevated aPTT at presentation (for stroke indication only)
- Platelet count <100,000/mm3 (for stroke indication only)
- Hypersensitivity (for central venous access device occlusion indication only).

Use Cautiously in:

- Recent (within 10 days) major surgery, trauma, GI or GU bleeding
- Cerebrovascular disease
- Systolic BP ≥175 mmHg and/or diastolic BP ≥110 mmHg
- High likelihood of left heart thrombus
- Hemostatic defects
- Severe hepatic impairment
- Hemorrhagic ophthalmic conditions
- Septic thrombophlebitis
- Previous puncture of a noncompressible vessel
- Subacute bacterial endocarditis or acute pericarditis
- Severe neurological deficit (NIHSS >22) at presentation (for stroke indication only)
- Major early infarct signs on CT scan (for stroke indication only)
- Known or suspected infection in catheter (for central venous access device occlusion indication only)
    - Geri: >75 ys; ↑ risk of intracranial bleeding
    - OB: Lactation: Pedi: Safety not established.

Exercise Extreme Caution in: Patients receiving concurrent anticoagulant therapy (↑ risk of intracranial bleeding).

b. Intra-arterial therapies / mechanical thrombectomy

Using a second-generation stent retriever device is the preferred mode of therapy for eligible patient, whether or not the patient has received intravenous thrombolysis.
Patients ≥18 years if they have minimal pre-stroke disability, (modified Rankin Scale < 1), Have a causative occlusion of the internal carotid artery or proximal middle cerebral artery, Have a NIHSS score of ≥ 6, have a reassuring non-contrast head CT (ASPECT score of ≥ 6), And if they can be treated within 6 h of last known normal.

B. Subarachnoid hemorrhage:

Reduce the chances of re-bleeding: maintaining the patient's pre-bleed blood pressure (or MAP <130 mmHg if baseline blood pressure is unknown). IV titratable labetalol (10 to 20 mg over 1 to 2 min; continuous infusion dosage at 2 mg/min, titrated to effect).
Nimodipine (60 mg PO every 4 hours) may decrease vasospasm.
Emergent neurosurgical consultation is indicated.
Administer medications and antiemetics as needed.
Seizure prophylaxis is controversial,

a. General measure:

Strict bed rest in a quiet environment to diminish hemodynamic fluctuations, pain control with titrated doses of opioid analgesics.
Deep venous thrombosis (DVT) prophylaxis with pneumatic compression stockings.
Pharmacologic DVT prophylaxis can be added after definitive treatment for the aneurysm.
GI ulcer prophylaxis and stool softeners.
Fever should be managed with antipyretics and adequate source control.
Correct hypoglycemia or Control glycemia at the level ~150mg/dL

b. Specific Measure:

Surgical clipping of the neck of the aneurysm and Endovascular aneurysmal obliteration by metal coils are the options available for aneurysmal repair

C. Intracerebral Hemorrhage:

Management of blood pressure for spontaneous ICH remains controversial.
SBP greater than 220 mm Hg, indicate a continuous IV drug infusion and close BP monitoring to lower SBP. The optimal goal blood pressure is uncertain, SBP of 140 to 160 mmHg is a reasonable target. Aggressive reduction can increase renal adverse events.
Early neurosurgical consultation is indicated for patients with ICH with evidence of increased ICP or in other conditions where surgical intervention may be indicated, (For example, cerebellar stroke). All non-surgical measures to reduced ICP should be considered.
Rapid reversal of anticoagulation to INR < 1.6 may improve survival.
Decompressive craniotomy and evacuation for all patients with ICH is not indicated.
For Supratentorial ICH, surgery is usually avoided and should be considered on an individual basis based on assessment of prognosis with or without surgery.

Measures to reduce intracranial pressure (ICP)

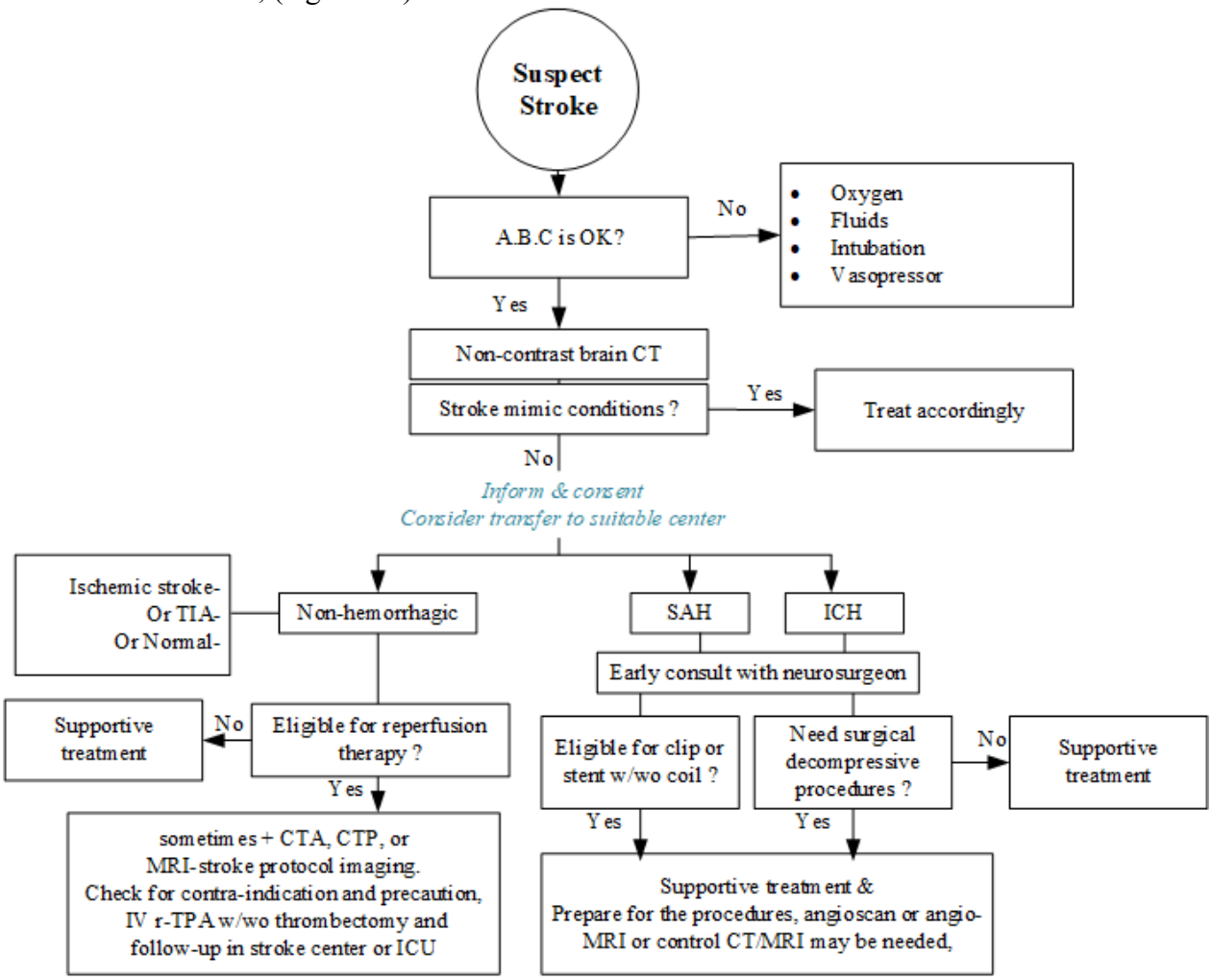
- Raise Head of Bed (reduce veinous volume)
- Hyperosmolar (NS 3%, mannitol) [Reduce (remove) some water from brain tissue]
- Hyperventilate (Vasoconstriction, reduce cerebral blood flow)
- Sedation (reduce sympathetic nervous system tone)

- Control fever / seizure (Reduce cerebral oxygen demand, reduce the cerebral blood flow)
- Ventriculostomy [Remove (reduce) volume of CSF]

6. Treatment adjustment

   In case of patient arrived hospital late, or the criteria for re-perfusion therapy was not fulfilled, the treatment is directed to active-supportive treatment and prevent the factors of secondary aggravating brain damage.

7. Decision tree, (algorithm)



MANAGEMENT OF PATIENT WITH STROKE SYNDROME

SAH: subarachnoid hemorrhage, ICH: intracerebral hemorrhage, r-TPA: recombinant- tissue plasminogen activator, w/wo: with or without. CTA: CT angiography, CTP: CT perfusion

Priority on arrival is making sure that airway (A), breathing (B), and circulation (C) are OK. Maintain SpO2>94%, if need, administer oxygen by mask. Make sure that patient was not hypovolemic, put a good IV line and RL to keep line open. Patient with GCS≤ 8 need intubation and supported ventilation. Hypotension is the worst factors of exacerbation; moderate hypertension is desirable. Inform-consent form should be completed as soon as stroke is clinically diagnosed to catch the time when patient is eligible for the procedures, and if they refuse the intervention, some investigations exam may be omitted. If consented, consider transfer patient to hospital or center where the specific treatments (Thrombolysis, thrombectomy, clip, neurosurgery) are available, as soon as possible.

VIII. SPECIAL CASES

1. Ischemic stroke with concomitant myocardial infarction

Troponin elevation in acute ischemic stroke is not uncommon (prevalence, 0% to 34%), is associated with multiple disease processes (e.g., acute coronary syndrome, congestive heart failure, renal failure, myopericarditis, chronic obstructive pulmonary disease, pulmonary embolism, sepsis, atrial fibrillation), and is independently associated with worse all-cause mortality. Troponin elevation in acute stroke is most probably secondary to acute coronary syndrome if other obvious causes are excluded, especially if typical ECG findings for acute coronary syndrome are present. Simultaneous acute ischemic stroke and myocardial infarction can be therapeutically problematic because treating one condition with a procedure may delay a time-dependent indicated procedure for the other. In addition, there are some therapies for acute myocardial infarction (e.g., heparin) that are contraindicated in acute stroke.

"For patients presenting with concurrent AIS [acute ischemic stroke] and acute MI [myocardial infarction], treatment with IV alteplase at the dose appropriate for cerebral ischemia, followed by percutaneous coronary angioplasty and stenting if indicated is reasonable." (AHA/ASA guidelines, 2018). Obtain emergent neurology and cardiology consults on these patients, but do not delay thrombolysis for stroke if the patient qualifies.

2. Transient ischemic attack (TIA)

TIA treatment is important, even all symptoms were disappeared. The patient returned to normal but the risk of developing a real stroke is high especially during the first month. Treatment of TIA primarily focuses on prevention of subsequent stroke.

- Anti-platelet agents

Can select among: Aspirin (75-81mg), clopidogrel (75mg), Dipyridamole (75-100mg qid), alone or combined clopidogrel or dipyridamole with aspirin take every day.

- Anticoagulation

The risk of recurrent stroke in the presence of atrial fibrillation without anticoagulation is low, probably <5% over the next 48 hours; moreover, the risk of hemorrhagic transformation of an acute stroke is also greatest in the first 48 hours.

The use of unfractionated heparin, low molecular-weight heparin, or heparinoids for emergent treatment of a specific stroke subtype or TIA cannot be recommended based on available evidence, even in the presence of atrial fibrillation.

- Carotid artery endarterectomy or stent

In TIA patients with medically treated high-grade internal carotid artery lesions, The Carotid Revascularization Endarterectomy or carotid stenting should be performed promptly, because surgical benefit is greatest within 2 weeks of the TIA. Carotid stenting may be especially useful in patients <70 years old or in patients with higher surgical risks.

IX. EVOLUTION & PROGNOSIS

The prognosis of stroke depends on: (1) Type of stroke, (2) Location and size of the stroke, (3) Severity of symptoms, (4) Age and overall health.

The prognosis of ischemic stroke is generally better than for hemorrhagic stroke.

Strokes affecting the speech center or motor cortex, are more likely to cause lasting disabilities.

Larger strokes also tend to have a worse prognosis than smaller strokes.

People with mild symptoms are more likely to make a good recovery than those with severe symptoms. Prompt diagnosis and treatment of an acute cerebral vascular accidents can improve the chances of a good recovery.

The recovery aspect of stroke:

- 1-3 months: the brain exhibits the most remarkable plasticity and potential for improvement. During this time, most patients undergo intensive rehabilitation in hospitals or specialized centers, focusing on regaining lost function in movement, speech, and cognitive skills. Significant progress is often observed during this phase.
- 3-6 months: the rate of recovery slows down but can still be substantial
- 6-12 months: The improvement becomes less dramatic,
- 1 year and beyond: While some individuals achieve near-complete recovery, others may have permanent disabilities.

X. COMPLICATIONS

Acute ischemic stroke may complicate malignant cerebral edema, venous thromboembolism, symptomatic intracranial hemorrhage (post-thrombectomy), angioedema (post-thrombolysis), dysphasia, infection.

The main complications of SAH:

- Re-bleeding (within the first 24h, particularly within 6h).
- Vasospasm and delay cerebral ischemia (3-4day after rupture, peak at 7-10d and resolves by 14-21d).
- Raise ICP and hydrocephalus (within 3 days of rupture, in 20% of patient)

Other complication:

- Seizure 20% (mostly at first 24h); risk: thick clot, ICH, prior seizure, middle cerebral artery aneurisms, delayed infarct.
- Hyponatremia (SIADH, and Salt-wasting sd.).
- Cardiac change (neurogenic stunned myocardium).
- Neurogenic pulmonary edema (NPE), usually resolves in 48-72h.

The early complications of ICH are Intracranial pressure (ICP) elevation causing local neuronal damage, and vasoconstriction mediated by blood breakdown products or neuronal mechanisms causing remote perfusion changes.

XI. PREVENTION AND RECOMMANDATION

- Primary prevention of cardiovascular disease (pre-stroke): control the chronic hypertension, Diabetes, dyslipidemia; life-style change.
- Early seek medical advice when suspect a stroke. Stroke is time-dependent disease.
- Do no harm to patient (multiple-transfers, waiting-treatment), “time is brain”
- Important of rehabilitation therapy immediately after stroke
- Secondary prevention of cardiovascular diseases (post-stroke)

XII. REFERENCES

1. NINDS. (2018). NIH Stroke Scale. National Institute of Neurological Disorders and Stroke. https://www.ninds.nih.gov/sites/default/files/documents/NIH_Stroke_Scale_508C_2.pdf
2. Steven Go. (2020), Stroke Syndromes. In: Judith E. Tintinalli, Emergency Medicine. A comprehensive Study Guide, 9th edition, Mc Graw Hill; p. 1119-36
3. Vinit Suri, Kunal Suri, (2020), Acute Ischemic Stroke. In: Rajesh Chawla, Subhash Todi Editors: ICU Protocols, A step-wise Approach, vol 1. 2nd Edition Springer. P 276-88
4. Richard P, Goddeau Jr, Majaz Moonis, (2023), Cerebrovascular Diseases. In : Craig M, Irwin, Richard S, Boyle, Walter A, Kelly, William F. Irwin and Rippe's Intensive Care Medicine 9th edition, Wolters Kluwer Health. Kindle Edition; p. 6798-865

COMA

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I. DEFINITION

Altered mental status and coma are broad clinical categories used to describe disorders of arousal (awake) and content of consciousness (aware). Arousal behaviors include wakefulness and basic alerting. Content of consciousness includes awareness, memory, language, reasoning, spatial relationship integration, emotions, complex attention, and the myriad integration processes that make us human.

Coma is characterized by failure of both arousal and content functions of consciousness.

A coma is the most severe of consciousness altered.

II. EPIDEMIOLOGY

In a study by Keun Tae Kim et al., in South Korea 2022, among patient in ED 80.738 they found 2028 patient (2.51%) had consciousness altered. Most of those patients were in their 70s (546, 26.9%) followed by their 80s (506, 25.0%). The study also found that the etiology of consciousness altered in South Korea ED is as follow:

Etiology	N (%)
Systemic infection	581 (28.6)
Metabolic cause	455 (22.4)
Stroke	271 (13.4)
Toxicity	222 (10.9)
Cardiovascular	149 (7.3)
Seizure	128 (6.3)
Psychiatric disorder	39 (1.9)
Head trauma	17 (0.8)
CNS infection	22 (1.1)
Undetermined	144 (7.1)

III. ETIOLOGY

Coma or consciousness altered may have different cause

- a structural cause
    - traumatic / non-traumatic
- toxic, metabolic cause
- inflammation or infection cause

Table 1_ Etiology of consciousness altered / coma

Causes affecting the brain diffusely

- Encephalopathies
  - Hypoxic encephalopathy
  - Metabolic encephalopathy
  - Hypertensive encephalopathy
- Hypoglycemia
- Hyperosmolar state (e.g., Hyperglycemia)
- Electrolyte abnormalities (e.g., hypo/hypernatremia, hypercalcemia)
- Organ system failure
  - Hepatic encephalopathy
  - Uremia / renal failure
- Endocrine (e.g., Addison's disease, hypothyroidism, etc.)
- Hypoxia
- Carbon dioxide narcosis
- Toxins
- Drug reactions (e.g., neuroleptic malignant syndrome)
- Environmental causes_ hypo / hyperthermia
- Deficiency state_ Wernicke's encephalopathy
- Sepsis

Primary CNS disease or trauma

- Direct CNS trauma
  - Diffuse axonal injury
  - Subdural hematoma
  - Epidural hematoma
- Vascular disease
- Intraparenchymal hemorrhage (hemispheric, basal ganglia, brainstem, cerebellar)
- Subarachnoid hemorrhage
  - Infarction
  - Hemispheric, brain stem
- CNS infections
- Neoplasms
- Seizures
  - Nonconvulsive status epilepticus
  - Postictal State

IV. PHYSIOPATHOLOGY

The function of the brainstem and/or both hemispheres must be impaired for unresponsiveness to occur. Coma can result from

- deficiency of substrates needed for neuronal function (as with hypoglycemia or hypoxia).
- a brainstem disorder such as hemorrhage or
- bilateral cortical dysfunction.
- Cerebral edema and infection of the brain and/or surrounding

Cerebral blood flow is constant at mean arterial pressures of 50 to 100 mm Hg due to the process of cerebral autoregulation. Cerebral perfusion pressure (CPP) is the pressure that maintain the blood flow to the brain. It is the net pressure gradient between mean arterial pressure (MAP) and intracranial pressure (ICP): CPP = MAP- ICP

In extreme uncontrolled elevation of the ICP, cerebral perfusion pressure is diminished which may causes brain ischemia. The Cushing reflex (Hypertension and bradycardia in a comatose patient): may be observed with increased ICP.

V. DIAGNOSIS

a. Signs & symptoms

The clinical features of a coma vary with both the depth of coma and the cause. Examination, laboratory procedures, and neuroimaging allow differentiation between structural and metabolic causes of coma in almost all patients in the ED

- Structural Coma

Patient may have hemiparesis, the eyes may conjugately deviate toward the side of brain lesion.

- Toxic-metabolic coma

The diffuse CNS dysfunction is reflected by the lack of focal physical examination findings that point to a specific region of brain dysfunction. Pupillary response is generally preserved in toxic-metabolic coma.

A posterior fossa or infratentorial expanding lesion, such as cerebellar hemorrhage or infarction, may cause abrupt coma, abnormal extensor posturing, loss of pupillary reflexes, and loss of extraocular movements.

A Pseudo coma or psychogenic coma is occasionally encountered.

General examination may reveal signs of trauma or suggest other diagnostic possibilities for the unresponsiveness. However, asymmetric findings on examination of cranial nerves through pupillary examination, assessment of corneal reflexes, and testing of oculovestibular reflexes may suggest focal CNS lesions. Asymmetric muscle tone or reflexes raise the suspicion of a focal lesion. The goal of the physician is to rapidly determine if the CNS dysfunction is from diffuse impairment of the brain or if signs point to a focal (and perhaps surgically treatable) region of CNS dysfunction.

Liberal use of CT scanning is encouraged because exceptions to the tentative clinical diagnosis are frequent.

The Glasgow Coma Scale (Table-2) is a widely used clinical scoring system for alterations in consciousness. GCS stratify consciousness altered from 15 (alert) to 3 (deep coma). Typically, a score of 8 or below is indicative of coma.

Table 2_ Glasgow com scale

Glasgow Coma Scale (GCS)	
Eye Opening Response	
Spontaneous	4
To verbal stimuli	3
To pain only	2
No response	1
Verbal Response	
Oriented	5
Confused, but able to answer questions	4
Inappropriate words	3
Incomprehensible speech	2
No response	1
Motor Response	
Obeys commands	6
Purposeful movement to noxious stimuli	5
Withdrawal to noxious stimuli	4
Flexion to noxious stimuli	3
Extension to noxious stimuli	2
No response	1
Total Score	**3-15**

b. Investigation

CT is the neuroimaging procedure of choice. Acute hemorrhage is readily identified, as is midline shift and mass lesions. Consider lumbar puncture if CT scan findings are unremarkable and subarachnoid hemorrhage or CNS infection is suspected.

Suspect basilar artery thrombosis in a comatose patient with "normal" results on head CT, in which the only finding may be a hyperdense basilar artery. MRI or cerebral angiography is needed to make the diagnosis of basilar artery thrombosis.

VI. DIFFERENTIAL DIAGNOSIS

Delirium, dementia, and coma may each affect consciousness, but their clinical presentations are distinct. Prompt and accurate differentiation between the three conditions is essential for appropriate management in the ED setting.

Delirium, acute encephalopathy, refer to an abrupt disorder characterized by impairment of attention and cognition. The literature suggests that at least 1 out of 10 elderly ED patients and at least 1 out of 4 elderly hospitalized patients have delirium at the time of admission.

Delirium typically develops over days. Disordered attention and acute fluctuating course are the hallmarks of the condition, which may also affect cognition, level of consciousness, language, and perception. Activity levels may be either increased or decreased.

Dementia is a chronic, major neurocognitive disorder entailing a gradual loss of mental capacity. Executive, social, and cognitive abilities deteriorate, and behavioral problems can develop. The typical course of dementia involves insidious symptom onset. Hallucinations, delusions, repetitive behaviors, depression, and anxiety are all common.

<table>
<tr><td rowspan="2">Coma</td><td>Awake: No</td><td rowspan="2">Delirium / Dementia</td><td>Awake: Yes</td></tr>
<tr><td>Aware: No</td><td>Aware: Abnormal / no</td></tr>
<tr><td colspan="4">arousal = Awake,
content of consciousness = cognitive function + psychic function = Aware</td></tr>
</table>

Compare Delirium with Dementia

	Delirium	**Dementia**
Onset	Acute (a few h, few days)	Insidious, many years
Progress	Fluctuated during the day	Aggravated progressively
Prognosis	May be recover, known cause & treat	Not reversible
Signs & symptoms	a disturbance in a person's thoughts, mood, and behavior. It causes inattention, distractibility disorganized thinking, and confusion. → inattention, or difficulty focusing, shifting, or maintaining attention In some case, a person may have altered mental status and delirium	Memory & decision-making disorders People with dementia may forget recent events, older memories and events, names of familiar people and places. In some cases, a person may have Dementia + delirium

VII. MANAGEMENT

1. Objectives of Management

Maintain vital function, in the same time, find and correct the possible reversible causes
Treat and prevent the structural and functional derangement caused by coma (elevation ICP, respiratory depression) and treat its cause.

2. Critical signs

Depth of coma, GCS lower or egal 8, the lower is the more severe
Coma secondary to prolong shock, hypoxia or hypoglycemia
Coma on Cardiac arrest with return of spontaneous circulation post resuscitation (CPR)
Coma which GCS drops abruptly (secondary deterioration of brain injury, herniation)

3. Mortality risk factor

Age and medical conditions of patient
Coma associated with condition that deteriorates hemodynamic (hypotension/ bleeding)
Coma associated with condition that deteriorates oxygenation (pneumonia, chest trauma)
Systemic factors that exacerbated the secondary brain injury: fever, agitation, hypoxia, hypercapnia, hypotension, hyponatremia.
Localize factors that exacerbated the secondary brain injury: expansion of intracranial hematoma, cerebral edema, intracranial herniation, cerebral vasospasm, Intracranial Pressure elevation.

4. Outpatient management

All patient with acute loss of consciousness should be evaluated and follow-up in emergency department. Coma is a Medical Emergency. While waiting for, and during the transport, be cautious about aspiration pneumonia (patient may vomit).

Check breathing and pulse. If breathing OR pulse is absent then start first aid CPR. If breathing AND pulse is present then put the patient on recovery position.

5. First-line treatment

Treatment of coma involves identification of the cause of the brain failure and initiation of specific therapy directed at the underlying cause.
Attend to airway, ventilation, and circulation. Evaluate and treat for readily reversible causes of coma, such as hypoglycemia and opioid toxicity.
Rapid point-of-care glucose determination can identify the need for dextrose. Give D50% 50ml IV in once or divided in two doses followed by D10% infusion, check glycemic again 10-15min after the bolus. Give Thiamin 100mg IM/IV if suspect vitamin B1 deficiency. In case coma with bradypnea and myosis, suspect opioids overdose, give Naloxone 0.4-2mg IV repeat every 2-3min, or put into IV infusion with rate adjusted to patient response. In patient who is opioids dependent, too quick to reverse may trigger withdrawal syndrome.

The patient suspect to have intracranial hypertension (severe headache, nausea-vomiting, blur vision, secondary altered consciousness, pupillary dilated or unequal) need to be managed immediately:

- Raise Head of Bed (reduce veinous volume) to 30degree
- Hyperosmolar (NS 3%, mannitol) [Reduce (remove) some water from brain tissue]
- Hyperventilate (Vasoconstriction, reduce cerebral blood flow)
- Sedation (reduce sympathetic nervous system tone)
- Control fever / seizure (Reduce cerebral oxygen demand, reduce the cerebral blood flow)
- Ventriculostomy [Remove (Reduce volume of CSF)
- Intracranial Hematoma removal. (hematoma with midline deviated)

6. Treatment adjustment

Problem	**Management**
In cases of severe facial trauma	Intubation is indicated for airway protection.
If the patient is hypotensive and not responsive to fluid resuscitation	Start vasopressors to avoid cerebral hypoperfusion
In cases of traumatic coma	the cervical spine should be immobilized until it can be cleared
If the patient is hypertensive (And Intracranial hemorrhage or acute ischemic stroke)	consider beta-blockers and calcium channel blockers such as labetalol, or nicardipine for strict blood pressure control.
if there is clinical suspicion for raised intracranial pressure (with HTN)	Avoid sodium nitroprusside and nitroglycerin because of the risk of worsening intracranial pressure through cerebral vasodilation
If the patient had a cardiac arrest	therapeutic hypothermia should be initiated, regardless of whether the patient had a shockable or non-shockable rhythm
In cases of hypothermia and coma	warm the patient with a warming blanket.
hyperthermic patients	should be placed on cooling blankets.
Acute hyponatremia	should be treated with 3% hypertonic saline (raise natremia about 8-10mmol/l for first 24h)
Endocrine emergencies, including myxedema coma	should be treated with thyroid hormone and supportive measures to correct hypothermia and hyponatremia
diabetic ketoacidosis (DKA)	fluids, electrolyte repletion, and insulin
Infectious cause is suspect	broad coverage with antibiotics is recommended. If there is suspicion for meningoencephalitis, empiric treatment should be started at dosing adequate for CNS penetration with concomitant administration of dexamethasone.

In the event of structural brain injury because of intracranial hemorrhage or mass,	neurosurgery should be consulted for appropriate interventions, including ventriculostomy or surgery if necessitated
if suspected an intracranial hypertension	- raising the head of the bed at or above 30 - 45 degrees, maintaining the head midline and in a neutral position to facilitate intracranial venous drainage, - avoiding hypoxia, ($SpO_2 \geq 94\%$) - maintaining normotension and - normothermia. - If needed, 0.5-1 g/kg of 20% mannitol or 2.5-5 mL/kg of 3% hypertonic saline may be given as IV bolus over 15-20 minutes. - Hyperventilation for a goal partial pressure of carbon dioxide ($PaCO_2$) of 30–35 mm Hg should only be used as a bridging measure to definitive therapies
If basilar artery occlusion is identified on CT angiogram	stroke and neuro-interventional specialists should be consulted immediately for possible IV tissue plasminogen activator and/or mechanical thrombectomy.

7. Algorithm Initial management of patient with Coma
   (See Fig_3)

VIII. SPECIAL CONSIDERATION

1. Head trauma & coma.

If trauma is suspected, maintain stabilization of the cervical spine during assessment. If protection of the airway is in doubt or the coma state is likely prolonged, then protect the airway by intubating the patient.

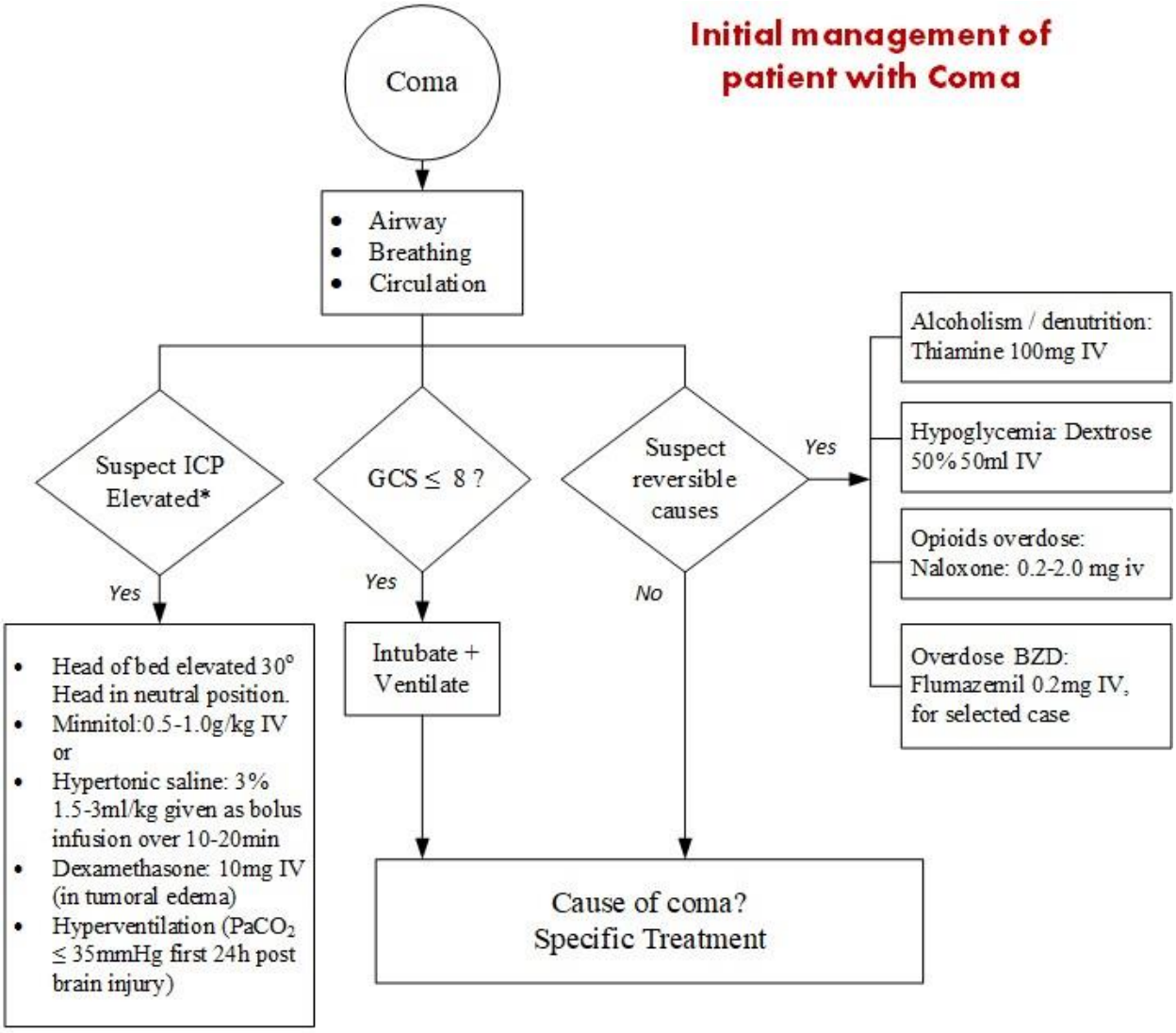
2. For children,

For children consider ingestions (intoxication), infections, and child abuse in the appropriate clinical setting.

3. nonconvulsive status epilepticus or subtle status epilepticus

A state of electromechanical dissociation of the brain and body after seizure. If the motor activity of the seizure stops and the patient does not awaken within 30 minutes, then consider nonconvulsive status epilepticus. Obtain neurologic consultation and electroencephalography.

Fig. 3_ Decisional tree of initial management



* Signs & symptomes of elevated ICP: severe headache, nausea-vomiting, blur vision, altered consciousness, pupillary dilated or unequal.
Note: some author recommend head of bed elevation ≥ 45°, HS: 3% dose 2.5-5ml/kg given in 15-20min

IX. EVOLUTION AND PROGNOSIS

The evolution and prognosis of coma is varied to its cause. Toxic and metabolic coma usually has better prognosis than structural coma. However, with the delay of treatment metabolic coma will transform to structural coma, e.g., hypoglycemia. In other condition that coma resulted from severe organ dysfunction, e.g., liver encephalopathy, multi-organs system dysfunction, the prognosis is poor.

X. COMPLICATIONS

Coma with GCS lower than 8 usually had a depressed ventilation; The resulting hypercapnia induced cerebral vasodilatation and elevation of intracranial pressure. In acute phase of head trauma patient often had a vomit that risks aspirated and compromised the airway. Other complications included, cerebral edema, aspiration pneumonia, bed-sore, deep-vein thrombosis infections, long-term handicaps, and complications link to the cause of coma.

XI. PREVENTION AND RECOMMANDATION

Acute coma is a medical emergency. Coma may be a sign of cardiac arrested; identify early, the first 10-15min is precious time for cardiorespiratory resuscitation (CPR). Coma patient may lose control on his airway and had high risk of aspiration (airway obstruction, pneumonia), put the patient on recovery position or other preventive measures taken. In poisoning, coma is the latest stage of any poison, treat early may prevent it from happen.

XII. REFERENCE

1. M. Kathryn Mutter, J. Stephen Huff, (2020). Altered Mental Status and Coma. In: Judith E. Tintinalli, Editor-in-Chief Emergency Medicine. A comprehensive Study Guide, 9th edition, Mc Graw Hill; p. 1137-42
2. Melissa B. Pergakis, Wan-Tsu W. Chang, (2023), Coma. In : Jean-Louis Vincent, Textbook of Critical Care, 8th Edition; Elsevier, p.264-76
3. Keun Tae Kim, Jae Cheon Jeon, 2022, Etiologies of altered consciousness in the emergency room, Sci Rep. 12: 4972. Published online 2022 Mar 23. Doi: 10.1038/s41598-022-09110-2

ALLERGIC REACTION

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I. DEFINITION

Allergic reaction is a various conditions caused by hypersensitivity of the immune system to typically harmless substances in the environment.

It can be classified into different types based on the underlying mechanisms involved. The four main types of allergic reactions are:

1. Type I (Immediate Hypersensitivity) Reactions:
   - These reactions occur rapidly, within minutes to hours of exposure to the allergen.
   - Examples include allergic rhinitis (hay fever), asthma, food allergies, and anaphylaxis.
2. Type II (Cytotoxic) Reactions:
   - These reactions involve antibodies targeting and attacking cells within the body, leading to cell destruction.
   - Examples include certain drug-induced hemolytic anemia and blood transfusion reactions.
3. Type III (Immune Complex-Mediated) Reactions:
   - These reactions involve the formation of immune complexes that get deposited in tissues, triggering inflammation and damage.
   - Examples include serum sickness and certain autoimmune diseases like lupus.
4. Type IV (Delayed-Type) Reactions:
   - These reactions typically occur 48-72 hours after exposure to the allergen and involve T-cell activation.
   - Examples include contact dermatitis (e.g., poison ivy rash) and certain drug hypersensitivity reactions.

Anaphylaxis is defined as a serious allergic or hypersensitivity reaction that is usually rapid in onset and may cause death.

The term “anaphylaxis” is derived from the Greek words “ana” (against) and “phylaxis” (protection). Anaphylaxis requires urgent recognition and treatment.

II. EPIDEMIOLOGY

The incidence and prevalence of anaphylaxis vary worldwide, with differences dependent on a number of variables. Anaphylaxis is likely underreported as well.

Worldwide incidence: recent studies estimate that the global incidence of anaphylaxis ranges from 50 to 112 episode per 100 000 person-years. Additionally, a population-based analysis found approximately 46 cases of anaphylaxis per 100 000 populations per year.

III. ETIOLOGY

- **IgE Mediated**
  1. Food Triggers: Most commonly peanuts or other nuts, fish or shellfish, eggs and cow’s milk. Asthma and others atopic diseases are a risk factor for food-based anaphylaxis.

2. Drug triggers:
    - Antibiotics: Penicilin-related antibiotics and sulphonamides. Reactions are twice as likely to occur after intravenous or intramuscular administration when compared to the oral route.
    - Other antivirals, antihelminthics and TB medications
    - Muscle relaxants
    - Antineoplastic/cytotoxic/immunomodulators.
3. Insect venom triggers: Bees, wasps, yellow jackets, hornets and fires ants. Venoms-allergic patients respond well to immunotherapy
4. Other triggers
    - Latex
    - Horse derived antitoxins (snake antivenoms)
    - Helminths

- **Non-IgE Mediated**
    1. Immune complex: Blood products, immunoglobulins and dextrans
    2. Non-immunological mast cell activators: Radiocontrast media
    3. Modulators of arachidonic acid metabolism: Aspirin and NSAIDs
    4. Idiopathic
    5. Exercise

IV. PHYSIOPATHOLOGY

The mechanism responsible for most cases of human anaphylaxis involves immunoglobulin E (IgE). Possible alternative mechanisms remain incompletely understood.

The term "anaphylaxis" has traditionally been reserved for **IgE-dependent** events, and the term "anaphylactoid reaction" has been used to describe **IgE-independent** events, although the two reactions are often clinically indistinguishable.

Instead, the World Allergy Organization has proposed that anaphylactic reactions be categorized as **immunologic** and **non-immunologic**.

- Immunologic anaphylaxis is typically described as IgE mediated. The traditional IgE-mediated mechanism of anaphylaxis begins with an antigen binding to an allergen-specific IgE. Antigen-bound IgE in turn binds to the receptor Fc-epsilon-RI on mast cells and/or basophils. This causes these cells to degranulate, releasing a number of inflammatory mediators.
- Non-immunologic anaphylaxis being a result of sudden basophil or mast cell degranulation in the absence of immunoglobulins.

V. DIAGNOSIS

1. **Clinical features**

Anaphylactic reactions vary in duration and severity but typically are rapid in onset with most occurring within 2 hours of allergen exposure. Clinical presentations depend on the degree of hypersensitivity, the quantity, route, and rate of antigen exposure, as well as the target organ sensitivity and responsiveness. Presentations include a combination of clinical characteristics, affecting an array of organ systems including the skin, respiratory tract, gastrointestinal tract, cardiovascular, or the central nervous system.

Clinical manifestations of anaphylaxis	
System	**Signs and symptoms**
ENT	Oropharyngeal or throat fullness Tongue swelling Uvular edema/hydrops
Respiratory	Shortness of breath and/or wheezing Pharyngeal or laryngeal edema Stridor Rhinitis
Cardiovascular	Hypotension Chest pain
Skin	Urticarial and/or angioedema Flushing Pruritus only
GI	Nausea, emesis, cramps, or diarrhea
Neurologic	Headache Seizure

Anaphylaxis is predominately a clinical diagnosis. Criteria for defining anaphylaxis were developed in 2004 by a panel of experts at the National Institutes of Health, which resulted in the publication of the NIAID/Anaphylaxis Network Definition of Anaphylaxis.

Clinical criteria for diagnosis anaphylaxis
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, or swollen lips-tongue-uvula) and at least one of the following: a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, or hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, or incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, or swollen lips-tongue-uvula) b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, or hypoxemia) c. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, or incontinence) d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain or vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP b. Adults: systolic BP of <90mmhg or greater than 30% decrease from that person's baseline

2. **Investigation**
    - There are currently no biomarkers or laboratory tests that can resolutely confirm or refute the diagnosis and no biomarker that increases in concentration irrespective of trigger.
    - Tryptase levels
        - These are now recommended for patients presenting with anaphylaxis, but this only needs to be done for one episode.

- When present, the degree of rise in tryptase does correlate with severity of the symptoms, but a rise may not be found in all patients.

- Skin prick tests and allergen-specific serum IgE levels can be performed by the allergy specialist after 3–4 weeks to avoid false-positive results.
- Challenge or provocation tests can be performed but should be done with caution in a facility that has the resources to manage any subsequent anaphylaxis.

VI. DIFFERENTIAL DIAGNOSIS

Differential Diagnosis of Anaphylaxis

Acute generalized urticarial
Asthma exacerbation
Myocardial infarction
Pulmonary embolus
Syncope
Adverse cutaneous drug reaction
Anxiety/panic attacks

Flush Syndrome
- Flushing associated with food
- Alcohol
- MSG
- Sulfites
- Scombroidosis
- Carcinoid tumor Peri-menopause
- Thyrotoxicosis
- Basophilic leukemia
- Mastocytosis (systemic mastocytosis and urticaria pigmentosa)
- Vasointestinal peptide tumors

Shock Syndromes
- Septic shock
- Hypovolemic shock
- Cardiogenic shock
- Distributive shock

Miscellaneous
- Hypoglycemia
- Acquired and HAE
- ACE-inhibitor-associated angioedema
- Red man syndrome (Vancomycin)
- Neurologic disorders (seizure, stroke, autonomic epilepsy)
- Vocal cord dysfunction syndrome
- Pheochromocytoma

ACE, Angiotensin-converting enzyme; *HAE,* hereditary angioedema; *MSG,* monosodium glutamate.

VII. MANAGEMENT

1. Objectives

Prompt recognition and initiation of the appropriate interventions remain key in avoiding adverse outcomes. Treatment delays, even by a few minutes, could potentially lead to hypoxia, circulatory collapse, and even death. It is also important to treat anaphylaxis promptly because it appears to be most responsive to treatment in its early phases, based on the observation that delayed epinephrine injection is associated with fatalities.

2. Critical sign

- Cardiovascular system:
  - Myocardial depression
  - Arrhythmias
  - Myocardial ischemia
- Respiratory system:
  - Bronchospasm
  - Laryngeal edema
  - Asphyxia

3. **Mortality risk factor**
   Risk factors for increased anaphylaxis severity and mortality:
   - Very young (under-recognition)
   - Elderly (Decrease physiologic reserves)
   - Comorbid conditions
     - Cardiovascular disease (heart failure, ischemic heart disease, hypertension)
     - Pulmonary disease (asthma, obstructive airway disease)
   - Others:
     - Concurrent use of anti-hypertensive agents, specifically beta-blockers and angiotensin-converting enzyme (ACE) inhibitors
     - Concurrent use of cognition-impairing drugs (e.g., alcohol, recreational drugs, sedatives, tranquilizers)
     - Recent anaphylaxis episode
     - Upright posture at the onset of symptoms

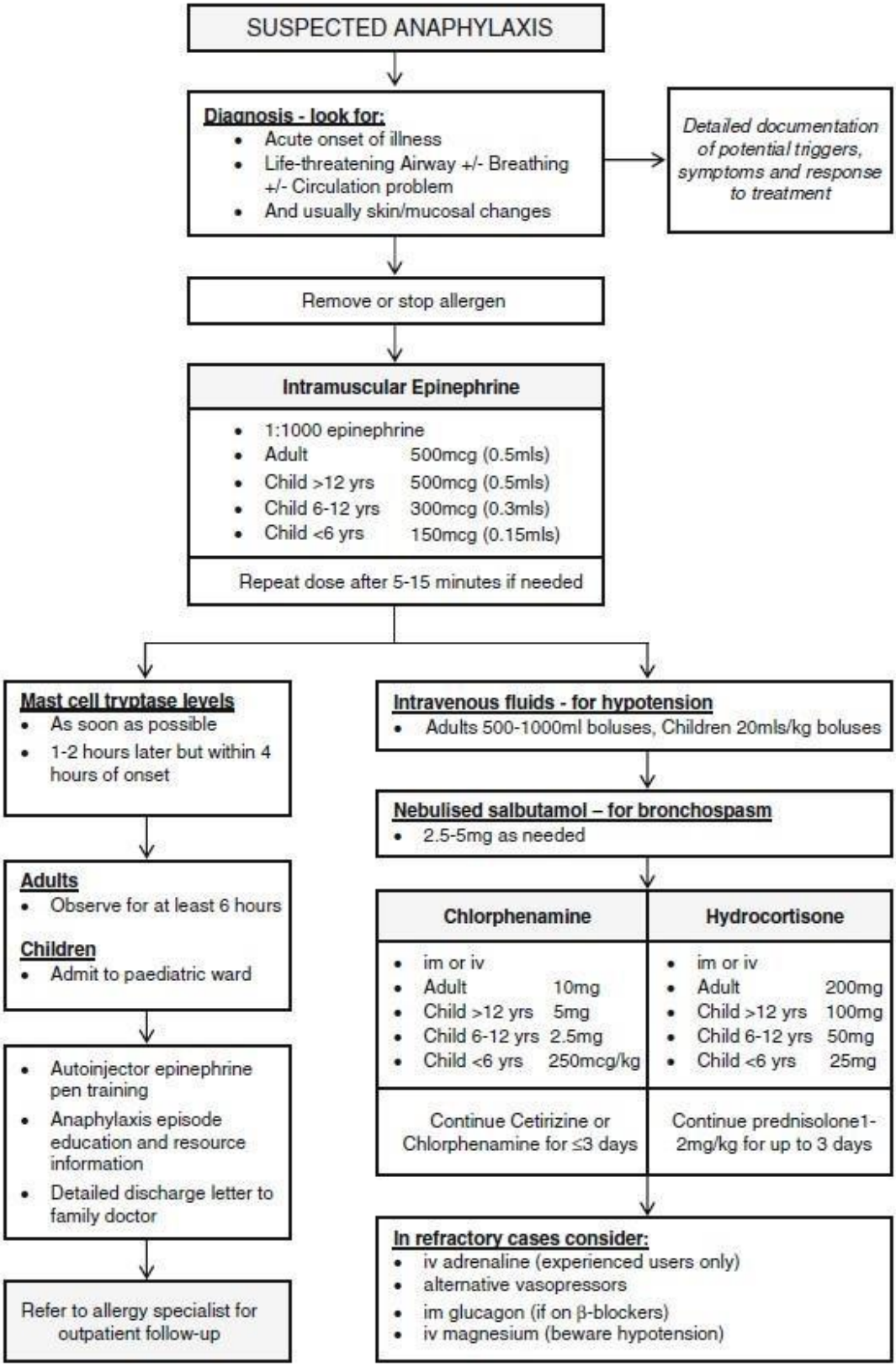
4. **Outpatient Management**
   The cornerstones of initial management are the following.
   - Removal of the inciting cause, if possible (stop infusion of a suspect medication).
   - Call for help
   - Intramuscular (IM) injection of epinephrine at the earliest opportunity, followed by additional epinephrine by IM or intravenous (IV) injection as needed.
   - Placement of the patient in the supine position with the lower extremities elevated, unless there is prominent upper airway swelling prompting the patient to remain upright (and often leaning forward). If the patient is vomiting, placement of the patient semi recumbent with lower extremities elevated may be preferable. Place pregnant patients on their left side.
   - Supplemental oxygen.
   - Volume resuscitation with IV fluids.

5. **First line treatment**
   - The first and most important treatment in anaphylaxis is epinephrine. There are no absolute contraindications to epinephrine in the setting of anaphylaxis.
   - **Air way –** Immediate intubation if evidence of impending airway obstruction from angioedema. Delay may lead to complete obstruction. Intubation can be difficult and should be performed by the most experienced clinician available. Cricothyrotomy may be necessary.
   - **IM epinephrine**
     - Adult: give epinephrine 0.3 to 0.5 mg IM in the mid-outer thigh. Can repeat every 5 to 15 minutes (or more frequently), as needed. If epinephrine is injected promptly IM, most patients respond to 1, 2, or at most, 3 doses. If symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion.
     - Pediatric: 0.01mg/kg (0.01ml/kg of 1:1000 dilution).
   - **Position –** Place patient in recumbent position, if tolerated, and elevated lower extremities
   - **Oxygen – Give 8-10l/MN** via facemask or up to 100% oxygen, as needed.

- **Normal Saline or Ringer lactate rapid bolus –** Rapid infusion of 1 to 2 liters IV or 10-20ml/kg in pediatric. Repeat, as needed. Massive fluid shifts with severe loss of intravascular volume can occur. Monitor urine output.

6. **Treatment adjustment**
   - **Albuterol (salbutamol) –** For bronchospasm resistant to IM epinephrine.
     - Adult: 2.5-5mg in 3 mL saline via nebulizer, or 4 to 6 puffs by metered dose inhaler (MDI). Repeat every 20mn as needed.
     - Pediatric: 1.25-2.5mg nebulized, or 4-6 puffs from MDI with holding chamber. Repeated every 20mn as needed
   - **H1 antihistamine –** for relief of urticarial and itching only.
     - Adult: Cetirizine (Zyrtec) 10 mg IV or chlorpheniramine 10mg IM/IV or diphenhydramine (Polaramine) 25 to 50 mg IV/IM/PO.
     - Pediatric: Diphenhydramine (Polaramine) 1mg/kg IV/IM/PO.
   - **H2 antihistamine –** for relief of urticarial and itching only.
     - Adult: Famotidine 20 mg IV or cimetidine 300mg or Ranitidine 50mg IV.
     - Pediatric: Ranitidine 0.5mg/kg IV or Cimetidine 4-8mg/kg IV.
   - **Glucocorticoid –** for prevention of protracted and biphasic reactions.
     - Adult: Methylprednisolone 80-125mg IV or hydrocortisone 250-500mg IV.
     - Pediatric: Methylprednisolone 1-2mg/kg IV or hydrocortisone 5-10mg/kg IV.
   - **Magnesium sulfate –** for treatment of bronchospasm.
     - Adult: 2g IV over 20mn.
     - Pediatric: 25-50mg/kg IV.
   - **Glucagon –** for treatment of patient on beta-blockers with refractory hypotension.
     - Adult: 1mg IV every 5mn until hypotension resolves followed by 5-15 mcg/mn infusion.
     - Pediatric: 50mcg/kg every 5mn.
   - **Monitoring –** Continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed. Urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock.

7. **Algorithm**


SUSPECTED ANAPHYLAXIS
Diagnosis - look for:
Acute onset of illness
Life-threatening Airway +/- Breathing +/- Circulation problem
And usually skin/mucosal changes
Detailed documentation of potential triggers, symptoms and response to treatment
Remove or stop allergen
Intramuscular Epinephrine
1:1000 epinephrine
Adult 500mcg (0.5mls)
Child >12 yrs 500mcg (0.5mls)
Child 6-12 yrs 300mcg (0.3mls)
Child <6 yrs 150mcg (0.15mls)
Repeat dose after 5-15 minutes if needed
Mast cell tryptase levels
As soon as possible
1-2 hours later but within 4 hours of onset
Adults
Observe for at least 6 hours
Children
Admit to paediatric ward
Autoinjector epinephrine pen training
Anaphylaxis episode education and resource information
Detailed discharge letter to family doctor
Refer to allergy specialist for outpatient follow-up
Intravenous fluids - for hypotension
Adults 500-1000ml boluses, Children 20mls/kg boluses
Nebulised salbutamol – for bronchospasm
2.5-5mg as needed
Chlorphenamine
im or iv
Adult 10mg
Child >12 yrs 5mg
Child 6-12 yrs 2.5mg
Child <6 yrs 250mcg/kg
Hydrocortisone
im or iv
Adult 200mg
Child >12 yrs 100mg
Child 6-12 yrs 50mg
Child <6 yrs 25mg
Continue Cetirizine or Chlorphenamine for ≤3 days
Continue prednisolone1-2mg/kg for up to 3 days
In refractory cases consider:
iv adrenaline (experienced users only)
alternative vasopressors
im glucagon (if on β-blockers)
iv magnesium (beware hypotension)

VIII. SPECIAL CASE

1. **Urticarial and Angioedema**

Urticarial is commonly encountered in the ED. It is characterized by the presence of wheals, angioedema, or both. Urticarial appears as papules or wheals that consist of central swelling with surrounding reflex erythema and is associated with itching or a burning type sensation. These lesions are a result of mediators (predominately histamine) released from mast cells. They tend to occur on the extremities and are usually transient, with skin often returning to its normal appearance within 24 hours. Urticarial can be classified based on its duration, with acute urticarial lasting less than 6 weeks and chronic episodes lasting longer than 6 weeks. There are also several types of inducible urticarial including cold contact, delayed pressure, heat contact, solar, aquagenic, or cholinergic.

Angioedema is characterized by edema of the subcutaneous or submucosal tissues, commonly involving the face, mouth, lips, tongue, extremities, or genitalia. It is a result of abrupt vasodilation and increased vascular permeability, allowing fluid to move from the vascular to the interstitial space. As the swelling is located in the deeper layers of the skin, the appearance is often normal in color and patients often complain of pain or a pressure sensation, rather than an itch. Of particular concern is when the tongue, posterior pharynx, or larynx is involved, which could progress to airway obstruction and compromise. Angioedema can be mediated by an allergic mechanism in response to exposure to foods, drugs, or physical stimuli or by a nonallergic mechanism such as Hereditary Angioedema (HAE), acquired angioedema, or ACE-inhibitor- induced angioedema.

2. **Management**

Angioedema with urticarial without airway threatening:

- H1-Antihistamine: cetirizine, loratadine, fexofenadine or Diphenhydramine
- H2-Antihistamine may also beneficial: Famotidine, Ranitidine or Cimetidine.
- Corticosteroids: prednisone as a second-line therapy
- Epinephrine: anaphylactic dosing for severe symptoms and no cardiac risk factors.
- Avoid exposure to potential triggering agents.

Angioedema with airway-threatening:

- Epinephrine at anaphylactic doses.
- Antihistamines
- Intubation if situation required and paralytics should be utilized with caution.
- Prepared for difficult airway algorithm using alternative measures (fiber optic laryngoscopy, surgical airway).

IX. EVOLUTION AND PROGNOSIS

- Biphasic reaction: reoccurrence of anaphylactic symptoms without re-exposure to the triggering agent within 8 hours to 72 hours.
- Prevention by administer corticosteroids but recent studies have failed to show significant effect.
- Risk factor for biphasic reactions include
  - Hypotension
  - Wide pulse pressure
  - Unknown trigger
  - Greater than 1 dose of epinephrine
  - Cutaneous signs and symptoms, prior anaphylaxis
  - And delayed epinephrine administration.

- Patients should be monitored for a minimum of 6 h after resolution of symptoms. This observation period may need to be longer depending on the presence of any of the following high-risk features:
  - Extremes of age
  - Significant co-morbidity
  - Severe reaction with slow onset
  - Severe asthma
  - Likely continued absorption
  - History of significant biphasic reaction
  - Evening or night presentation
  - Difficulty accessing emergency care
- Hospitalization should be strongly considered for patients who present with protracted anaphylaxis, hypotension, or airway involvement; receive more than two doses of IM epinephrine; or have poor outpatient social support, or inability to acquire an auto-injectable epinephrine device.

X. COMPLICATION

The main complications which can occur following an anaphylactic reaction include:

- Wheeze
- Stridor
- Hypoxemia
- Hypotension
- End-organ dysfunction
- Death

XI. PREVENTION AND RECOMMENDATION

Anaphylaxis is a potentially life-threatening allergic condition which can present with multiple symptoms.

Anaphylaxis should be treated with intramuscular epinephrine, supportive management, and adjunct medications as needed. The mainstay of management is avoidance of triggers and to carry an epinephrine auto-injector.

A prescription for an epinephrine auto-injector should be provided following treatment of anaphylaxis, and training should also be provided regarding its use. Patients should also be assessed and followed by an allergist.

XII. REFERENCES

1. Cardona V, Ansotegui IJ, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J 2020; 13:100472.
2. Anne K.Ellis, editor. Anaphylaxis A Practical Guide. Springer Nature Switzerland AG, c2020.
3. Rudders SA, Arias SA, Camargo CA Jr. Trends in hospitalizations for food-induced anaphylaxis in US children, 2000–2009. J Allergy Clin Immunol. 2014;134(4):960–2, e3.
4. Suresh S.David, Clinical Pathways in Emergency Medecine. Rosie F, editors. Anaphylaxis. Volume 1. India Springer; c2016. P. 19-30.
5. Rosen's, Emergency Medecine Concepts and Clinical Practice. Aaron N, Barksdale, Weston R, editor. Allergy, Anaphylaxis, and Angioedema. 10th ed, vol 1. St. 1600. Philadelphia: Elsevier; c2023. P1416-1427.
6. Tintinalli's, Emergency Medicine. Brian H, Brian G, editor. Allergy and Anaphylaxis. 9th ed. United States: Mc Graw Hill, c2020. P68-73.

GENERAL MANAGEMENT OF POISONING

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I. DEFINITION

Poisoning or intoxication is a serious condition that occurs when a person or an animal is exposed to a substance that can harm their health or even kill them.

II. EPIDEMIOLOGY

An epidemiological Surveillance report 2011 in Thailand found that the incidence of environmental pesticide poisoning is 3.20 per 100.000 person. The incidence of prescribed drugs poisoning is 3.81 and the intentional ingestion of toxic substances is 5.91 per 100.000. In Singapore, the incidence of alcohol consumption-related ED visit was remarkably increased from 48.7 per 100.000 person (in 2007) to 79.1 per 100.000 person (in 2016).

III. ETIOLOGY

Poisoning may be “acute” (occurs a few hours to few days after exposure) or “Chronic” (problems occur after repeated and long-time exposure). In emergencies most of the intoxication cases was acute poisoning. Intoxication or poisoning may be intentional or non-intentional. Intentional poisoning: suicide attempt, self-harm, abuse, misuse. Non-intentional poisoning: error dose, accidental, environmental toxics (air pollution, arsenic in water...), occupational poisoning, food, drink (methanol poisoning), animal bites. Poison can be a drug that is used in clinic (overdose), food, drink, chemical that use in industrial / agricultural works, or household-use, or biologic (mushroom, some fishes). Exposure route may be inhalation, skin contact, mucous membrane contact, ingestion, or injection. Animals or snakebites were also a kind of poisoning in which the poison or venom were injected into the subcutaneous tissue or muscle during the bite.

IV. PHYSIOPATHOLOGY

To initiate the poisoning, the organism is exposed to the toxic chemical. When a toxic level of the chemical is accumulated in the cells of the target tissue or organ, the resultant injury to the cells disrupts their normal structure or function. Symptoms and toxic signs then develop, and, if the toxicity is severe enough, death may result. Different groups of substances may have different mechanisms of toxicity to human. It may be a Systemic poisoning (Cyanide, lead, warfarin, pesticides), specific organ poisoning (paracetamol-liver, gentamycin-kidney, snake Viperidae-venom-hematologic / snake Elapidae-venom- neurologic), local poisoning (caustic, acid, snake Viperidae-venom), some substances may cause endocrine disruption (DDT, Bisphenol A, Dioxins), some other may be cancerogenic (arsenic-skin, Asbestos-lung, tobacco-lung). Substances belonging to a particular pharmaceutical or chemical class often produce a cluster of symptoms and signs, or

"toxidrome", enabling the identification of potential toxins when a clear history is unavailable.

V. DIAGNOSIS

The diagnosis of poisoning is based on the meticulous history, physical examination and/or toxidrome found in physical exam.

1. Signs & symptoms

The common toxidrome with signs and symptoms are shown in table_ 1

2. Laboratory analysis:

For clinical use, common laboratory tests were order:

- "Basic metabolic panel" for electrolytes (Na, K, Cl, HCO_3, Calcium) plus glucose, urea, creatinine) and to determine anion gap;
- ethanol, acetaminophen (paracetamol), and salicylate concentrations (if overdose is suspected)
- transaminases,
- serum osmolarity if toxic alcohol is suspected;
- blood gas for pH

The specific toxicology screens in general, are of limited utility and seldom impact care and outcome. False negative and positive results on urine drug screening may be confusing and potentially distract the clinician. It was indicated in some specific cases e.g., in mass poisoning or empoisoning cases or when the exact cause of poisoning was necessary.

VI. DIFFERENTIAL DIAGNOSIS

In emergency, one should consider a poisoning as a possible cause of unexplained coma / seizure or shock. In practice, patient who was intentionally poisoning usually take more than one drugs or substances. Besides, in intoxication with some products like insecticides, patient may be intoxicated also with the solvent (petroleum, benzene, xylene) of those products. Many compounds medicine has multiple active ingredients, (e.g., Codalgin® = paracetamol + codeine) so overdose of main component may be associated with others.

In the case of Ethanol, sedative hypnotic or opioids, different scenario may happen, patient may enter ED because, experience side-effects / allergic reaction, or present with toxic effects of overdoses, or withdrawal syndrome. In chronic poisoning, it is a challenge to link a clinical feather to a toxic cause, as it may take several years for the symptoms and signs to be uncovered.

Table-1_ Common toxidrome

Toxidrome physical exam	Cholinergic	Anti-cholinergic	Sympatho-mimetic	opioid	Sedative-hypnotic	Serotonin	Withdrawal opioid	Withdrawal Sedative-hypnotic
Mental status	Awake	Obtunded or delirious	Awake	Depressed	Depressed	Altered mental status, Hypertonia hyperreflexia	Awake	Agitated, awake, delirious
Pupils	Pinpoint Reactive	Dilated Unreactive	Dilated Reactive	Pinpoint reactive	Normal	Dilated	Dilated Reactive	Dilated reactive
Mucous membranes	Wet	Dry	Normal	Normal	Normal		Normal	Normal
Cardiovascular	↓ Heart rate	↑ Heart rate	↑ Heart rate	Normal	Normal	↑ Heart rate Dysrhythmia	Normal	↑ Heart rate
Pulmonary	Wheeze, rhonchi ↑Respiratory rate	Normal	Normal	↓Respiration rate ↓ depth of breathing	Normal	Tachypnea	Normal	Normal
Bowel sounds	Increase (↑)	Decrease (↓)	Normal	Decrease (↓)	Normal	Increase (↑)	Increase (↑)	Normal
Bladder	Not palpable	Palpable	Normal	May be palpable	Normal		Normal	Normal
Skin temp	Lower (↓)	Increase (↑)	Increase (↑)	Normal	Normal	Increase (↑)	Normal	Increase (↑)
Skin color	Normal	Flushed	Flushed	Normal or cyanotic	Normal	Flushed	Normal	Normal
Perspiration	Present	Absent	Presence			present		presence
Antidote	Atropine Pralidoxime	Physostigmine	Benzo-diazepines	Naloxone	Flumazenil	Cyproheptadine		Benzodiazepines
Example of substances	organophosphate, carbamates-insecticides, chemical warfare agents (Sarin, VX)	atropine, antihistamines, antipsychotics	Amphetamines, cocaine, Cathinone	codeine, Heroin, morphine	Benzo-diazepines, Barbiturates	SSRIs, MAOIs, TAD, amphetamines, Fentanyl, Bupropion		

SSRIs: Selective serotonin receptor inhibitors, MAOIs: monoamine oxidase inhibitors, TAD: tricyclic antidepressant

VII. MANAGEMENT

1. Objective of management

- Stabilize the vital signs (Resuscitation)
- Identify the substances, the amount, the route, the time of exposure or the present toxidrome.
- Provide antidote, or antivenom, if available
- Decontamination, and/or enhance the elimination.
- Supportive treatment (hypotension, respiratory failure, renal failure)
- Preventive treatment for recurrence poisoning.

2. Critical signs

The severity grading of poisoning depends on whether the poison is stimulant or depressant. Coma and cardiovascular collapse are common in the most severe, grade 4, of stimulant as well as depressant poisoning.

Table 2: Severity grade of poisoning, for stimulant and depressant substances

Physiologic grading of poisoning severity		
Severity	**Stimulant poisoning**	**Depressant poisoning**
Grade 1	Agitation, anxiety, diaphoresis, Hyperreflexia, mydriasis, tremors	Ataxia, confusion, lethargy, weakness, able to follow verbal commands
Grade 2	Confusion, fever, hyperactivity, Hypertension, tachycardia, tachypnea	Mild coma (non-verbal but responsive to pain); brainstem and deep tendon reflexes intact
Grade 3	Delirium, hallucinations, hyperpyrexia, tachyarrhythmias	Moderate coma (respiratory depression, unresponsive to pain); some but not all reflexes absent
Grade 4	Coma, Cardiovascular collapse, seizures	Deep coma (apnea, cardiovascular depression); all reflexes absent

3. Mortality risk factor

Multiple factors contributed to the risk of mortality

- Type of poisoning, intentional (suicide, of empoisoning)
- The dose of poison or duration of exposure to the toxic substances
- The degree or intensity of toxicity of the exposed substances or toxin
- Medical background of intoxicated patient, age group
- The delay of management
- Availability of supportive /substitutive treatment (Hemodialysis, mechanical ventilation)
- Some classical procedures may be harmful (gastric lavage-associated aspiration pneumonia)

4. Out-patient management

Only people who exposed to a known non-toxic substance and asymptomatic may be observed at home and contact with emergency personal for any abnormality.

5. First-line treatment

In all case, consider the supportive treatment first. The shock state, depressed respiration should be the first measure to be taken. If the poison was identified and it has antidote, it should be administered as soon as possible.

A. Gastrointestinal decontamination

i. Gastric lavage

If performed because of a potentially life-threatening poison ingestion, an experienced provider should perform the lavage based on the complications that can occur.

Gastric lavage involves a large-bore (36F–40F) orogastric tube passed into the stomach, after which small volumes (200–300 mL) of liquid are alternately administered and aspirated. Comatose patients and those with loss of their protective airway reflexes should have an endotracheal tube placed before this procedure.

Contraindications include loss of protective airway reflexes (unless the patient is endotracheally intubated), ingestion of a corrosive substance or a hydrocarbon, gastrointestinal pathology, and other medical conditions that could be worsened by the use of lavage. Complications of the procedure include aspiration, laryngospasm, hypoxia, hypercapnia, mechanical injury, and fluid and electrolyte imbalances in children.

ii. Single dose activated charcoal

Administration of activated charcoal may be considered if a patient has ingested a potentially toxic amount of poison that is known to be adsorbed to charcoal not longer than 1 hour before treatment, as its effectiveness decreases over time. There is no evidence that the administration of activated charcoal improves outcome.

The dose is 1 gram/ kilogram in children or 25 to 50 grams in adults. The minimal dose should be no less than a 10:1 ratio of AC to drug Same contraindication as gastric lavage.

iii. Whole-bowel irrigation

Whole-bowel irrigation consists of administration through a nasogastric tube of an osmotically balanced, polyethylene glycol–based electrolyte solution to decontaminate the entire gastrointestinal tract by physically expelling intraluminal contents. As much as 1500–2000 mL/hr can be administered to an “awake” adult patient.

Whole-bowel irrigation should not be used routinely in the poisoned patient. However, it can be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs and for drugs not likely to be adsorbed to activated charcoal (iron, lithium, potassium) and for the removal of illicit drug packets. Contraindications include bowel

pathology, unprotected or compromised airway, hemodynamic instability, and intractable vomiting. Complications are nausea, vomiting, and abdominal cramps.

iv. Multiple-dose activated charcoal

Multiple-dose activated charcoal decreases the re-absorption blood-enteral, also interrupts the enterohepatic and enterogastric circulation of drugs. Drugs with a prolonged elimination half-life, a small volume of distribution (less than 1 L/kg), and little protein binding are the most amenable to this sort of management. Multiple-dose activated charcoal should be considered if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. With all of these drugs, data confirm enhanced elimination, although no controlled studies have demonstrated clinical benefit.

The initial dose of charcoal is 50–100 g, and this treatment is followed every 1, 2, or 4 hours by a dose equivalent to 12.5 g/hr. More frequent, smaller doses may prevent vomiting. Multiple-dose activated charcoal can be continued until the patient improves clinically. Complications include bowel obstruction and vomiting with subsequent aspiration.

B. Urinary alkalinization

Urinary alkalinization is the administration of intravenous (IV) sodium bicarbonate to produce urine with a pH ≥7.5. The objective of treatment is pH manipulation, not forced diuresis. Hypokalemia is the most common complication. Alkalemia also can occur. Urinary alkalinization should be considered as first-line treatment in patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis. Urinary alkalinization is not recommended as first-line treatment for cases of phenobarbital poisoning, because multiple-dose activated charcoal is superior.

C. Ipecac and emetics

There is no role for syrup of ipecac in the hospital setting.

D. Antidote

Not all substances have their antidote. Table 2 shows Common antidotes used in Clinical practice. Outside the poison center, only a few are available.

Table 3_ common antidotes

CHEMICALS AND SPECIFIC ANTIDOTES

Agent / condition	Antidotes
Acetaminophen	N-acetylcysteine
Anticholinergic poisoning	Physostigmine
Anticoagulants (warfarin/heparin)	Phytonadione (vit. K) / protamine
Dabigatran	Idarucizumab (Praxbind)
Rivaroxaban, Apixaban	Andenaxet alfa
Benzodiazepines	Support care, Flumazenil
Botulism	Botulinum antitoxin
Beta-adrenergic antagonists	Glucagon, calcium salts
Calcium channel blockers	Calcium salts, Glucagon
Carbone monoxide	Oxygen, hyperbaric oxygen
Cholinergic syndrome	Atropine, pralidoxime
Cyanide	Nitrites, thiosulfate, hydroxocobalamin
Digoxin (digitalis)	Fab antibody fragments, magnesium
Dystonic reactions	Benztropine, diphenhydramine
Ethylene glycol	Ethanol, 4-methylpyrazole, pyridoxine, vit. B1
Envenomation (arthropod, snake)	Antivenins
Fluoride	Calcium and magnesium salts
Heavy metals (arsenic, mercury, lead)	Dimercaprol (BAL), D-penicillamine, calcium disodium, EDTA, DMSA
Hydrogen sulfide	Oxygen, nitrites
Iron	Deferoxamine
Isoniazid (hydrazines)	GABA agonists, pyridoxine
Methanol	Ethanol, 4-methylpyrazole, folate
Methemoglobinemia	Methylene blue
Opioids	Naloxone, nalmefene, naltrexone
Sympathomimetics	Adrenergic blockers
Tricyclic antidepressants	Sodium bicarbonate
Vacor (N-3-pyridylmethyl-N-p-nitrophenylurea)	Nicotinamide (niacinamide)

DMSA: Dimercaptosuccinic acid, EDTA: ethylenediamine tetraacetic acid, BAL: British antilewisite

Table-4_ Posology of antidotes use for acute poisoning

Common Antidotes used in Resuscitation of acutely poisoned Patient.

Antidote	Initial pediatric dose	Initial adult Dose	indication
Calcium chloride 10% 27.2mg/ml. element Ca	0.15 ml/kg IV	10 ml IV	Calcium channel blockers
Calcium gluconate10% 9mg/ml. elemental Ca	0.5 – 0.45 ml/kg IV	10–30 ml IV	Hypermagnesemia Calcium channel blockers
Cyanide antidote kit Amil nitrite	Not typically used	Crack vial and inhale over 30sec or place in chamber of ventilation bag and use 30sec on / 30sec off	Cyanide
Sodium nitrite (3% solution)	Dose according to hemoglobin level. If unknown assume Hb level is 12 g/dl and dose with 0.33ml/kg IV	10 ml IV	Cyanide Hydrogen sulfide (use only sodium nitrite)
Sodium thiosulfate (25% solution)	1.65 ml/kg IV	50 ml IV	Cyanide
Dextrose (glucose)	0.5-1.09 g/kg IV	1g /kg IV	Insulin Oral hypoglycemics
Digoxin Fab Acute toxicity	5-10 vials IV	10 vials IV	Digoxin and other cardioactive steroids
Flumazenil	0.01 mg/kg IV	0.2 mg IV	Benzodiazepines
Glucagon	30 micg/kg IV over 1-2 min for CCB toxicity and 30 -150 micg/kg IV over 1-2 min for BB toxicity	5 mg IV	Calcium Channel blockers Beta-blockers
Hydroxocobalamin	70 mg/kg (max. 5g) IV over 15min	5g IV over 15 min	Cyanide, Nitroprusside
IV lipid emulsion 20%	1.5 ml/kg IV bolus over 1min (may be repeated 2 times at 5 min interval), followed by 0.25ml/kg/min IV infusion for 20min	100 ml IV bolus over 1min (may be repeated 2 times at 5 min intervals), followed by 18ml/min IV infusion for 20min	Local anesthetic systemic toxicity Rescue therapy for lipophilic cardiotoxins
Methylene blue	1 mg/kg IV Neonates: 0.3-1.0 mg/kg IV	1 mg/kg IV	Oxidizing toxins (e.g. nitrites, benzocaine, sulfonamides)
Naloxone	As much as required. Start: 0.01 mg IV	As much as required Start 0.1- 0.4 mg	Opioid Clonidine
Pyridoxine	g for g if amount of isoniazid ingested is unknown, otherwise:		Isoniazid
	70 mg/kg IV (max. 5g)	5 g IV	

Sodium bicarbonate	1-2 mEq/kg IV over 1-2min followed by 0.3 mEq/kg/h IV infusion		Sodium channel blockers Urinary alkalinization
Thiamine	5-10 mg IV	100 mg IV	Wernicke's syndrome Wet beriberi

E. Other treatments procedures

According to its molecular properties, some substances can be removed from the body by different modalities of extra corporeal epuration. (Table 6)

Table-5_ Indication of extracorporeal Support, dialysis and hemoperfusion

Hemodialysis	**Hemoperfusion**	**Plasmapheresis**	**ECMO**
Methanol	Theophylline	Tricyclic antidepressants	Amiodarone
Ethylene glycol	Phenobarbital	Thyroxine	Beta-blocker
Boric acid	Phenytoin	Heavy metals	Calcium channel blockers
Salicylates	Carbamazepine	Theophylline	Opioids
Lithium	Paraquat		Organophosphorus
	Glutethimide		Paraquat
			Tricyclic antidepressants

ECMO: Extra corporeal membrane oxygenation

F. Supportive / substitution treatment

Supportive treatment is essential; in many situations it was the only feasible measure in poisoning management. Most of the substances do not have their antidote. The decontamination and enhanced elimination process were useful in limited cases only. Even the antidote is available and administered, it takes time for the organ dysfunction to reverse, during this time supportive measures is also needed. E.g., in cobra-snakebites, patient may have respiratory depressed or arrest while antivenom was administered. It takes a few hours for spontaneous respiration to re-appear. The active supportive treatment consists of maintaining the normal water, electrolytes acid-base equilibrium, a good oxygenation and perfusion; sometimes mechanical ventilation, hemodialysis and pharmacologically cardiac support were needed.

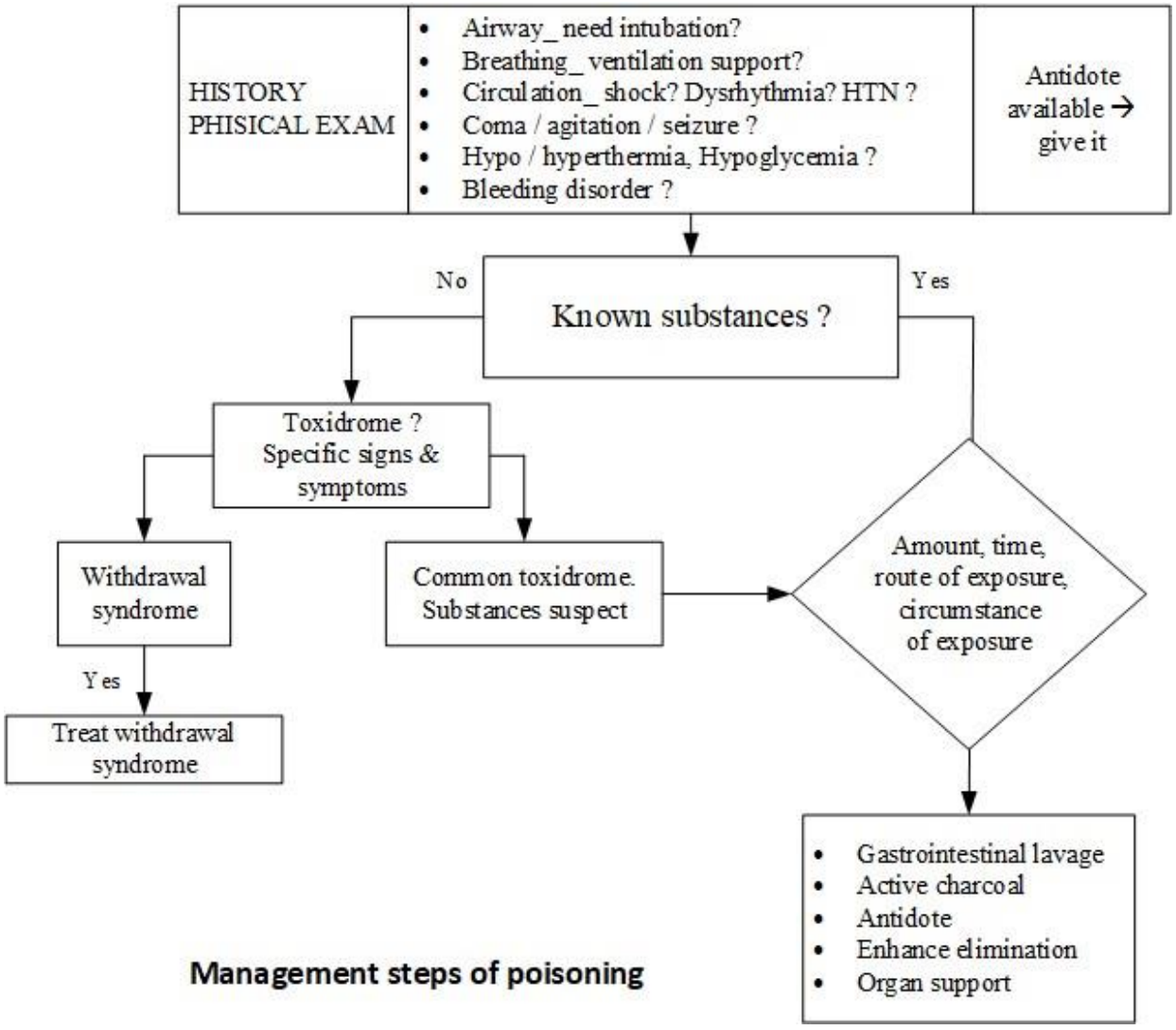
6. Treatment adjustment

In general, gastric lavage is not recommended when the patient arrived later than 1 hour after ingested the substances, it should be possible to try in case the patient took a large quantity of substance or/and the substance is known to slow the peristaltic. For the corrosive substance or a hydrocarbon, the gastric lavage is not recommended. For patient whose consciousness is altered, intubation and ventilation support should be done prior to lavage.

7. Decisional tree (graphic-1)

While taking history and physical examination, the treatment of vital signs disorders is starting. Once a poisoning or overdose has been identified, management can be determined. Management options can include gastrointestinal decontamination, enhancing elimination, and/or use of antidotes. Additionally, some poisonings and overdoses only require supportive care.

Graphic 1: Management step for poisoning



Management steps of poisoning

VIII. SPECIAL CASE

1. Poisoning during pregnancy

Intoxication during pregnancy can be a serious health concern for both the mother and the baby. Drinking alcohol during pregnancy can cause premature labor, miscarriage, stillbirth, and a range of developmental, physical, mental, and emotional disabilities and disorders in the baby. The effects of intoxication on a developing fetus can vary greatly depending on several factors, including the type of substance used, the amount ingested, and the gestational age of the fetus.

- First trimester of pregnancy: Intoxicants can disrupt organogenesis process, leading to birth defects, developmental delays, and miscarriage.
- Second trimester: _ growth and development. Exposure to toxins can affect weight, height, and brain development. Risk of cleft palate or other facial malformations
- Third trimester: brain development may interfere by intoxication, risk of premature birth.

Management of acute poisoning in pregnant women follow the same principle.

2. Poisoning in children

Children 1-3 years old are prone to acute poisoning. Children's bodies are still developing, and their brains are particularly sensitive to the effects of alcohol and drugs. Even small amounts can cause significant harm. For some substances they are more vulnerable than adult, e.g., lead poisoning. Young children (age 6 months to 7 years) are at the highest risk due to their developing brains and bodies, which readily absorb lead. Effects can range from developmental delays and learning difficulties to behavioral problems, anemia, and even coma in severe cases. Lead poisoning (chronic poisoning) can also affect growth and stature, hearing, and kidney function.

IX. EVOLUTION AND PROGNOSIS

The evolution and prognosis of patients who are intoxicated can vary widely, depending on the substance involved, the amount ingested, the patient's overall health, and the timeliness and effectiveness of treatment. With proper management, most intoxication patients gradually improve and regain consciousness. Patient who repeatedly intentional intoxicate should be checked and follow up with psychiatric.

X. COMPLICATION

In acute poisoning, the complications link to intrinsic effect of substances may consist of, seizures, coma, shock, acute respiratory failure, acute kidney failure, acute liver failure and death. Complications may be link to the supportive procedures like mechanical ventilation or hemodialysis. In chronic exposure to toxic substances, long-term complications may be serious e.g., alcohol may lead to liver cirrhosis or/and liver cancer. Chronic exposure to Lead in small children may develop a learning difficulty, behavioral problems, affect growth and kidney function, anemic and hearing problem.

XI. PREVENTION AND RECOMMENDATION

- Store chemicals and medications safely.
- Read and follow instructions carefully
- Dispose of old or unused products and dangerous substances responsibly
- Install childproof safety latches
- Educate children about the dangers of poisoning
- Advocate for proper labeling and packaging
- Do not forcing patient to vomit by any mean; do not try to neutralize the toxic effects by forcing patient to swallow the solution (lemon and sugar) especially when his/her mental status was altered.

XII. REFERENCE

1. Shaun Green. (2020), General management of Poisoned Patients in: Judith E. Tintinalli. Emergency medicine. A comprehensive study guide 9th edition Mac Graw Hill; P. 1187-94
2. Brenna Farmer, (2023). Poisoning: Overview of approaches for evaluation and treatment in: Jean-Louis Vincent, Frederick A. Moore Rinaldo Bellomo, john j. Marini. Textbook of Critical Care, 8th Edition Elsevier; p 1123-30
3. "Annual epidemiological surveillance report 2011," Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, 2011, http://www.boe.moph.go.th/Annual/AESR2011/index.html.
4. Zhenghong Liu 1, Desmond Ren-Hao Mao,2022, Nationwide Alcohol-related visits In Singapore's Emergency departments (NAISE): A retrospective population-level study from 2007 to 2016, Drug Alcohol Rev 2022 Jul;41(5):1236-1244. doi: 10.1111/dar.13472.

PARACETAMOL POISONING

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I. DEFINITION

A disorder characterized by hepatic necrosis following large acetaminophen (or Paracetamol) ingestions.

II. EPIDEMIOLOGY

In USA, hospitalizations due to acetaminophen toxicity from 1998 to 2011 were 67% due to intentional ingestion, 16% from unintentional ingestion, and 17% unspecified.

Of the hospitalizations related to acetaminophen toxicity, 83% were primarily adults and 69% were female (95% CI 0.68–0.69%). From 2008 to 2012, about 49% of unintentional acetaminophen-related poison-control calls were regarding children aged ≤5 years.

In Thailand, among 184 patients with paracetamol overdosed, had median age 22 (15- 76), 79.9% was female. Most overdoses were intended self-poisoning (90.8%) with a median dose of 10.5g (4.5-50). Overall, 15.6% developed severe hepatotoxicity and 3 patient developed acute liver failure.

III. ETIOLOGY

Paracetamol preparation has many forms:

-Rapid-release form_ onset of action: 10-30min, duration of action: 4-6h; half-life: 2-3h

-Extend-release form_ onset of action: 30-60min, duration of action: 8-12h

-Paracetamol combined formular_ associated with opioids (e.g., Codalgin®) or caffeine (e.g., Kinal®) to increase its strength. Some flu-medicines may include with paracetamol, pseudoephedrine, antiallergic, dextromethorphane in their constituents.

Mode of poisoning:

-poisoning from a single large dose, or

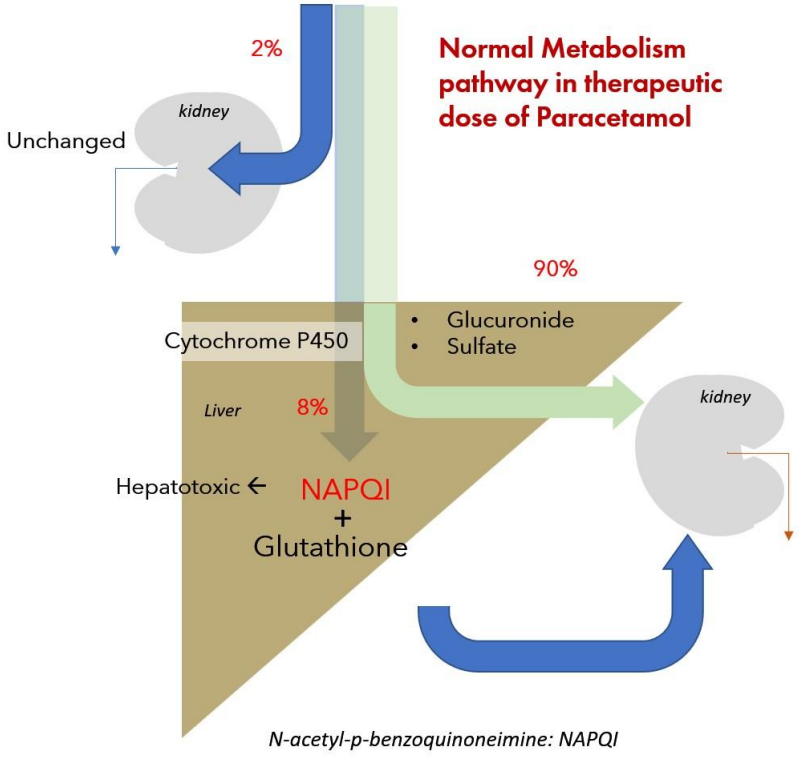
-prolong-repeat of mild overdose or

-normal therapeutic dose in patients with liver disorders or malnourished alcoholism.

IV. PATHOPHYSIOLOGY

In a therapeutic dose and normal people, paracetamol is safe. About 2% of administered dose exit unchanged in urine. About 98% is metabolized in the liver. More than 80% by conjugated with glucuronide or sulfate to form a non-toxic fraction that eliminate by urine. About 8% of administered dose metabolized with cytochrome P450 enzymes to produce N-acetyl-p-benzoquinoneimine (NAPQI). NAPQI is a by- product, toxic to the liver. In normal people, this product existed in a very short time without any harm to the liver. It was combined by liver glutathione to form a non-toxic NAPQI and eliminate in urine. In the situation of toxic overdose, the metabolism pathway with

glucuronide and sulfate is saturated, the CYP450 pathway increased, more NAPQI was produced; when Glutathione is not enough, NAPQI will damage the liver.



Graphic-1: mechanism of paracetamol intoxication

V. DIAGNOSIS

Diagnosis of paracetamol poisoning is based on history, clinical signs with blood-paracetamol concentration assessment.

Signs and symptoms of paracetamol poisoning develop over the first 24 hours following large ingestions. Symptoms may develop gradually in those with a history of long-term ingestion near supratherapeutic doses

A toxic exposure to acetaminophen is suggested when a patient ≥6 years old ingests:

(1) >10 grams or 200 milligrams/kg as a single ingestion,

(2) >10 grams or 200 milligrams/kg over a 24-hour period, or

(3) >6 grams or 150 milligrams/kg per 24-hour period for at least 2 consecutive days.

For children <6 years old,

ingestion of 200 milligrams/kg or more of acetaminophen as a single ingestion or over an 8-hour period, or of 150 milligrams/kg per 24-hour period for the preceding 48 hours is considered a toxic exposure.

These values are empiric and not validated in human trials, but they are widely used as recommendations for emergency evaluation.

I. Clinic

Presentation of symptoms varies and is divided into four stages:

Stage 1—first 24 hours after ingestion

- Patients may be asymptomatic in the first 8 hours following ingestion.
- Symptoms may include nausea, emesis, anorexia, and diaphoresis.
- Laboratory results are usually unremarkable at this time.

Stage 2—days 2 to 3 following ingestion

- Typically, less nausea, vomiting, diaphoresis, and malaise than in stage 1; right upper quadrant pain and hepatomegaly may become evident.
- Elevated aminotransferases are usually seen.

Stage 3—days 3 to 4 following ingestion

- Stage I symptoms such as nausea, vomiting, and malaise reappear.
- Severe poisonings may result in jaundice, confusion, somnolence, and coma.
- Marked liver enzyme elevations which usually peak at this point; prolonged prothrombin time (PT)/international normalized ratio (INR); typically, negative acetaminophen levels.
- Multiorgan failure and death most commonly occur in this stage.

Stage 4—days 5+ after ingestion

- Possible recovery stage in patients with resolving stage 3 symptoms.
- recovery may be prolonged but is typically complete and without long- term sequelae.
- Laboratory abnormalities typically resolve.
- Fulminant hepatic failure occurs in <1% of adults and is very rare in children <6 years of age.

2. Investigation

Plasma acetaminophen level is an essential laboratory test that help decide to use antidote early, before the liver injury occurred. Draw plasma acetaminophen levels on all patients ≥ 4 hours after ingestion (levels peak at 4 hours). Draw additional levels at 6 and 8 hours if extended-release form was ingested. Plot the result on the paracetamol nomogram and see if it is above the treatment line? (See Graphic-2) Liver functions test: alanine transaminase (ALT), aspartate transaminase (AST), PT/INR, bilirubin, lactate dehydrogenase (LDH) is important, but it usually evident after 24h post ingestion.
Additional labs: electrolytes, glucose, BUN, creatinine, urinalysis, serum alcohol, and salicylate

VI. DIFFERENTIAL DIAGNOSIS

Consider the presence of co-ingestants, especially alcohol, opiates, and aspirin.

Other ingested toxins that produce severe acute hepatic injury include mushrooms, products containing yellow phosphorus or carbon tetrachloride. Consider other causes of hepatitis: alcoholic, viral, ischemic

VII. MANAGEMENT

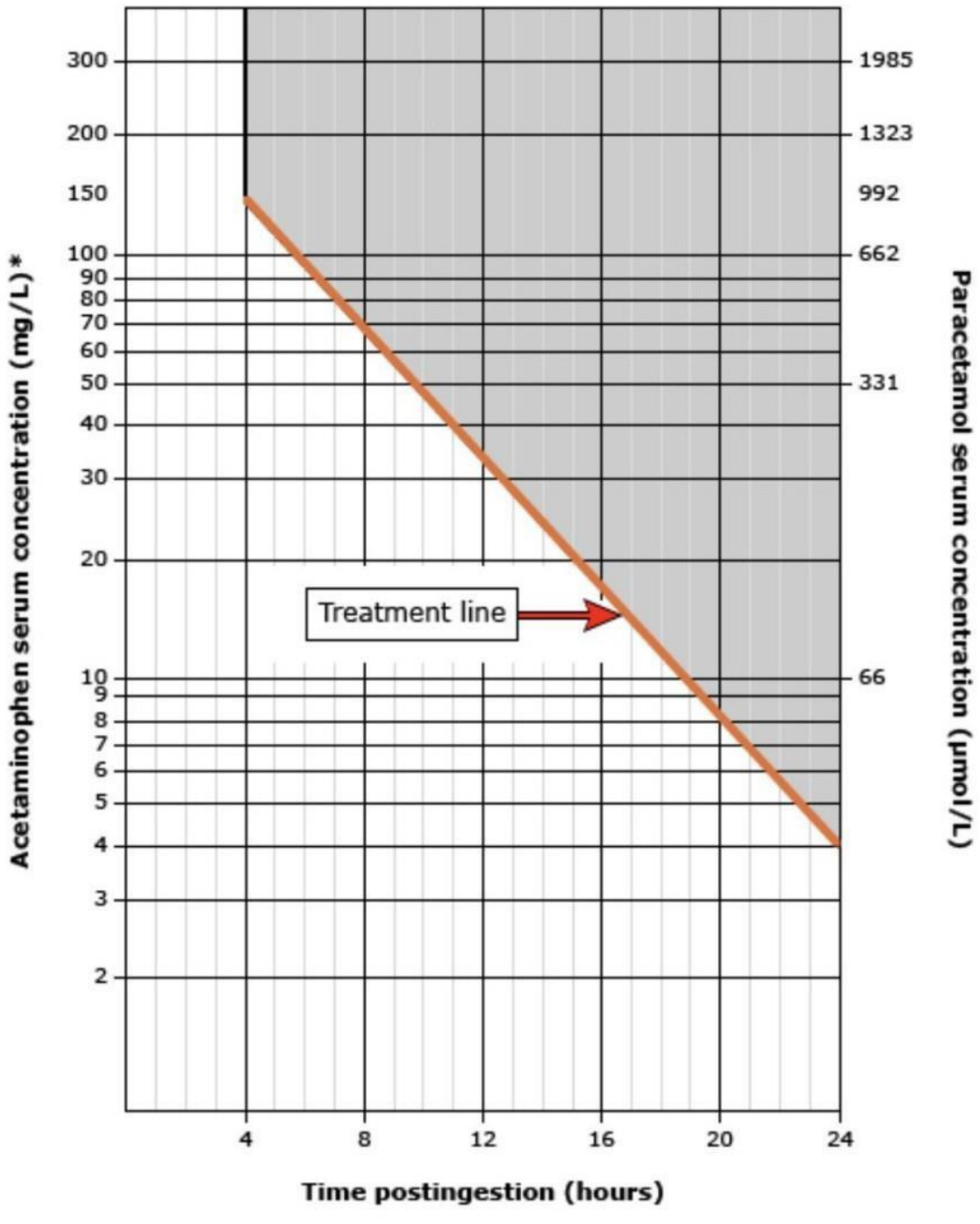
1. Objectives of management
- Stabilized the vital signs
- Check if patient needs antidote & administer NAC as soon as possible
- Supportive treatment

2. Critical Signs

Hepatic encephalopathy, fulminant liver failure,
Hight Transaminase elevation (ALT or SLT) > 1000.
Acute kidney failure, Severe acidosis, bleeding disorders, Coma

3. Mortality risk factor
- Concurrent poisoning with other substances impacting hepatic metabolism
- A psychiatric illness or history of suicide attempts
- Regular ingestion of large amounts of alcohol; chronic malnutrition

4. Outpatient Management
- Behavioral health evaluation for intentional ingestions
- Consider hospitalization for toxic ingestions with vital instability and/or laboratory abnormalities (liver function tests).
- Consider transfer to a psychiatric facility for intentional ingestions when medically stable.



Graphic-2
Paracetamol nomogram (the modified Rumack-Matthew nomogram) intent to use for rapid-release form of paracetamol, single oral overdose, in the window of 4-24h post-ingestion.

4. First-line treatment

Stabilization of A.B.C is the first priority.

NAC (N-acetylcysteine) is paracetamol antidote. For severe form of paracetamol poisoning (transaminase levels >1,000 mg/L, severe acidosis, coma/hypotension, or renal failure), additional measure like Hemodialysis, or ECMO is needed. Some patients may need liver transplant to survive.

A. Gastric decontamination:

Ipecac and gastric lavage are no longer recommended for routine use at home or in health care facilities.

Adequate GI decontamination consists of the early administration (< 4h) of active charcoal orally or through a nasogastric tube. More aggressive forms of decontamination, such as gastric lavage or whole-bowel irrigation, are unnecessary because of the rapid GI absorption of paracetamol. Patients who arrived later than 4h, and patients whose airway was not well controlled are not the candidate for active charcoal administration.

B. Active charcoal:

Single dose activated charcoal (1 g/kg PO) may be effective if given within 1 to 4 hours of ingestion. Never delay oral NAC for activated charcoal.

C. Enhanced elimination: no indication

D. Antidote treatment

a. <u>N-acetyl-cysteine (NAC)</u>

N-acetyl-cysteine (NAC), detoxify acetaminophen metabolites and replenish glutathione stored in the liver. NAC administration may reduce mortality from 5% to 0.7%. Give NAC when acetaminophen plasma levels measured ≥4 hours after ingestion are at the "treatment line" or higher on the Rumack-Matthew nomogram. In most cases, liver enzymes will be elevated only after 24h.

Empirically start NAC within 8 hours for suspect case or even while awaiting lab results. It may be effective up to ≥36 hours after ingestion.

NAC may be given PO or IV, depending on situation and availability. IV NAC has been shown to decrease the length of hospitalization compared to PO NAC.

Begin with a 200 mg/kg IV dose over 4 hours followed by a 100 mg/kg IV dose over 16 hours. A total of 300 mg/kg IV NAC over a 20-hour period.

Oral route: oral loading dose of 140 mg/kg and then 70 mg/kg q4h for 17 additional doses (72-hour regimen).

b. <u>NAC precautions:</u>

Consider a nasogastric tube, if nausea, vomiting with Oral route. Metoclopramide, 1 to 2 mg/kg IV, or ondansetron, 0.15 mg/kg IV may be effective.

IV NAC may cause anaphylactoid reactions, (3–6%) including rash, bronchospasm, pruritus, angioedema, tachycardia, or hypotension. Reactions usually occur with the loading dose. To prevent this, slow or temporarily stop the infusion; may concurrently treat with antihistamines.

E. Second Line

In massive ingestions (levels >1,000 mg/L, severe acidosis, coma/hypotension) or when severe renal failure is present, hemodialysis may improve survival.

Supportive treatment

5. Treatment adjustment

Metoclopramide, 1 to 2 mg/kg IV, or ondansetron, 0.15 mg/kg IV for nausea or vomiting.

IV fluids are generally provided for hydration purposes.

E.g., Muclear® 600mg tab; patient 60kg, give 14 tab dissolved in water, drink or via NG tube, then 7 tab every 4h for additional 17 doses. Mucomyst® oral come with 200mg packet. Injectable Acetyl cysteine usually available as 6g/30ml solution (200mg/ml).

6. Algorithm (see Graphic 3)

VIII. SPECIAL CASE

1. **Geriatric Considerations**

There is an increased risk of hepatic damage in frail, elderly patients due to decreased hepatic metabolism and co-ingestion of other hepatotoxic medications. Keep dose of acetaminophen ≤3,000 mg/day in seniors and in patients with liver disease and/or alcohol abuse disorders.

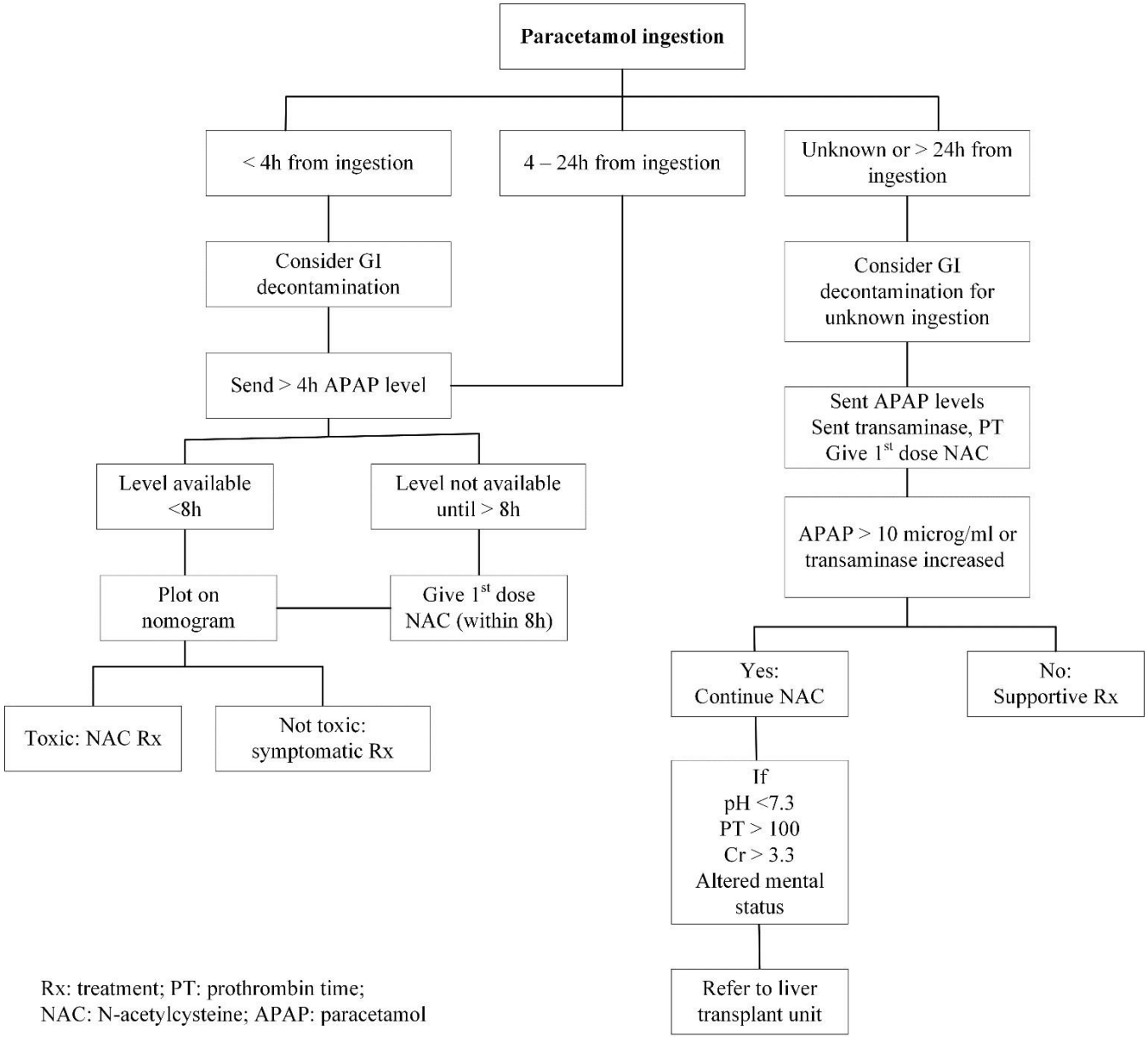
2. **Pediatric Considerations**

Hepatic damage after ingestion of toxic acetaminophen doses can be less severe in young children, potentially because they have more stores of glutathione.

3. **Pregnancy Considerations**

There is an increased incidence of spontaneous abortion in pregnant patients with acetaminophen poisoning, especially with overdose at an early gestational age. Abortion incidence and possible fetal death is increased if N-acetylcysteine (NAC) treatment is delayed. IV NAC is generally preferred in pregnancy due to greater bioavailability.

TREATMENT GUIDELINES FOR PARACETAMOL INGESTION



Graphic_3_ Guideline for paracetamol ingestion;
(Adapted from Tintinalli, Emergency Medicine. A comprehensive Study Guide, 9th edition)

IX. EVOLUTION AND PROGNOSIS

Complete recovery with early therapy (with NAC) is possible and more likely in stage 4 of toxicity. 10% of adult patients with severe liver complications develop necrosis, hepatic encephalopathy, or require transplant. Hepatic failure is rare in children <6 years of age.

X. COMPLICATION

Recovery after acute poisoning is complete, and sequelae are rare.

XI. PREVENTION AND RECOMMENDATION

In the situation where plasmatic paracetamol level measurement is not available, consider administer NAC early, in the first 8h, based on history and suspect toxic dose.

- 10g in adult, as single dose or in 24h, or > 6g per day for 2 consecutive days.
- For children < 6y, ingestion of ≥ 200 milligrams/kg as a single ingestion or over an 8-hour period, or of 150 milligrams/kg per 24-hour period for the preceding 48 hours)
- For people with liver disease (cirrhosis) the maximum dose is lower may be 2-3g/24 depend on the severity of liver disease.

Outpatient management is adequate for nontoxic accidental ingestions.

Transaminase elevation usually occurred from day 2, repeat measurement is necessary to follow up. The elevation of liver enzymes seen on the first few hours after paracetamol ingestion may indicate an anterior liver problem than the paracetamol-acquired one but, in patient with history liver disorders, standard dose of paracetamol can be toxic also.

Educate parents/caregivers during well-child visits regarding appropriate OTC dosing and medication storage. Provide anticipatory guidance for caregivers, family, and cohabitants of potentially suicidal patients.

XII. REFERENCES

1. Rachel S. Wightman, Lewis S. Nelson, 2020. Acetaminophen. in: Judith E. Tintinalli, Editor-in-Chief Emergency Medicine. A comprehensive Study Guide, 9th edition, Mc Graw Hill; p. 1252-8
2. Mark B. Stephens, Grant M. Reed, (2023), Acetaminophen poisoning. In: Frank J. Domino, The 5-minute Clinical Consult; 32nd edition, Walters Kluwer Health Lippincott Williams & Wilkins, Unbound Software platform c2000-2023
3. J Clin Transl Hepatol. 2019 Jun 28; 7(2): 132–139. Published online 2019 Jun 14. doi: 10.14218/JCTH.2018.00066

METHAMPHETAMINES POISONING

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I. AMPHETAMINES & METHAMPHETAMINES

Amphetamines were synthesized in 1887 (by Lazãr Edeleanu, a Romanian scientist who was working in Germany), and in 1932, they were marketed medicinally in an inhaler form as a bronchodilator. Methamphetamines (N-methyl amphetamine) were first synthesized in 1883 (Nagai Nagayoshi, a Japanese scientist).

The crystalized form of methamphetamine was first synthesized in 1919 by scientist Akira Ogata. The use of methamphetamine to enhance physical and intellectual performance began in the 1930s.

Amphetamines may be use medically in "attention deficit hyperactivity disorders" (ADHD), and narcolepsy. Some derivatives were used as weight-loss treatment. Nowadays, amphetamines have limited therapeutic roles but are widely used as drugs of abuse. Methamphetamines is purely produced as illicit drugs.

II. EPIDEMIOLOGY

The use of methamphetamine and amphetamine has increased rapidly throughout the world, with more than 34 million users worldwide. East and Southeast Asia and North America remain the two main subregions for methamphetamine trafficking worldwide.

During the first half of the 2023, Cambodia authorities had arrested 9034 drugs-related suspects. 52% were drug traffickers, manufacturers, possessors, and transporters. A total of 993 kg of illicit drugs, 9kg of dry marijuana and some 326kg of chemical substances used for drug manufacturing were also confiscated. The seized drugs included heroin, ecstasy, cocaine, crystal methamphetamine, methamphetamine pills, cathinone and ketamine, among others*.

III. ETIOLOGY

Methamphetamines is an illicit street drug with no medical usage. People may expose to it by -smoking, - swallowing, - snorting, - injecting (s/c, IM, IV)- intra rectal, - intravaginal. Methamphetamines enters the brain quicker than other amphetamine drugs, leading to quick and intense effects. When it is used, a chemical, dopamine, is released in the brain, bringing about a sense of well-being. This high is addictive and causes people to crave the drug repeatedly in order to achieve it.

Physiological adaptation occurs through receptor or coupling down-regulation; this tolerance and an accompanying psychological tolerance (need more and more drug to obtain the same effects) can lead to escalating use of the drug and increased toxicity. Some people may expose by misused amphetamine derivatives as weight-loss medicine.

Yama, Yaba, ice (crystal meth.); MDMA (3-4 methylenedioxymethamphetamine, "ecstasy" or "molly") are common name found in Cambodia.

IV. PATHOPHYSIOLOGY

Methamphetamine is an indirect sympathomimetic, it increased arousal and decreased fatigue. On cardiovascular system it induced, tachycardia, dysrhythmias, hypertension and/or coronary vasospasm (sympathomimetic toxidrome). Other central effects: movement disorders, schizophrenia, and euphoria, hallucinogenic and anorexic.

Pharmacokinetic of Methamphetamine

Route of exposure	Onset of action	Peak Action	Duration of Action
IV	15 – 30s	30 min	10-12h
Nasal insufflation (snorting)	3 – 5 min	1 – 2 h	10 -12h
Inhalation (smoking)	10 – 30s	5 – 10min	8 – 12 h
GI	15 – 20min	2 – 3h	10 – 12h

V. DIAGNOSIS

1. Clinic

Clinicians should consider the diagnosis of methamphetamine intoxication in any diaphoretic patient with hypertension, tachycardia, severe agitation, and psychosis.

Acutely intoxicated patients may become extremely agitated and pose a danger to themselves, other patients, and medical staff. Other symptoms include headache, hyperactivity, toxic psychosis, coma, focal neurologic deficits, or seizures. Some abusers develop stereotyped, compulsive behavior such as cleaning or buttoning shirts.

Psychosis from amphetamines can present as paranoid delusions and perceptual disturbances; these may persist long after the drug has been stopped and can result in homicidal or self-destructive behavior.

2. Investigation

Many patients who are admitted users of methamphetamine but are clinically well with normal vital signs do not need any lab testing. However, other methamphetamine users with moderate to severe intoxication can develop several dangerous manifestations and complications. The following tests should be obtained:

- Basic serum electrolytes (i.e., sodium, chloride, potassium, bicarbonate)
- Serum lactate
- Creatine phosphokinase (CPK)
- Aminotransferases (ALT, AST)
- Clotting times (prothrombin time, activated partial thromboplastin time)
- Renal function studies (creatine, BUN)
- Urinalysis

VI. DIFFERENTIAL DIAGNOSIS

Other substances overdoses that produce sympathomimetic toxidromes: Cocaine, cathinone, Ecstasy, amphetamine; the clinical presentation of these different agents is largely indistinguishable, especially initially. The treatment of sympathomimetic intoxication is generally the same across different agents.

Medical conditions in which the present symptoms may be of concerned: Chronic stress, anxiety disorders, post-traumatic-stress- disorders (PTSD), hyperthyroidism, heart disease.

VII. MANAGEMENT

1. Objective of management
- Reduce the toxic effects of the drugs.
- Reduce morbidity.
- Prevent complications.

2. Critical Signs
hypertension, tachycardia, severely agitated delirium, hyperthermia, metabolic acidosis, seizures and coma.

3. Mortality risk factors
Prognostic factors for mortality include:
- coma,
- shock,
- body temperature >39°C,
- acute renal failure,
- metabolic acidosis,
- hyperkalemia (K 5.6 to 8.5 mmol/L)

4. Outpatient management
Methamphetamines overdose without disturbance of vital signs, without critical signs can be managed supportively at home.

5. First line treatment
Follow the standard protocol of "General Management of Poisoned Patients".
- Decontamination
  Gastrointestinal decontamination — Activated charcoal is rarely indicated due to the route of methamphetamine administration (e.g., intranasal, inhalation, injection, intravaginal). If methamphetamine has been ingested, the greatest benefit of activated charcoal occurs if administered within 1 to 2 hours of ingestion.
  In case of body packing or stuffing, indication may be a whole bowel irrigation, or immediate laparotomy to prevent bowel ischemia from local vasoconstriction.
- Enhanced elimination— Urine acidification, formerly used to promote the elimination of methamphetamine, is no longer recommended. The administration of acidic intravenous fluids may exacerbate life-threatening metabolic acidosis
- Antidote: not existed
- Supportive treatment: is the main treatment
  - **Hyperthermia**. Antipyretics have no role in the management of acute methamphetamine intoxication. Aggressive sedation, neuromuscular paralysis, and fluid resuscitation are used to control methamphetamine-induced hyperthermia; these measures can be supplemented with external cooling blankets or evaporative cooling techniques. Paralyzed patients at risk for seizures should receive continuous bedside electroencephalography.
  - **Rhabdomyolysis**: (muscle pain or weakness, dark red or brown urine, abdominal pain) Aggressive IV hydration is the primary treatment for rhabdomyolysis. One method is rapid correction of the fluid deficit with IV

crystalloids followed by infusion of 4 mL/kg/h, with the goal of maintaining a minimum urine output of 3 to 4 mL/kg/h (1-2ml/kg/h). Another method is a goal of 200 to 300 mL of urine output each hour. Any isotonic fluids can be used (attention: patient may have hyperkaliemia).

- **Seizures** are initially treated with benzodiazepines, status epilepticus requires aggressive treatment, propofol or thiopental may be used. Attention of blood pressure falling and / or respiratory depression that necessitate supportive ventilation. Obtain a head CT to identify intracranial pathology as the cause of seizures. Phenytoin should be avoided.
- **Agitation**: Lorazepam, 2 milligrams IV, or diazepam 5 milligrams, midazolam 2.5mg IV, can be administered and titrated with repeated doses after 8-10min. May start by double the dose and give IM, then about 10min later, give IV dose (up to 30-50mg with appropriate airway monitoring). If it was not effective enough, use antipsychotics: Haloperidol (5-10mg IM / IV), droperidol or chlorpromazine. Ziprasidone 10mg IM (check ECG for long QT first). Physical restraints should be avoided if possible. Patients who struggle against physical restraints undergo isometric muscle contractions that can be associated with lactic acidosis, hyperthermia, sudden cardiac collapse, and death.
- **Chest pain**: Cocaine users with suspected acute coronary syndrome are managed with aspirin and nitroglycerin and IV Diltiazem 5-20mg IV if ST-segment elevation or depression was observed.
- **Dysrhythmia**: may response to sedation, cooling and IV fluid rehydration; other anti-dysrhythmia used is a calcium channel blocker, blood alkalinization with sodium bicarbonate (to pH 7.50-7.55), and Lidocaine. If beta-blocker is necessary, use labetalol (alfa and beta-adrenergic antagonist).
- **Hypertension**: Severe hypertension not response to sedation should be treated with phentolamine (initial dose, 2.5 to 5.0 mg IV), or nitroglycerine, nicardipine, or sodium nitroprusside, but do not use beta blockers except labetalol.

6. Treatment adjustment

ACUTE WITHDRAWAL_ After heavy or prolonged use, abrupt discontinuation of methamphetamine can cause a withdrawal syndrome. Symptoms may develop within hours, typically peak within 1 to 2 days, and most often decrease within two weeks. Symptoms of withdrawal are strongest during the first 48 hours, but milder symptoms can last up to 2 weeks.

During the acute withdrawal phase ("the crash"), patients may have dysphoria, anhedonia, fatigue, increased sleep, vivid dreams, insomnia, agitation, anxiety, drug craving, and increased appetite.

A subacute withdrawal phase: may persist for up to three weeks with insomnia, hypersomnia, appetite changes, depression, and possibly suicidal thoughts.

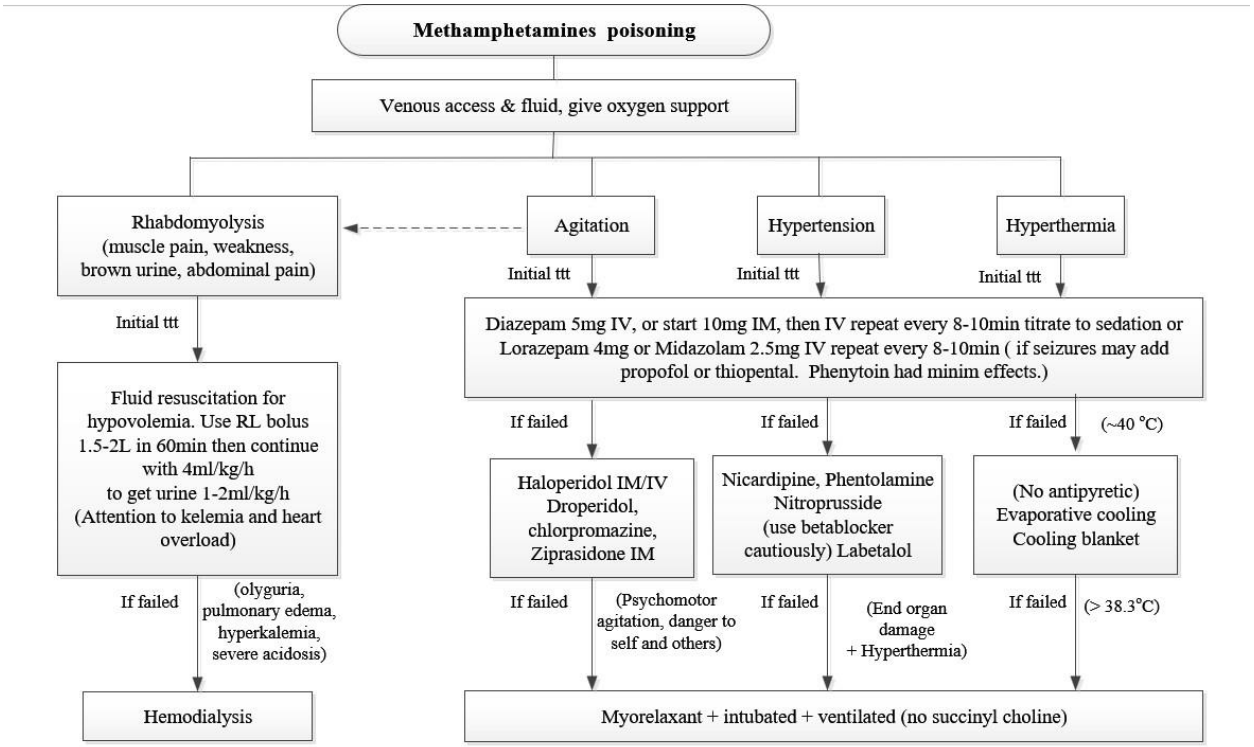
Treatments: There is no specific methamphetamine withdrawal medication approved. The combinations of the following drugs, have been used with variable efficacy: benzodiazepines, antidepressants, antipsychotics, riluzole, naltrexone,

and behavioral therapy. Some studies found that injectable naltrexone plus oral bupropion was safe and effective.

7. Algorithm

Graphic-1_ management of methamphetamines poisoning

Initial emergent control of psychomotor agitation and hyperthermia is of the highest priority to limit life-threatening sequelae.
Aggressive supportive care with supplemental oxygen, sedation, fluid administration, prevention and treatment of hyperthermia, and close monitoring while addressing the specific myriad complications that can occur.



VIII. SPECIAL CASES

Pregnancy and lactation — In utero exposure to methamphetamine is associated with low birth weight and decreased head circumference, among several abnormalities, and may produce withdrawal symptoms in the perinatal period.
Amphetamines, including methamphetamine, are excreted into breast milk.
Pediatric_ Although sympathomimetic and neuropsychiatric manifestations of methamphetamine exposure should be similar in a pediatric patient, inadvertent exposure may be difficult to diagnose. The most frequent signs and symptoms noted in pediatric patients exposed to methamphetamine are nonspecific.

Asymptomatic children taken from clandestine production sites may also have been exposed to methamphetamine and other chemicals (eg, ephedrine) used to synthesize methamphetamine. These children are particularly vulnerable to child abuse, neglect, serious injury, exposure to toxic chemicals, and malnutrition. The hypersexuality and drug-seeking behaviors of adult methamphetamine users may lead to sexual abuse of such children, or they may be prostituted for money or drugs.

IX. EVOLUTION AND PROGNOSIS

Methamphetamine user rapidly became addicted. Addicted people show the "methamphetamine-use disorders" symptoms:

- A compulsive use of the drug despite harmful consequences.
- Taking larger amounts of meth or using it for a longer period than planned
- Unsuccessful attempts to cut down or quit
- Giving up activities due to meth use
- Inability to keep up with responsibilities at home, work.

The physiologic tolerance process makes the user use higher and higher dose to get the same effects, increase the risk of intoxication.
It is a chronic brain disease.

X. COMPLICATIONS

Long-term use of the drugs can lead to myonecrosis and dilated cardiomyopathy or myocardial infarction. Use of methamphetamine during pregnancy has been associated with intrauterine growth restriction and preterm birth. Incidental injuries from blunt and penetrating trauma are common.
Complications of methamphetamine use include (substance-induced disorders):

- Rhabdomyolysis
- Acute kidney injury
- Seizures
- Stroke with permanent deficits
- Coma
- Acute coronary ischemia or infarction
- Congestive heart failure (CHF)
- Ventricular arrhythmias
- Psychosis (paranoid delusion, may be dangerous to surrounding)
- Addiction (substance-use disorders)
- Death
- HIV and viral hepatitis
- Periodontal disease
- Skin infections

XI. PREVENTION AND RECOMMANDATION

Early to have consultation (better, is in the Emergency room, when the vital signs were stable) with psychiatric specialist for continue the treatment. Be aware that Methamphetamine addiction is notoriously difficult to treat successfully.

XII. REFERENCES

1. Edward W Boyer, Christina Hernon, Methamphetamine: acute intoxication. In: UpToDate, Wolters Kluwer
2. Rachel S. Wightman, Jeanmarie Perrone (2020). Cocaïne and amphetamines in: Judith E. Tintinalli. Emergency medicine. A comprehensive study guide 9th edition Mac Graw Hill; p. 1238-42
3. English.news.cn Source: Xinhua, 2023-7-02 11:37:33 Editor: huaxia. Asia&Pacific, Access: Monday, September 4, 2023

ORGANOPHOSPHATE AND CARBAMATE INSECTICIDES POISONING

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I. DEFINITION

Organophosphate insecticides are a class of chemical compounds that are derived from phosphoric acid. They work by inhibiting the enzyme acetylcholinesterase, which is responsible for breaking down the neurotransmitter acetylcholine. This leads to a buildup of acetylcholine in the nervous system, which can cause a variety of symptoms, including muscle weakness, tremors, convulsions, and even death.

II. EPIDEMIOLOGY

There are approximately 385 million cases of acute pesticide poisoning each year globally, resulting in around 11,000 deaths. A significant proportion of these cases are due to intentional self-poisoning, particularly in low- and middle-income countries[1].

Agricultural workers and individuals in areas with heavy pesticide use are at higher risk of accidental poisoning.

Older pesticides like DDT and lindane, though banned in many developed countries, are still in use in some developing regions, contributing to ongoing health risks

III. ETIOLOGY

In Cambodia, Organophosphates is one group of chemical compounds commonly use as insecticides among other group like pyrazole, thiazole, neonicotinoid, pyrethroids, organochlorines. Organophosphate can be further categorized into several subgroups based on their chemical structure and mode of action:

- ***Phosphates***: These include compounds like malathion and parathion, which are commonly used in agriculture
- ***Phosphorothioates***: ex. diazinon and chlorpyrifos, metamidophos, (commonly use in Cambodia)
- ***Thiophosphates***: phosmet, which is used in both agricultural and residential settings
- ***Dithiophosphates***: dicrotophos.

Example of tradename of metamidophos (OP) available in Cambodia market:

- Bamate
- Bent 600
- Filitox 50EC
- Filitax 60DD
- Filitax 70SC
- Glant 50% WW EC
- Giant 70DD
- L. Talon
- Marathon
- Methamidophos 70SL
- Methamidophos 60
- Methamidophos 70%
- Methaphos 70SC
- Monitor 50EC
- Monitor 50SC
- Monitor 60SC
- Monitor 70DD
- Methon
- Morris
- Ovansu
- Sigtifos
- Siter-Nissan
- Tom 50EC
- Tom 60EC
- Tom 70EC
- U-T 70
- U-T 80
- Vindo

Carbamate insecticide is another chemical group classified into two main subgroups based on their chemical structure:

- ***Phenolic Carbamates***: ex. Carbaryl, pirimicarb, Propoxur, Bendiocarb
- ***Oxime Carbamates***: Examples of this subgroup include aldicarb and methomyl,

The most use carbamate in Cambodia is Propoxur, and Bendiocarb, commonly used to control pests like cockroaches, flies, mosquitoes, and lawn insects.

IV. PHYSIOPATHOLOGY

Organophosphates (OPs)

- Primary toxic mechanism is inactivating acetylcholinesterase (AChE)
- OPs cause alkyl phosphorylation of the AChE enzyme. The phosphorylated AChE is inactive. AChE is thereby unable to degrade and hydrolyze acetylcholine into choline and acetic acid. Resulting accumulation of acetylcholine at the synaptic junction throughout the nervous system causes overstimulation of receptors.
- Potential locations where cholinergic synaptic transmission can be paralyzed——
  - Central nervous system
  - Autonomic ganglia
  - Parasympathetic nerve endings
  - Some sympathetic nerve endings (such as sweat glands)
  - Somatic nerves
- Direct myocardial injury can occur during the acute, early phase in severe OP poisoning

Carbamates

- When a carbamate binds to AChE the enzyme undergoes an allosteric change which prevents breakdown of acetylcholine. Carbamates undergo carbamylation of the serine hydroxyl group. The carbamylated AChE is inactive. AChE activity can be spontaneously regenerated.
- Clinical signs of toxicity often occur more rapidly than Ops

Organophosphates (OPs) and carbamates are highly lipophilic, and therefore readily absorbed across the skin, respiratory, and gastrointestinal mucosa.

Onset and severity of symptoms depends on the specific compound, amount, route of exposure, and rate of metabolic degradation. Symptoms are proportional to the decrease in cholinesterase activity

V. DIAGNOSIS (ACUTE POISONING)

- **History**
  - Substance(s) involved or suspected (including specific product name when available)
  - Timing, duration, and mode of exposure (such as inhalation, ingestion, or cutaneous)
- **Classic symptoms of cholinergic toxicity**

Muscarinic effects

- SLUDGE: **S**alivation, **L**acrimation, **U**rination, **D**iarrhea, **G**astrointestinal upset, **E**mesis (literature meaning: Sludge = soft, wet soil, muddy deposit)
- "3 Killer Bees" **B**radycardia, **B**ronchospasm, **B**ronchorrhea,

Nicotinic effects

- Nausea, vomiting, increased salivation, muscle cramping and weakness, headache, dizziness
- Can also produce opposing symptoms to muscarinic effects, including mydriasis, tachycardia, and hypertension

Central nervous system

- Headache, insomnia, giddiness, confusion, dizziness, ataxia, emotional lability, slurred speech, drowsiness, seizures, unconsciousness, coma

Laboratory

- RBC and plasma cholinesterase levels to confirm diagnosis:
  - RBC (true) cholinesterase level is best for synaptic inhibition
  - Plasma (pseudo)cholinesterase level not as reliable but more timely:
    - These are markers for poisoning
    - Depending on the agent and the patient, these levels may vary
  - Cholinesterase levels:
    - Latent exposure: >50% of normal value
    - Mild exposure: 20–50% of normal value
    - Moderate exposure: 10–20% of normal value
    - Severe exposure: <10% of normal value
  - Do not wait for cholinesterase results before administering treatment
  - CBC, electrolytes, glucose, BUN, creatinine
  - ABG when respiratory symptoms are present

Imaging

- CXR if respiratory difficulty is present or suspect pulmonary edema:
  - Pneumonitis from hydrocarbon aspiration
- ECG
  - Dysrhythmias (atrial fibrillation, ventricular tachycardia, torsades de pointes, QT prolongation)
  - Bradycardia
  - Heart block
  - ST–T-wave abnormalities
- CT scan of head for altered mental status when diagnosis is uncertain

Definitive diagnosis: There is no specific assay readily available to screen for individual agents.

Suspecting the diagnosis:

- History of exposure to/contact with a cholinergic agent
- Clinical signs and symptoms of cholinergic toxicity
- Decreased red blood cell cholinesterase activity
- Symptom improvement following atropine or oxime administration

VI. DIFFERENTIAL DIAGNOSIS

- Mild to moderate exposure:
  - Gastroenteritis
  - Asthma
  - Venomous arthropod bite (black widow, scorpion)
  - Progressive peripheral neuropathy (Guillain–Barré syndrome)
  - Carbon monoxide
- Severe exposure:
  - Narcotic overdose
  - Coma and miosis:
    - PCP, meprobamate, phenothiazine, clonidine
    - Muscarinic-containing mushrooms – cholinergic crisis without nicotinic symptoms
    - Nicotine poisoning
- Metabolic and infectious:
  - Ketoacidosis, sepsis, meningitis, encephalitis
  - Hypoglycemia
  - Reye syndrome
- Neurologic:
  - Cerebrovascular accident
  - Subdural or epidural hematoma
  - Postictal state

VII. MANAGEMENT

1. Objectives
   - Maintain stability of vital signs
   - Neutralize the toxic effects (on muscarinic, nicotinic and central receptors)
   - Prevent or minimize the treatment-related disorders
   - Prevent the recurrence intoxication
2. Critical signs
   - Shock, seizures or coma, difficult breathing or respiratory failure
3. Mortality risk factors
   - Advanced age
   - OP poisoning: elevated lactate, low blood pH, and poor lactate clearance
   - Hypoglycemia
   - The insecticide of group Ia (Parathion, Methyl parathion, Aldicarb, Metamidophos)
   - Delay from accident to emergency care

4. Outpatient management

Pre-Hospital (if patient have normal vital signs, and cooperated)

- Decontamination is initial priority:
    - Decontaminate, airway, breathing, circulation (DABC)
    - Remove all clothes (in spillover accident) and store as toxic waste (double bagged)
    - Protection of health care workers of utmost importance:
        - Impenetrable gloves (neoprene, nitrile), gowns, eye protection
    - Decontaminate skin with soap and water:
    - Shower or gentle scrubbing ideal if done before entrance into the ED
- Maintain airway and oxygenate
- IV access and place on cardiac monitor

5. First line treatment

Initial Stabilization/Therapy

- Decontaminate and ABCs:
    - Decontamination and protection of staff
    - Maintain airway and oxygenate
    - For unstable airway, intubate, and ventilate (caution: succinylcholine may produce a long myorelaxant time)
    - IV access with D5W 0.9% NS
- Altered mental status: Administer thiamine, glucose, or naloxone if suspect alcoholic overdose, hypoglycemia or overdose opioids respectively.

ED Treatment/Procedures

Atropine:

- Blocks acetylcholine at muscarinic receptor sites
- No effect on nicotinic receptors
- Onset of action is 1–4 min, peaks at 8 min
- Goal of therapy/end point:
    - Drying secretions of tracheobronchial tree
- Administer test dose 1–2 mg IV/IM:
    - No clinical response: Double dose q5min until muscarinic findings subside
- Dose: 1–4 mg IV q5min (peds: 0.05–0.2 mg/kg)
- Common pitfalls in therapy:

- Not giving enough atropine
- Using pupillary findings (mydriasis) as end point of treatment
- Dilated pupils or tachycardia are not contraindications to atropine

Pralidoxime (2-PAM):

- Regenerates cholinesterase by reversing the phosphorylation of the enzyme
- Synergistic with atropine – muscarinic signs/symptoms will start to resolve in 10–40 min
- 1–2 g (peds: 25–50 mg/kg) dissolved in 0.9% NS over 30 min IV; repeat in 1 hr if necessary, then q6h as needed:
  - Some propose continuous infusion (500 mg/hr) for serum concentration of 4 mg/L
- Side effects: Neuromuscular blockade with rapid infusion, respiratory arrest, HTN, nausea/vomiting, dizziness, blurred vision
- End point is resolution of muscle weakness and fasciculations
- Effective before enzyme aging occurs (permanent inactivation of cholinesterase)
- Onset of aging varies among products
- No restriction to its use even if 24–48 hr have passed

Supportive care:

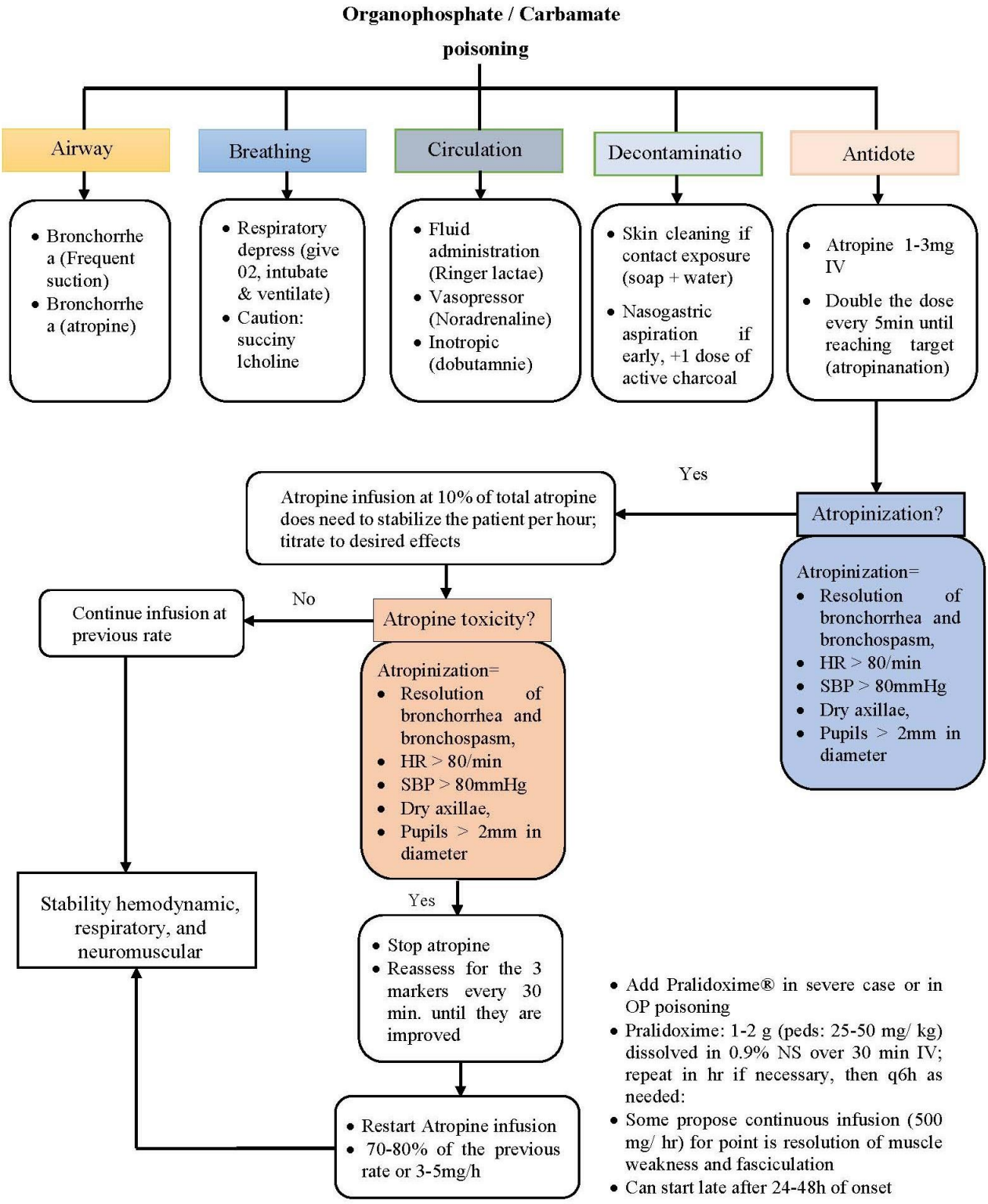
- Dermal decontamination: Remove clothes and flush skin with water
- Gastric lavage (early presentation of severe ingestion):
  - Gastric emptying with continuous suction via a nasogastric tube
  - Handle contents with care – avoid direct contact to prevent personal exposure
- Respiratory difficulty:
  - Frequent oropharyngeal suction
  - Treat bronchospasm with atropine, not bronchodilators
  - Tachycardia may result from hypoxia (pulmonary secretions and bronchospasm)
  - Atropine will dry secretions and paradoxically lower the heart rate
  - Intubate and ventilate if necessary
  - Avoid succinylcholine; may have prolonged duration as it is metabolized by cholinesterase

6. Treatment adjustment

- In case of carbamate intoxication, Pralidoxime was usually no need.
- Treat hypovolemia (from gastrointestinal losses) with IV crystalloid
- Treat vomiting with antiemetics such as ondansetron
- Vasopressors: Can be used as an adjunct to treat hypotension
- Diazepam recommended for seizure control. Phenitoine was not effective.
- Prophylaxis with diazepam has been shown to decrease neurocognitive dysfunction after OP poisoning

7. Algorithm (next page)

The management of organophosphate and Carbamate insecticides poisoning



VIII. SPECIAL CASES

Pediatric Considerations

- Symptoms are difficult to differentiate in toddlers
- Common symptoms: Miosis, salivation, and muscle weakness
- Seizure activity in 25% of pediatric cases. Only 3% in adults

Pregnancy Consideration

- Organophosphate poisoning during pregnancy can be particularly dangerous due to the potential for both maternal and fetal toxicity.
- These toxic effects can be exacerbated in pregnant women due to physiological changes during pregnancy, such as increased cardiac output and decreased plasma cholinesterase levels. Additionally, there is concern that organophosphate exposure may have adverse effects on fetal development, including birth defects and neurodevelopmental problems.
- The management of organophosphate poisoning in pregnant patients follows similar principles as in non-pregnant individuals.

IX. EVOLUTION AND PROGNOSIS

Mortality rate from acute organophosphate (OP) poisoning varies between 10% and 20% and is generally due to respiratory failure.

X. Complications

- Pulmonary: aspiration pneumonitis/pneumonia, respiratory failure
- Cardiovascular: arrhythmias, hypotension
- Neurological: seizures, muscle fasciculations, paralysis
- Delayed sequelae
  - Intermediate syndrome
    - Symptom onset typically 1-4 days after OP poisoning
  - Delayed polyneuropathy—
    - Referred to as organophosphate-induced delay peripheral neuropathy (OPIDN)
    - Onset 7-14 days after large exposures to OP
  - Long-term effects

XI. PREVENTION AND RECOMMENDATIONS

- ***Consult with psychologists*** for mental disorders.

Preventing accidental insecticide poisoning involves several essential measures:

- ***Read Labels Carefully***: Always read and follow the instructions on the pesticide label. This includes proper application methods, protective equipment, and first aid measures.
- ***Use Personal Protective Equipment (PPE):*** Wear appropriate PPE such as gloves, masks, goggles, and long-sleeved clothing when handling or applying insecticides.
- ***Store Safely***: Keep insecticides in their original containers, tightly sealed, and stored in a locked cabinet out of reach of children and pets
- ***Avoid Mixing Chemicals***: Never mix insecticides with other chemicals, as this can create toxic reactions
- ***Proper Disposal***: Dispose of empty pesticide containers and unused chemicals according to local regulations to prevent accidental exposure.

- ***Ventilation***: Ensure good ventilation when using insecticides indoors to avoid inhaling harmful fumes.
- In case of accidental exposure or suicidal encounter***, early contact with Emergency service.***

XII. REFERENCES

1. Vinodinee L. Dissanayake, Organophosphate poisoning, in “5 minute Emergency Consult”, U-Central, Unbound Medicine platform, Wolters Kluwer Health Lippincott Williams & Wilkins, access Nov-2024
2. Kenneth D Katz, MD, Sage W weiener, MD; “organophosphate Toxicity” in Medscape, emedicine.medscape.com; Access Nov 2024
3. Anita K, Mudan MD, Jacob A, Lebin MD; Cholinergic Toxicity-Emergency management in DynaMed platform, EBSCO; Access Nov, 2024

METHANOL AND ETHYLENE GLYCOL INTOXICATION

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I. INTRODUCTION

Methanol is considered toxic alcohol, due to its metabolite_ the formic acid. It is not intended for ingestion. Methanol poisoning typically occurs from ingestion of methanol-containing substances that may include denatured alcohol, homemade or illegally produced alcohol, or commercial products. More rarely methanol poisoning may be caused by inhalation or dermal absorption.

II. EPIDEMIOLOGY

Methanol poisoning outbreaks occur when illegally produced or homemade grain spirits are fortified with methanol due to its low cost.

According to the World Health Organization (WHO), outbreaks of methanol poisoning have occurred in various countries, including Cambodia, Czech Republic, Ecuador, Estonia, India, Indonesia, Kenya, Libya, Nicaragua, Norway, Pakistan, Turkey, and Uganda. These outbreaks often result from methanol being added to these drinks, either accidentally or deliberately.

In Cambodia, methanol intoxication is a sporadic accident, from time to time the outbreaks of methanol poisoning have occurred with a few to many dozens of deaths and many more hospitalized. One of the largest outbreaks was in 2012 involving 49 deaths and 318 persons hospitalized. Many events happened after funeral ceremony in rural area when people often consume illegally produced alcohol.

III. ETIOLOGY

Common sources of methanol:

- Wood alcohol
- Paint solvents
- Windshield washer fluid
- Inhalational abuse of carburetor cleaners
- Fuel antifreeze solutions
- Formalin (10-12% of it volume is methanol)
- Gasoline (racing car)
- Household cleaners
- Sterno® cans (cooking fuel)
- Moonshine
- Photocopying fluid
- Perfumes

IV. PHYSIOPATHOLOGY

Dose toxic

- lethal doses are not well-established and vary from person to person, generally estimated at 1-2 mL/kg of pure methanol. Doses as low as 0.1 mL/kg (6-10 mL in adults) have been reported to cause permanent blindness and death.

Toxicodynamic

- Methanol has low toxicity on its own, but is metabolized into toxic products (formic acid)
- First metabolized in liver by alcohol dehydrogenase to produce formaldehyde (slowly) which is then oxidized by aldehyde dehydrogenase to produce formic acid (1- to 2-minute half-life) and does not accumulate most formic acid dissociates into hydrogen cation and formate anion hydrogen cation reduces pH of body fluids, resulting in acidemia.
- Formate accumulates and inhibits cellular functions by disrupting oxidative phosphorylation in mitochondria and decreasing production of adenosine triphosphate (ATP). Decrease in ATP produces effects similar to hypoxia, although tissue oxygenation may be increased with reduced cellular oxygen uptake.
- Formate is toxic to:
    - central nervous system
    - basal ganglia and subcortical white matter in untreated patients.
    - retinal and optic nerves.
        - Retinal dysfunction occurs at lower formic acid concentrations than optical neuropathy
        - Acidosis enhances toxicity by increasing diffusion of undissociated formic acid into cells, especially optic disc and retrolaminar section of optic nerve.
- Estimated formate elimination half-life is 1-3 hours for low concentrations and 24 hours for high concentrations.
- small amounts of methanol are excreted in urine and eliminated by lungs (due to high vapor pressure)

V. DIAGNOSIS

A. Clinic

- Clinical presentation is characterized by early, latent, and delayed stages.
    - ***Early stage*** of methanol intoxication usually presents with similar symptoms as ethanol inebriation, including mild euphoria, drowsiness, gastric symptoms, sedation and central nervous system (CNS) depression, and faint alcoholic odor on breath.
    - ***Latent period*** occurs after inebriation subsides and methanol is slowly metabolized to formic acid, lasting from 6-30 hours. Patients may be asymptomatic or have blurred vision during this period.
    - ***Delayed period*** begins after significant amounts of methanol have been metabolized, formate accumulates, and acidosis worsens. Serious effects of methanol poisoning begin to present. Visual disturbances and central nervous system symptoms (such as seizures) predominate.
- Gastrointestinal symptoms may include hemorrhagic gastritis or pancreatitis.
- Hyperpnea (Kussmaul respirations) may be present with severe metabolic acidosis.

B. Investigation

- Confirmed ingestion of methanol-containing substances from patient or witness may facilitate diagnosis.
- Positive serum methanol concentrations can offer definitive diagnosis, but methanol concentrations below limit of detection cannot rule out methanol poisoning. Co-ingestion of ethanol or other substances may affect methanol metabolism and serum methanol levels.
- Routine toxicity evaluations are especially important in patients with incomplete or unknown histories.
    - Measure arterial pH in all patients.

- Severe metabolic acidosis with increased osmolar or anion gaps suggests methanol or ethylene glycol poisoning.
- Arterial blood gases suggest methanol poisoning if metabolic acidosis is severe.
- Low total carbon dioxide measurements may suggest metabolic acidosis.

- Brain imaging indicated in patients presenting with altered mental status, seizures, coma, or focal neurological abnormalities. Computed tomography is often normal within the first 24 hours of exposure.
- Nonenhanced head computed tomography findings in patients with severe methanol poisoning may include putamen hypodensity or caudate nucleus.
- Calculate anion gap = $(Na+) – (Cl− + HCO3−)$: Normal = 8–12
- Determine serum osmol gap: Osmol gap = measured osmolality – calculated osmolarity
- Calculated osmolarity = 2(Na+) + glucose/18 + BUN/2.8 + ethanol (in mg/dL)/4.6

VI. DIFFERENTIAL DIAGNOSIS

Few conditions other than methanol and ethylene glycol intoxication present with a profound metabolic acidosis (serum bicarbonate less than 8 mEq/L), and most of these conditions present in a characteristic fashion (e.g., status epilepticus, profound shock, ischemic bowel).
other causes of elevated serum osmolar gap or anion gap, including

- diabetic ketoacidosis
- alcoholic ketoacidosis
- multiple organ failure
- chronic kidney failure
- critical illness
- spurious hyponatremia secondary to hyperlipidemia or hyperproteinemia
- endogenous solutes (such as amino acids during end-stage organ failure)
- exposure to some other substances.

Methanol and Ethylene glycol poisoning have some similarity as cause of severe metabolic acidosis, neurologic symptoms. Ocular toxicity from methanol is more frequent than from Ethylene glycol. The antidote treatment is the same for the two: Fomepizole or ethanol. The difference is on the toxic metabolite that is formic acid from methanol, and Glycolic acid from ethylene glycol. The onset of symptom of ethylene glycol poisoning is sooner than methanol, and ethylene glycol causes acute renal failure (from calcium depot), more frequent than methanol poisoning.
Clinical poisoning of Ethyle glycol has historically been divided into three stages, although timing may vary, and stages may overlap:

- The first or “neurologic” stage typically begins 30 minutes to 12 hours after ingestion due to the intoxicating effects of the ethylene glycol parent compound
- The second or “cardiopulmonary” stage begins 12 to 24 hours after ingestion. Arrythmia, multiorgan dysfunction, hypocalcemia. Most deaths occur during this stage.
- The third or “renal” stage is often delayed 24 to 72 hours after ingestion. Renal failure, delay neuropathy

VII. MANAGEMENT

1. Objectives
   - Block or delay methanol and ethylene glycol metabolism,
   - Treat the toxic effects of formic acid glycolic acid
   - Facilitate the elimination of formic acid and methanol

- Prevent and early treatment of acute kidney injury (ethylene glycol)

2. Critical signs
   - Rapid and deep respiration (Kussmaul respiration)
   - Blurred vision
   - seizures
3. Mortality risk factors
   - Severe metabolic acidosis, pH< 7.2
   - Coma
   - Acute kidney failure
   - High concentration of methanol
4. Out-patient treatment
   - Transport all possibly ingested substances
   - Dermal decontamination of a methanol spill by clothing removal, irrigation with soap and water
   - Monitor airway and CNS depression
5. First line treatment

- **Initial Stabilization/Therapy**

Airway, breathing, and circulation (ABCs)
Dextrose, naloxone, and thiamine for altered mental status and known hypoglycemia, suspect opioids overdose or alcoholism respectively.
Prevent further methanol absorption:

- ❖ Gastric lavage with nasogastric tube: no indication
- ❖ Activated charcoal: may be use for co-ingestants.

- **Ed Treatment/Procedures**
  - ❖ Prevent methanol conversion to toxic metabolites with fomepizole (preferable) or ethanol infusion
  - ❖ Fomepizole (4-MP, Antizol®):
    - Competitive inhibitor of alcohol dehydrogenase
    - Indications:
      - Intentional methanol ingestion OR
      - Accidental methanol ingestion of more than a sip OR
      - Altered mental status or visual symptoms associated with unexplained osmol gap >10 mmol/L and/or elevated anion gap metabolic acidosis, bicarbonate <20 mmol/L, serum pH <7.3
    - Initiate before serum methanol level returns if intentional ingestion or more than a sip OR if serum methanol concentration is >20 mg/dL
      - Fomepizole Loading dose: 15 mg/kg slow infusion over 30 min
      - Maintenance dose: 10 mg/kg q12h for 4 doses, then 15 mg/kg q12h until methanol levels reduced <20 mg/dL
      - Dosing related to hemodialysis:
        - Do not administer dose at beginning of dialysis if last dose was <6 hr previously
        - Administer next dose if last dose was >6 hr previously
        - Dose q4h during dialysis
        - If time between last dose and end of dialysis was <1 hr from last dose, do not administer new dose
        - If time between last dose and end of dialysis was 1–3 hr from last dose, administer 1/2 of next scheduled dose

            - If time between last dose and end of dialysis was >3 hr from last dose, administer next scheduled dose
    - Continue until methanol level is <20 mg/dL
    - Advantages:
        - No need for continuous infusion
        - No inebriation/CNS depression
        - Ease of dosing
        - No hypoglycemia, no hyponatremia, no hyperosmolality
        - No checking serum concentrations
        - Reduced nursing care and monitoring
        - Occult methanol exposure can often be ruled out before 2nd dose is needed
    - Disadvantages:
        - Blurry vision
        - Transient elevation of liver function tests
- **Ethanol therapy**
    - Not FDA approved for treatment of methanol
    - Ethanol has greater affinity than methanol for alcohol dehydrogenase:
        - Slows metabolism to formaldehyde and formic acid by competitive inhibition
    - Ethanol is the 2nd-choice antidote if fomepizole is not available
    - Initiate before methanol level returns if potentially toxic ingestion is highly suspected or confirmed by history:
        - Therapeutic range is 100 mg/dL
        - Oral: 50% ethanol solution (100-proof liquor) via nasogastric tube:
            - Loading dose 2 mL/kg
            - Maintenance dose 0.5 mL/kg/hr
            - Maintenance dose during hemodialysis 1 mL/kg/hr
        - IV: 10% ethanol in D5W:
            - Loading dose 8 mL/kg over 30–60 min
            - Maintenance infusion 2 mL/kg/hr
            - Maintenance infusion during hemodialysis 4 mL/kg/hr
    - Continue until methanol level is <20 mg/dL
    - Indications for ethanol therapy:
        - Intentional methanol ingestion
        - Accidental methanol ingestion of more than a sip OR
        - Altered mental status or visual symptoms associated with unexplained osmol gap > 10 mmol/L and or elevated anion gap metabolic acidosis, bicarbonate <20 mmol/L and serum pH <7.3 OR
        - Serum methanol concentration >20 mg/dL
    - Advantages:
        - Easily accessible
        - Oral and IV routes
    - Disadvantages:
        - CNS depression especially in children
        - Respiratory depression
        - Hyponatremia or hypernatremia
        - Hypoglycemia
        - Hyperosmolarity
        - Continuous infusion

        - Frequent lab testing
        - Contraindicated in pregnancy
        - Pancreatitis
        - Gastritis
- Folic acid and folinic acid (leucovorin):
    - Folic acid: Cofactor required for conversion of formic acid to carbon dioxide and water
    - Folic acid: 50 mg (or 1–2 mg/kg) IV q4h for 24 hr
    - Supplemental folate important in malnourished individuals (alcoholics)
- Correct acid–base abnormalities:
    - Sodium bicarbonate for severe acidosis (pH <7.3)
    - Sodium bicarbonate: 1–2 mEq/kg in 1 L of D5W with 40 mEq KCl at 250 mL/hr
    - The goal of the sodium bicarbonate drip is to maintain a normal serum pH
    - Full compensation (mmol) = 0.3 x body weigh x Base deficit
- Hemodialysis:
    - Decreases elimination half-life of methanol
    - Removes formaldehyde and formic acid
    - Indications:
        - Ingestion of >1 mL/kg of 100% methanol OR
        - Ophthalmologic manifestations OR
        - Severe metabolic acidosis, bicarbonate <20 mmol/L and serum pH <7.3 OR
        - Serum methanol level >50 mg/dL alone without above criteria
- Continue hemodialysis until methanol level approaches <20 mg/dL and the metabolic acidosis has resolved

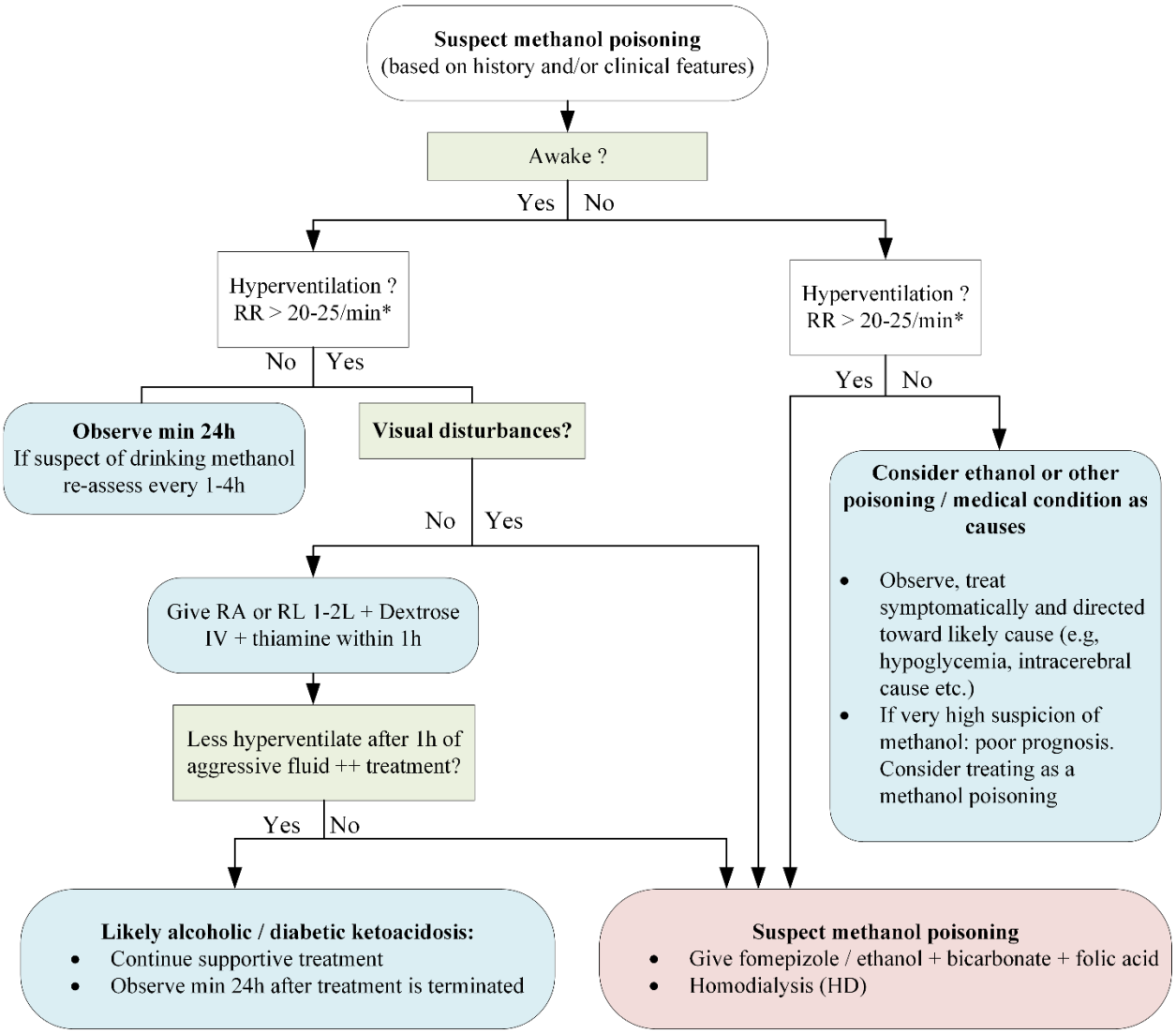
6. Treatment adjustment
    - Not all patients will have an elevated osmol and anion gap. Early presenters will have an osmol gap only, because methanol is osmotically active, and there are no toxic metabolites yet. Late presenters may have an anion gap only, because the osmotically active parent compound has metabolized to the toxic acidotic metabolites. Patients who are present in between will have a combination of an anion gap and an osmol gap.
    - supportive therapy for methanol poisoning includes treatment with
        - IV fluids
        - sodium bicarbonate in patients with severe metabolic acidosis. Dose to give (mmol) = 0.3 x body weight (kg) x base deficit
        - antiseizure medications in patients with seizures
        - Cofactors
            - In a methanol-poisoned patient, administer either leucovorin 50 mg IV or folic acid 50mg IV every six hours.
            - In an ethylene glycol-poisoned patient, administer thiamine 100 mg IV and pyridoxine 100 mg IV daily.
            - If toxic alcohol poisoning is possible or suspected but the exact alcohol is unknown, especially in the presence of a metabolic acidosis, it is reasonable to empirically administer all three cofactors

7. Algorithm
Approach to possible methanol or ethylene glycol poisoning when confirmatory

toxicologic testing is not available.

Note that Fomepizole an intravenous ethanol is not available in most hospital in Cambodia, as well as measurement of blood methanol level, at least until this day (end of 2024).

Diagnosis algorithm for methanol poisoning without ABGs

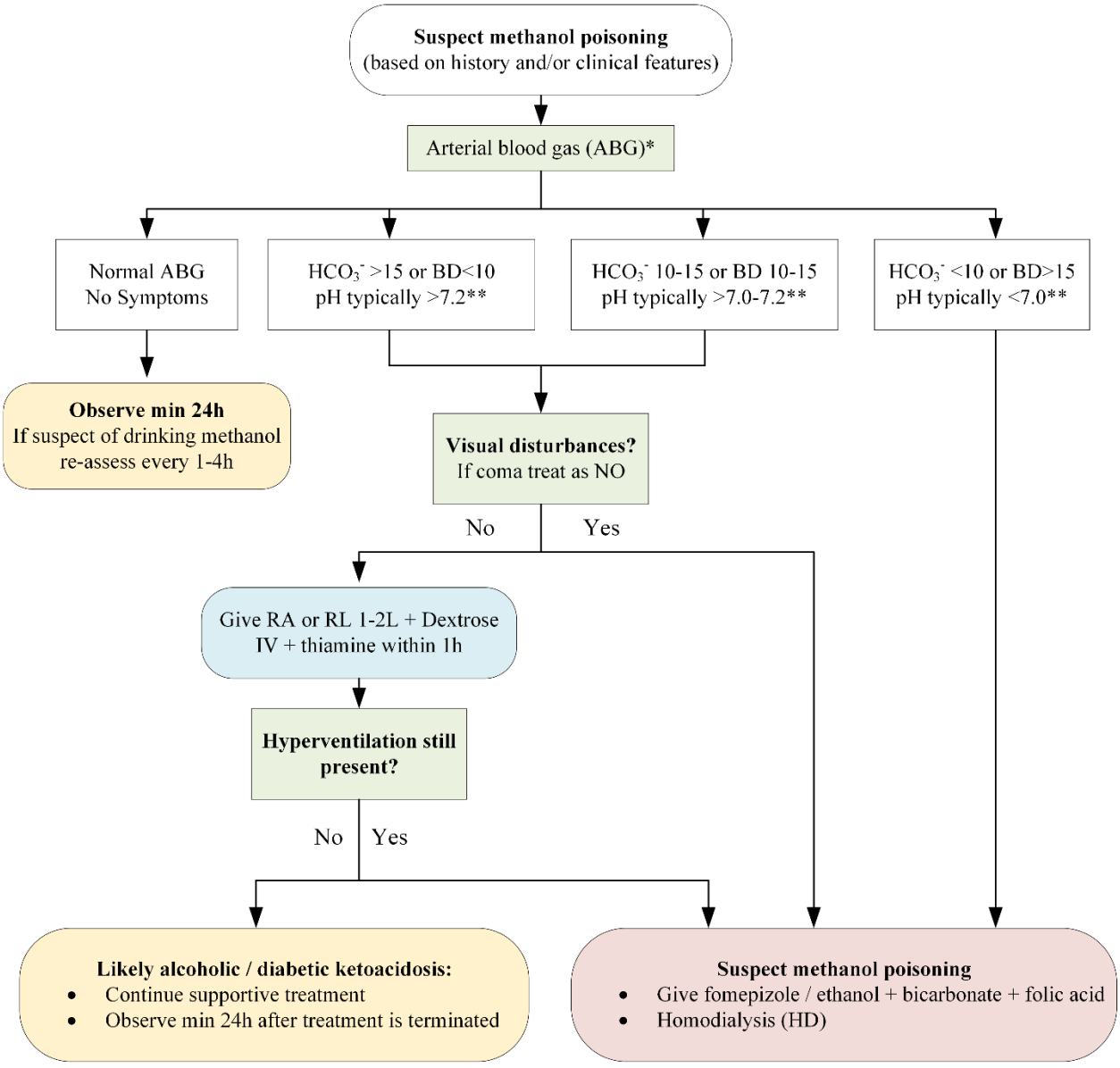


* Always consider other causes of metabolic acidosis
- Diabetic ketoacidosis: known diabetic? Check blood glucose
- Renal failure: known renal failure? Diuresis? Creatinine?
- Sepsis: other signs of infection? Fever? WBC? CRP? Etc..

RA: Ringer acetate, RL: Ringer lactate, ABG: arterial blood gas

Adapted from Methanol poisoning-protocol-EMACC-WG / MSF Norway / Oslo University Hospital - 2023

Diagnosis algorithm for methanol poisoning with ABGs



* Always consider other causes of metabolic acidosis
- Diabetic ketoacidosis: known diabetic? Check blood glucose
- Renal failure: known renal failure? Diuresis? Creatinine?
- Sepsis: other signs of infection? Fever? WBC? CRP? Etc..

** pH will always depend on degree of hyperventilation. Therefore focus primarily on base deficit (BD) or HCO3
RA: Ringer acetate, RL: Ringer lactate, BD: base deficit,
ABG: arterial blood gas

Adapted from Methanol poisoning-protocol-EMACC-WG / MSF Norway / Oslo University Hospital - 2023

VIII. SPECIAL CASES

Unavailability of antidotes (Fomepizole, or ethanol for injection), consider ethanol oral

(usually not practical), and hemodialysis. Check the alcohol content (%) of spirit to use if medical product 50% was not available. Mind also the ingredients used in that spirit.
Severe patients (pH<7.2, visual disturbance, bicarbonate <20 mmol/L) should be transferred to institution where Hemodialysis is available, and early indication should be considered.

IX. EVOLUTION AND PROGNOSIS

The prognosis in methanol poisoning correlates with the amount of methanol consumed and the subsequent degree of metabolic acidosis; more severe acidosis confers a poorer prognosis. The prognosis is further dependent on the amount of formic acid that has accumulated in the blood, with a direct correlation existing between the formic acid concentration and morbidity and mortality. Little long-term improvement can be expected in patients with neurologic complications.

X. COMPLICATIONS

- visual dysfunction (33%-40% of patients reported to have permanent visual sequelae)
- acute pancreatitis
- Parkinson-like extrapyramidal syndrome
- rare neurological complications include
    - transverse myelitis
    - pseudobulbar palsy
    - cognitive defects
    - brain hemorrhage
- myoglobinuria is rare but may lead to acute kidney injury
- fatal intracranial hemorrhage reported 46 hours after methanol poisoning from ingesting windshield wiper fluid.

XI. PREVENTION AND RECOMMENDATION

- Increase public awareness about the dangers of methanol poisoning and the importance of consuming safe alcoholic beverages
- Strengthen regulations and enforcement to prevent the sale of illicit or adulterated alcohol.
- Ensure healthcare facilities are equipped to diagnose and treat methanol poisoning promptly.

XII. REFERENCES

1. Kirk L. Cumpston. Methanol poisoning in 5 minutes Emergency Consult, Unbound Medicine platform, 2024, Wolters Kluwer Health Lippincott Williams & Wilkins. Accessed Nov 2024
2. DynaMed. Methanol Poisoning. EBSCO Information Services. Accessed November 16, 2024. https://www.dynamed.com/condition/methanol-poisoning
3. UpToDate. Methanol and Ethylene glycol poisoning. Walters Kluwer. Accessed Nov 2024 https://www.uptodate.com/contents/methanol-and-ethylene-glycol-poisoning-pharmacology-clinical-manifestations-and-diagnosis

CARDIOPULMONARY ARREST
BASIC AND ADVANCE CARDIAC LIFE SUPPORT

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I. DEFINITION

Cardiac arrest is the cessation of cardiac mechanical activity resulting in the absence of circulating blood flow, confirmed by the absence of a pulse, apnea or agonal breathing ("gasping") and unconsciousness. Cardiac arrest stops blood from flowing to vital organs, depriving them of oxygen, and, if left untreated, results in death.

II. EPIDEMIOLOGY

Cardiac arrest (or cardiocirculatory arrest) in adults is a common syndrome and constitutes an absolute life-threatening emergency. It occurs most often outside the hospital and affects twice as many men as women with an average age of 60 years. The main cause is coronary ischemia through a mechanism of ventricular rhythm disturbance (ventricular fibrillation or tachycardia).

III. ETIOLOGY

- Acute coronary syndrome (40%-77% depending on the study)
- Other cardiac and vascular etiologies
  - Rhythm disorder in ancient ischemic heart disease.
  - Hypertrophic cardiomyopathy or dilated cardiomyopathy.
  - Arrhythmogenic right ventricular dysplasia.
  - Arrhythmia-conduction disorder
    - Idiopathic ventricular fibrillation (VF)
    - Brugada syndrome
    - Paroxysmal auriculoventricular (AV) block (elderly +)
    - Congenital or drug-induced long QT syndromes
    - Congenital short QT syndromes.
    - Wolff-Parkinson-White syndrome
  - Congenital cardiopathy (Tetralogy of Fallot)
  - Acute myocarditis
  - Tamponade.
  - Aortic dissection
  - Massive pulmonary embolism
  - Aneurysm rupture.
  - Non-cardiovascular origins (5 to 25%): The most common are toxic, traumatic causes, acute respiratory failure or drowning.
- Risk factors associate with atherosclerotic coronary artery disease.
  - Smoking
  - Hypercholesterolemia
  - High blood pressure
  - Diabetes
  - Familial histories of coronary artery disease

- **In infants and children**, cardiac causes of cardiac arrest are less common than in adults. The predominant cause of cardiac arrest in infants and children is respiratory failure due to various respiratory disorders (eg, airway obstruction, drowning, infection, sudden infant death syndrome [SIDS], smoke inhalation).

IV. PATHOPHYSIOLOGY

We divide in two sections depending on whether respiratory arrest or cardiac arrest occurs first. Respiratory arrest (blood circulation continues, there is no cardiac arrest yet) lead to hypoxia, hypercapnia, and acidosis (muscular hypoxia produces lactic acid) and then, these three conditions cause secondary cardiac arrest.
A victim may be in cardiac arrest (absence of pulse) and continue to breathe (agonal breathing).

V. DIAGNOSIS

The diagnosis of cardiopulmonary arrest should be rapid (<10 seconds), confirmed by loss of consciousness (coma), apnea or agonal breathing ("gasping"), absence of arterial pulse either in the carotid or femoral artery.



At the moment of high-quality cardiopulmonary resuscitation (CPR), blood and radiological investigation may be needed; like blood sugar; serum potassium; EKG (Pulseless ventricular tachycardia (VT); Ventricular fibrillation; Asystole; Pulseless electrical activity (PEA)), Heart ultrasound.

It is essential to diagnose the signs of aspirations of a foreign body in the respiratory tract, which includes severe stridor, dyspnea, suprasternal and intercostal retractions. It is recommended to do the Heimlich maneuver if we are suspecting aspiration.

VI. DIFFERENCIAL DIAGNOSIS

- Coma
- Syncope
- Seizure
- opiate overdose

VII. MANAGEMENT

1. Objective

- To maintain an open and clear airway (A).
- To maintain breathing by external ventilation (B).
- To maintain blood circulation by external cardiac massage (C).

2. Warning signs of sudden cardiac arrest (But often has no warning)

- Chest pain,
- Sweating,
- Shortness of breath,
- Palpitation or Dizziness

3- Mortality risk factors of cardiac arrest

- History of cerebrovascular disease
- Higher lactate and presence of PEA or asystole.
- Being aged 45-60 years old.

4- Out hospital management of Out hospital cardiac arrest (OHCA)

Adult chain of survival



Adult OHCA Chain of Survival

Basic life support (BLS) for adult

BLS for adults focuses on doing several tasks simultaneously. In many situations, more than one person is available to do CPR. This choreographed method includes performing chest compressions, managing the airway, delivering rescue breaths, and using the automatic external defibrillation (AED), all as a team. By coordinating efforts, a team of rescuers can save valuable seconds when time lost equals damage to the heart and brain.

Danger **(Make sure it's safe to help)**	Wear personal protective equipment (PPE) (gloves, apron, mask) if available Look out for blood spills, sharps, electric wire, etc.
Responsiveness **(Check the victim for a response)**	Tap shoulder. Say 'Hello, hello are you OK?'
Shout for help **(Ask for help and defibrillator)**	Emergency! Emergency! Bring the resus trolley and Defibrillator!

Circulation **(Start chest compression)**	High quality chest compression - Middle of chest and lower half of sternum - Depth: 5-6 cm - Rate: 100-120/mn - Full recoil after each compression - Minimize interruption. - 30 compressions / 2 ventilations - Each ventilation in 1 second. Ventilation methods: • Bag Valve Mask (BVM) • Mouth to mask • Mouth to mouth rescue breathing • Mouth to nose rescue breathing • Mouth to stoma
Defibrillation **(Assess for need to shock)**	- Attach AED - Do not interrupt chest compression. - Follow AED voice prompt. - Immediately continue CPR
Airway **(Open the airway)**	Perform head tilt-chin lift or Jaw thrust (if suspected cervical injury) Do Heimlich maneuver if we are suspecting a foreign body in the respiratory tract.
Breathing **(Assess for normal breathing)**	Look for normal breathing in not more than 10 seconds. Start chest compressions if not breathing or abnormal breathing (gasping) is seen.
Reassessment **(Every 5 cycles or 2mn of CPR)**	If the patient recovers with normal breathing?
Recovery position	After the victim has normal breathing but is still unresponsive, place the victim in recovery position.

5- First-line treatment of n hospital cardiac arrest (IHCA)

Adult chain of survival

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Advance cardiac life support (ACLS) for adult (A-B-C-D)

Adult IHCA Chain of Survival

Airway **(Open the airway)**	- Maintain an open airway at all times. - Decide if the benefit of adding an advanced airway outweighs the risk of pausing CPR. If the individual's chest is rising without using an advanced airway, continue giving CPR without pausing. - if you are in a hospital or near trained professionals who can efficiently insert and use the airway, consider pausing CPR.
Breathing **(Assess for normal breathing)**	- Administer 100% oxygen (SaO2 ≥ 94%). - High-quality CPR should produce an End-Tidal CO2 (ETCO2) between 10 to 20 mmHg (if < 10 mmHg after 20 minutes of CPR for an intubated individual (Over ventilated), then you may consider stopping resuscitation attempts). Normal partial pression of CO2 (PaCO2) is between 35 to 40 mmHg.
Circulation **(Start chest compression)**	- Evaluate rhythm and pulse - Defibrillation/cardioversion - Obtain IV/IO access - Give rhythm-specific medications - Give IV/IO fluids if needed
Defibrillation **(Assess for need to shock)**	- Identify and treat reversible causes. - Cardiac rhythm and patient history are the keys to differential diagnosis. - Assess when to shock versus medicate

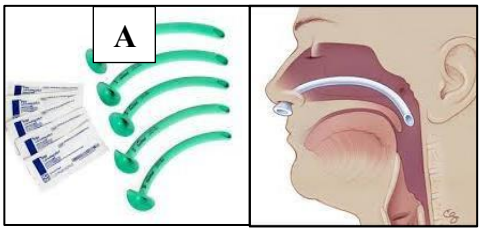
Airway management

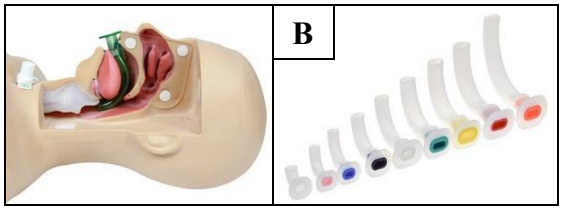
a) Basic airway adjuncts

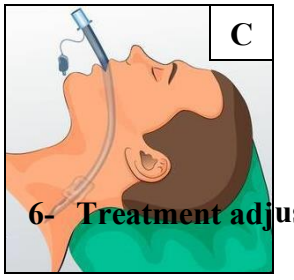
- Nasopharyngeal airway (NPA) **(A)**
- Oropharyngeal airway (OPA) **(B)**
- Suctioning

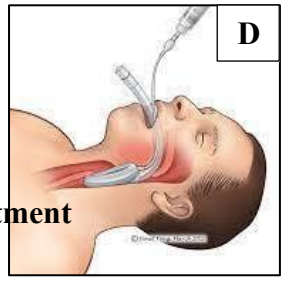
b) Advanced airway adjuncts

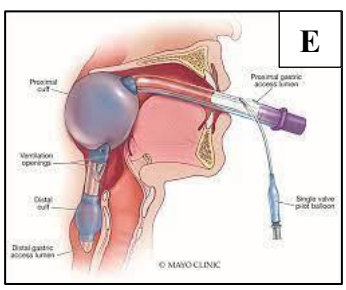
- Endotracheal tube **(C)**
- Laryngeal mask airway **(D)**
- Laryngeal tube **(E)**
- Esophageal-tracheal tube **(F)**

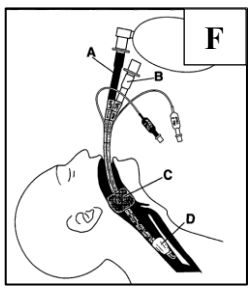












6- Treatment adjustment

6. Treatment adjustment

A) Pharmacological tools

Doses, Routes, and Uses of Common Drug

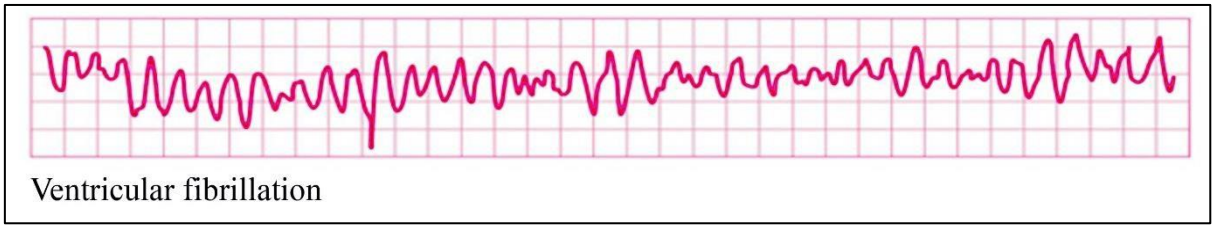
DRUG	MAIN ACLS USE	DOSE/ROUTE	NOTES
Adenosine	• *Narrow PSVT/SVT* • *Wide QRS tachycardia, avoid adenosine in irregular wide QRS*	• *6 mg IV bolus, may repeat with 12 mg in 1 to 2 min.*	• *Rapid IV push close to the hub, followed by a saline bolus* • *Continuous cardiac monitoring during administration* • *Causes flushing and chest heaviness*
Amiodarone	• *VF/pulseless VT* • *VT with pulse* • *Tachycardia rate control*	• *VF/VT: 300 mg dilute in 20 to 30 mL, may repeat 150 mg in 3 to 5 min*	• *Anticipate hypotension, bradycardia, and gastrointestinal toxicity* • *Continuous cardiac monitoring* • *Very long half-life (up to 40 days)* • *Do not use in 2nd or 3rd-degree heart block* • *Do not administer via the ET tube route*
Atropine	• *Symptomatic bradycardia*	• *1 mg IV/IO every 3 to 5 minutes* • *Max dose: 3 mg*	• *Cardiac and BP monitoring* • *Do not use in glaucoma or tachyarrhythmias* • *Minimum dose 1 mg*
	• *Specific toxins/overdose (e.g. organophosphates)*	• *2 to 4 mg IV/IO may be needed*	
Dopamine	• *Shock/CHF* • *Symptomatic bradycardia*	• *2 to 20 mcg/kg/min* • *Titrate to desired blood pressure*	• *Fluid resuscitation first* • *Cardiac and BP monitoring*
Epinephrine	• *Cardiac Arrest*	• *Initial: 1.0 mg (1:10000) IV or 2 to 2.5 mg (1:1000)* • *Maintain: 0.1 to 0.5 mcg/kg/min Titrate to desire blood pressure*	• *Continuous cardiac monitoring* • *Note: Distinguish between 1:1000 and 1:10000 concentrations* • *Give via central line when possible*
	• *Anaphylaxis*	• *0.3-0.5 mg IM* • *Repeat every five minutes as needed*	
	• *Symptomatic bradycardia/Shock*	• *2 to 10 mcg/min infusion* • *Titrate to response*	
Lidocaine ***(Lidocaine is recommended when Amiodarone is not available)***	• *Cardiac Arrest (VF/VT)*	• *Initial: 1 to 1.5 mg/kg IV loading* • *Second: Half of first dose in 5 to 10 min* • *Maintain: 1 to 4 mg/min*	• *Cardiac and BP monitoring* • *Rapid bolus can cause hypotension and bradycardia* • *Use with caution in renal failure*
	• *Wide complex tachycardia with pulse*	• *Initial: 0.5 to 1.5 mg/kg IV* • *Second: Half of first dose in 5 to 10 min* • *Maintain: 1 to 4 mg/min*	
Magnesium Sulfate	• *Cardiac arrest/ Pulseless torsades*	• *Cardiac Arrest: 1 to 2 gm diluted in 10 mL D5W IVP*	• *Cardiac and BP monitoring* • *Rapid bolus can cause hypotension and bradycardia* • *Use with caution in renal failure* • *Calcium chloride can reverse hypermagnesemia*
	• *Torsades de Pointes with pulse*	• *If not cardiac arrest: 1 to 2 gm IV over 5 to 60 min* • *Maintain: 0.5 to 1 gm/hr IV*	
Procainamide	• *Wide QRS tachycardia* • *Preferred for VT with pulse (stable)*	• *20 to 50 mg/min IV until rhythm improves, hypotension occurs, QRS widens by 50% or MAX dose is given* • *MAX dose: 17 mg/kg* • *Drip: 1 to 2 gm in 250 to 500 mL at 1 to 4 mg/min*	• *Cardiac and BP monitoring* • *Caution with acute MI* • *May reduce dose with renal failure* • *Do not give with amiodarone* • *Do not use in prolonged QT or CHF*
Sotalol	• *Tachyarrhythmia* • *Monomorphic VT* • *3rd line anti-arrhythmic*	• *100 mg (1.5 mg/kg) IV over 5 min*	• *Do not use in prolonged QT*

B) Defibrillation

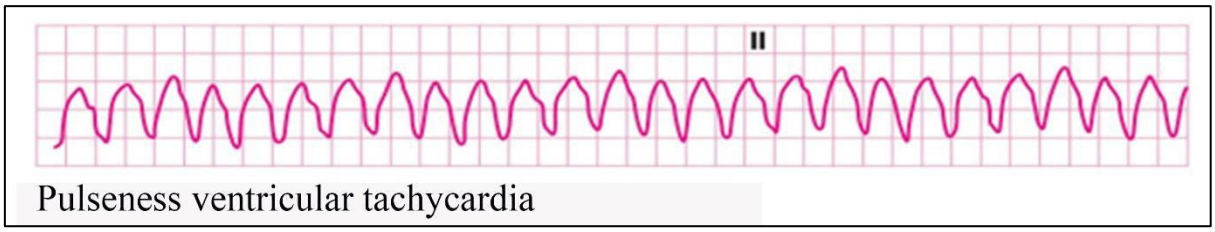
i. Patient selection

- Shockable rhythms: Ventricular fibrillation (VF) and Pulseless Ventricular tachycardia (VT)
- Unshockable rhythms: Asystole or PEA

Defibrillation is contraindicated for sinus rhythm, conscious patient with a pulse, or when there is danger to the operator or other (e.g., from a wet patient or wet surroundings).



Ventricular fibrillation



Pulseless ventricular tachycardia

ii. Equipment

There are two types of defibrillation's waveforms: monophasic and biphasic. The amount of energy required for successful defibrillation is typically lower with biphasic waveforms.

Manual defibrillators require a manual analysis of the patient's cardiac rhythm, as well as manual delivery of the shock through paddles or self-adhesive pads by the operator.

Automated external defibrillators (AED) may be fully or semi-automated. Fully automated external defibrillators will analyze the rhythm automatically, and if indicated, charge and deliver the shock, whereas semi-automated external defibrillators will require an operator to manually deliver the shock after analysis and charging.

iii. Patient positioning and skin preparation

Ensure that scene is safe for performing defibrillation including water and environmental scene dangers such as traffic. The patient should be in the supine position with ongoing CPR. To avoid skin burns, remove all metallic objects, jewelry, or medication patches (wipe off any residue). If there is excessive chest hair over the areas where the pads or paddles are to be placed, quickly shave the hair off to ensure a good contact with skin. Remove all direct sources of oxygen to avoid fire.

a) Placement of pads/paddles

There are several possible positions for the placement of the pads or paddles:

- **Antero apical position**: place one paddle/pad to the right of the upper half of the sternum, just below the patient's right clavicle, and place the other pad just below and to the left of the left nipple. With a female patient, place the

paddle/pad just below and to the left side of the breast. Do not place it over the breast.

- **Anteroposterior position**: Place one pad/paddle at the left lower sternal border and the posterior pad/paddle below the left scapula
- Pacemakers automated implantable cardiac defibrillators, and other implants: such devices are implanted under the skin and palpable on examination. Ensure that the placement of the pads is at least four fingerbreadths away from such devices.

iv. Step-by-step technique

❖ **Manual defibrillation**

a. Prepare the patient and equipment as described earlier. **CPR should be ongoing**.
b. If using paddles, attach the **rhythm monitoring electrodes**. Alternatively, the paddles may be applied to the chest directly in "quick look" mode to read the rhythm.
c. If pads are used, the rhythm will be read by the pads, and additional rhythm electrodes are not necessary.
d. Interrupt chest compressions only briefly (<10 seconds) to **analyze the rhythm** manually.
e. Confirm that the rhythm is ventricular fibrillation or pulseless ventricular tachycardia, then **resume CPR immediately.**
f. Select the appropriate **energy level.** For biphasic defibrillators, select according to the manufacturer's recommendation (150 to 200 J for biphasic truncated exponential waveforms and 120 to 200 J for rectilinear biphasic waveforms). If the recommendation is unknown use the maximum energy available. For monophasic defibrillators, begin with an initial 360-J shock. If starting with less than the maximum energy, consider escalation of shock energy for failed shocks or recurrence of fibrillation.
g. Ensure that the defibrillator is in **unsynchronized mode.**
h. If using paddles, apply the paddles and **charge.** CPR should NOT be interrupted during charging. All other personnel may begin to stand clear at this point.
i. Call out, **"Stand clear,"** and ensure that no one is in contact with the patient or trolley. CPR is interrupted only briefly (<10 seconds) at this point.
j. With the CPR interrupted, quickly confirm the rhythm remains shockable, then **deliver the shock**. The operator's eyes should be back on the patient at the time of shock delivery, to ensure safety.
k. Resume CPR immediately once the shock has been delivered. Do NOT pause to check the pulse or reanalyze the rhythm at this time.
l. Continue management according to the local resuscitation protocol.

❖ **Automated external defibrillation (AED)**

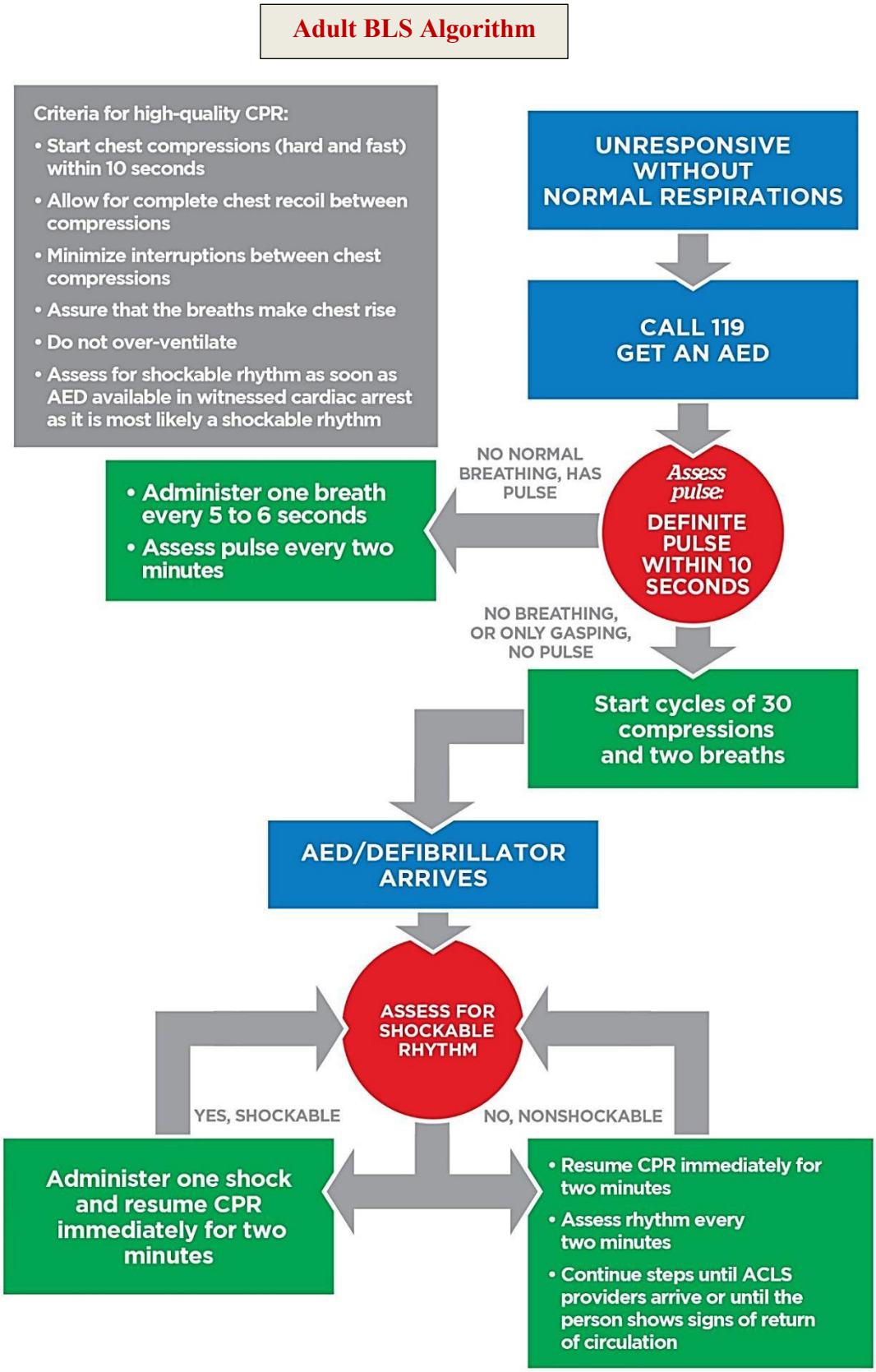
a. Prepare the patient and equipment as described earlier. **CPR should be ongoing.**
b. **Turn on** the automated external defibrillator (follow the voice prompts according to your device).

c. Open the package containing the **defibrillation pads** with the attached cable and connector. With the chest prepared, carefully pull off the protective backing from the pads and apply the pads to the chest, taking care to avoid air pockets. The pads should be placed at least 2 inches away from any automated implantable cardiac defibrillators.
d. Initiate **analysis** of the rhythm. This may be automatic or require pressing a button to activate analysis. Ensure that there is no movement of the patient during analysis, including a brief interruption of CPR.
e. If a shock is advised, the device will **automatically charge** to a preset energy level. If a semi-automated external defibrillator is used, CPR should immediately resume while charging. All other personnel may begin to stand clear at this point. Note that fully automated defibrillators do not require the operator's input to discharge a shock, and all rescuers should stay clear at the time of charging. Follow the voice prompts of the device.
f. Call out, **"Stand clear,"** and ensure that no one is in contact with the patient or trolley. CPR is interrupted only briefly (<10 seconds) at this point.
g. **Deliver the shock**.
h. Resume CPR immediately once the shock has been delivered. Do NOT pause to check the pulse or reanalyze the rhythm at this time.
i. Continue management according to the local resuscitation protocol.
j. There are increasing numbers of automated external defibrillators that provide CPR "guidance" in the form of metronome beats or active feedback on the correct rate and depth of chest compressions in real time. Achieving optimal CPR quality increases the likelihood of successful defibrillation.

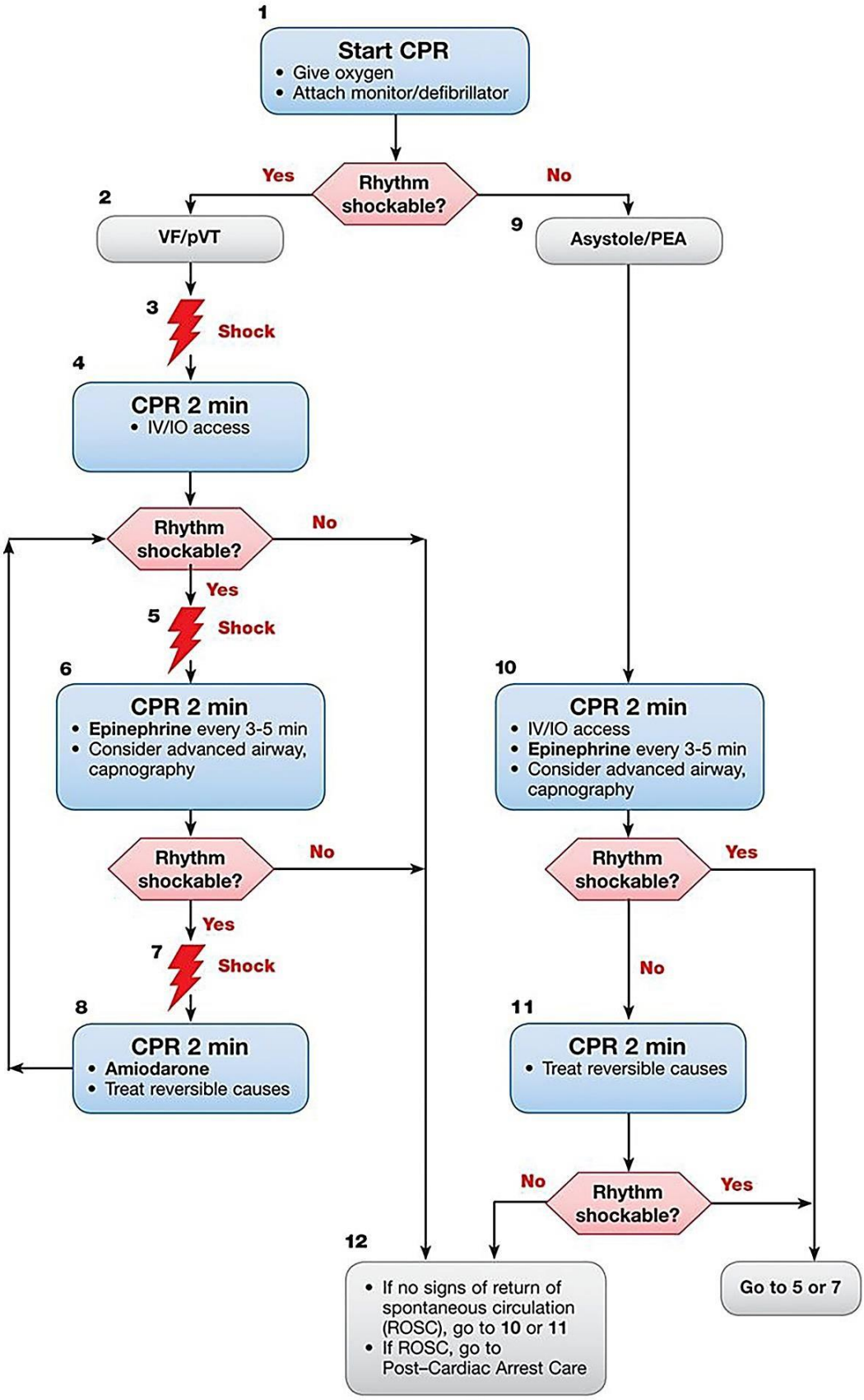
v. Risks and precautions

Electrical energy can terminate an abnormal rhythm, but if inappropriately delivered, it may also induce ventricular fibrillation. This can happen if the electric shock is delivered during the relative refractory period of the cardiac electrical cycle. Movement artifacts or loose leads may resemble ventricular fibrillation and result in an inappropriate shock. New defibrillator technology is available that can filter compression or movement artifacts to "see through" the artifacts to reveal underlying rhythm. However, when using automated external defibrillators, all manufacturers currently still recommend stopping all compressions and patient movement (e.g., during transport) before initiating rhythm analysis.

A. Algorithm


Adult BLS Algorithm
Criteria for high-quality CPR:
• Start chest compressions (hard and fast) within 10 seconds
• Allow for complete chest recoil between compressions
• Minimize interruptions between chest compressions
• Assure that the breaths make chest rise
• Do not over-ventilate
• Assess for shockable rhythm as soon as AED available in witnessed cardiac arrest as it is most likely a shockable rhythm
UNRESPONSIVE WITHOUT NORMAL RESPIRATIONS
CALL 119 GET AN AED
Assess pulse:
DEFINITE PULSE WITHIN 10 SECONDS
NO NORMAL BREATHING, HAS PULSE
• Administer one breath every 5 to 6 seconds
• Assess pulse every two minutes
NO BREATHING, OR ONLY GASPING, NO PULSE
Start cycles of 30 compressions and two breaths
AED/DEFIBRILLATOR ARRIVES
ASSESS FOR SHOCKABLE RHYTHM
YES, SHOCKABLE
NO, NONSHOCKABLE
Administer one shock and resume CPR immediately for two minutes
• Resume CPR immediately for two minutes
• Assess rhythm every two minutes
• Continue steps until ACLS providers arrive or until the person shows signs of return of circulation

Adult ACLS Algorithm



CPR Quality

- Push hard (at least 2 inches [5 cm]) and fast (100-120/min) and allow complete chest recoil.
- Minimize interruptions in compressions.
- Avoid excessive ventilation.
- Rotate compressor every 2 minutes, or sooner if fatigued.
- If no advanced airway, 30:2 compression-ventilation ratio.
- Quantitative waveform capnography
  - If P_{ETCO_2} <10 mm Hg, attempt to improve CPR quality.
- Intra-arterial pressure
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality.

Shock Energy for Defibrillation

- **Biphasic:** Manufacturer recommendation (eg, initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 J

Drug Therapy

- **Epinephrine IV/IO dose:** 1 mg every 3-5 minutes
- **Amiodarone IV/IO dose:** First dose: 300 mg bolus. Second dose: 150 mg.

Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6 seconds (10 breaths/min) with continuous chest compressions

Return of Spontaneous Circulation (ROSC)

- Pulse and blood pressure
- Abrupt sustained increase in P_{ETCO_2} (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible Causes

- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

H: HYPOVOLEMIA OR HEMORRHAGE

History of fluid or blood loss may be available. Rectal examination can identify massive lower GI bleeding; nasogastric intubation can identify massive upper GI bleeding; and bedside FAST can diagnose massive intraperitoneal bleeding. Treat with fluids and blood products.

H: HYPOXIA

Hypoxia occurs with lack of oxygen and alveolar ventilation. Make sure that the airway adjunct is placed correctly. Check breath sounds at intervals to ensure that the endotracheal tube has not slipped out of the trachea or to identify pneumothorax. Verify the source of oxygen—an oxygen cylinder or the piped oxygen supply.

H: HYPOTHERMIA

Treat hypothermia with gradual rewarming with blankets and warm IV fluids. If there is no recovery of consciousness in the hypothermic patient following ROSC, maintain a body core temperature of 33°C until further assessment and decisions can be made.

H: HYDROGEN ION (ACIDOSIS)

The acidosis of cardiac arrest is a combination of respiratory and metabolic acidosis. Respiratory acidosis is addressed by early endotracheal intubation and alveolar ventilation. Metabolic acidosis can be somewhat addressed by good-quality CPR. Sodium bicarbonate can be administered for severe metabolic acidosis from prolonged or poor initial resuscitation, at a dose of 1 to 1.5 mEq/kg. Half the initial dose can be readministered after 10 to 15 minutes, depending on pH. However, data currently do not support routine administration of sodium bicarbonate for acidosis, with no controlled studies demonstrating improved hemodynamics with sodium bicarbonate.[62] If administered, ventilatory rate should be increased to counteract the increased CO_2 produced by sodium bicarbonate. Continuous venovenous hemodialysis may be required for severe acidosis.[62]

H: HYPER- OR HYPOKALEMIA, OTHER METABOLIC DISORDERS

Suspect hyperkalemia in patients on hemodialysis or peritoneal dialysis (look for presence of arteriovenous fistula or dialysis catheter). Other metabolic disorders are extremely difficult to confidently identify in cardiac arrest. If hyperkalemia is suspected, administer calcium chloride, sodium bicarbonate, insulin, and glucose. Treat hyperkalemia from suspected digitalis toxicity with IV magnesium sulfate or digoxin-specific Fab fragments (Digibind®).

T: THROMBOSIS (PULMONARY EMBOLISM)

Pulmonary embolism causing cardiac arrest requires fibrinolysis or embolectomy. However, the diagnosis is rarely made at time of collapse, and even then, most systems are not geared to make such prompt diagnosis and initiate the necessary procedures for embolectomy. Fibrinolytic agents could be considered during cardiac arrest from suspected pulmonary embolism on a case-by-case basis.[72] A single-center case series of patients with diagnosed pulmonary embolism suffering PEA arrest found that rapid administration of alteplase 50 milligrams IV to be safe and effective, with 20 of 23 patients demonstrating ROSC.[73-75] High-quality compressions should be continued after thrombolytic therapy is administered, with several studies recommending 60 to 90 seconds of compression after the drug is given. Factors suggestive of pulmonary embolism causing cardiac arrest include two of three signs or symptoms (prearrest respiratory distress, altered mental status, or shock); arrest witnessed by a physician or emergency medical technician; and PEA as the first or primary arrest rhythm.

T: "TABLETS" (DRUG OVERDOSE)

Drug overdose is rarely identified as a cause of cardiac arrest during the resuscitation process. In the event of antidepressant overdose, administer IV sodium bicarbonate. Lipid emulsion infusion may be useful in cardiac arrest associated with cyclic antidepressants or local anesthetics. β-Blocker or calcium channel–blocker overdose may require high-dose insulin therapy and lipid emulsion infusion.

T: CARDIAC TAMPONADE

Cardiac tamponade is best identified during resuscitation by bedside transthoracic US. This requires brief interruption of chest compressions. Treatment of tamponade causing cardiac arrest is bedside pericardiocentesis.

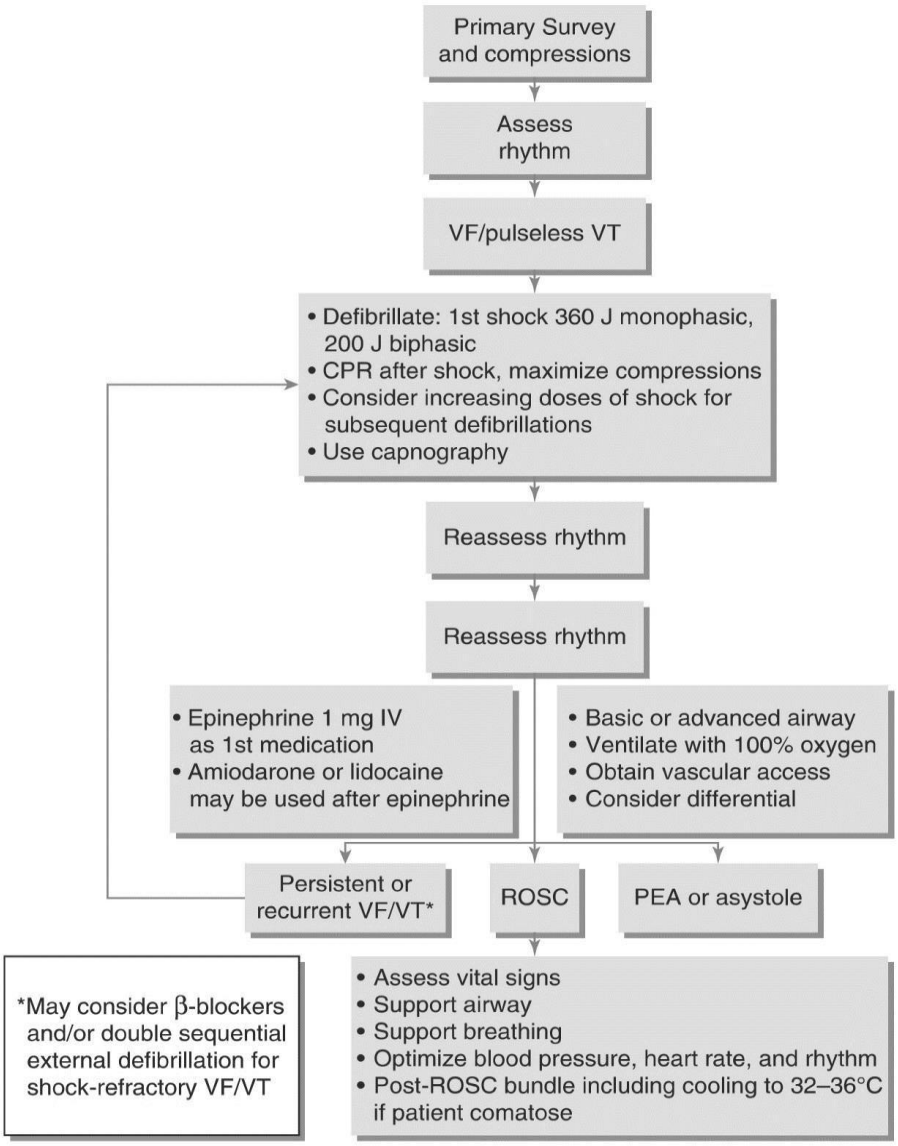
T: CORONARY THROMBOSIS

Acute coronary thrombosis or acute myocardial infarction is one of the most common causes of cardiac arrest. Risk factors are a history of coronary artery disease and initial rhythm of VF/VT.[63-67] Cardiac catheterization after resuscitation is an underused procedure.[67] A 12-lead ECG in the immediate post–cardiac arrest state can identify an ST-segment elevation acute myocardial infarction and allow arrangements for immediate coronary angiography. Myocardial and neurologic function can improve after percutaneous coronary intervention following cardiac arrest.[68] The 2015 American Heart Association/American College of Cardiology guidelines[1] provide a class I recommendation to activate the cardiac catheterization laboratory in patients with OHCA with ST-segment elevation acute myocardial infarction on ECG. Thus, after ROSC, especially in the face of post-ROSC ECG evidence of acute myocardial infarction, advocate for cardiac catheterization and percutaneous coronary revascularization if available and appropriate. A few case reports describe fibrinolysis during CPR with resultant ROSC and good neurologic outcome.[69] Coronary angiography is reasonable in select patients with suspected cardiac origin of arrest but without ST elevation or in those electrically unstable patients without ST-segment elevation with suspected cardiovascular lesions. The absence of ST-segment elevation on postarrest ECG does not exclude acute coronary thrombus, as approximately one third of patients without ST-segment elevation myocardial infarction on postarrest ECG demonstrate a culprit lesion on angiography.[70] Reports are too few to determine whether thrombolysis together with CPR results in more severe bleeding than thrombolysis without CPR.[71]

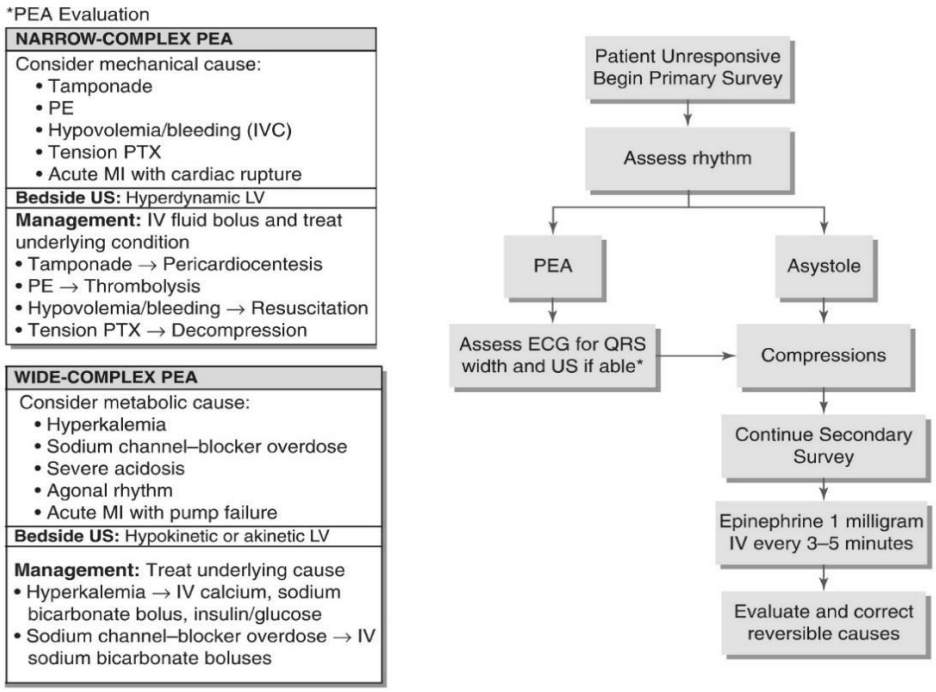
T: TENSION PNEUMOTHORAX

Suspect tension pneumothorax during cardiac resuscitation if breath sounds are unequal on chest auscultation after verifying correct endotracheal tube placement. Treatment is immediate needle decompression.

Algorithm for VF/ pulseless VT management



Algorithm for PEA management



VIII. Special case

1- BLS for children (Age 1 to puberty) and Infant (Newborn to age of 12 months

Children/ Infant	
CPR	- **For Child:** Use the heel of one hand on the lower half of the sternum in the middle of the chest. Put your other hand on top of the first hand. Straighten your arms and press straight down. Compressions should be about two inches (5 cm) into the child's chest and at a rate of 100 to 120 compressions per minute. **For infant:** Place 2 or 3 fingers of one hand on the sternum in the middle of the nipple line. Press straight down. Compressions should be 1.5 inches (4 cm) into the infant's chest (or about 1/3 the diameter of the chest) and at a rate of 100 to 120 compressions per minute. - Be sure that between each compression you completely stop pressing on the chest and allow the chest wall to return to its natural position to make CPR less effective. - After 15 compressions, stop compressions and open the airway by tilting the head and lifting the chin or jaw thrust (neck injury is suspect) - Give a breath while watching the chest rise. Repeat while giving a second breath. Breaths should be delivered over one second. - Resume chest compressions. Switch quickly between compressions and rescue breaths to minimize interruptions in chest compressions.
Defibrillate	- Attach the AED when it becomes available. Use pediatric pads for infant and children under the age of 8 and less than 55 pounds (25 kg). place the pads in an anterior-posterior position if they would overlap on the front of the chest. - Listen to the AED and perform the steps as directed.

Child/infant mouth-to-mask ventilation



child/infant bag-valve-mask ventilation



Pediatric defibrillation

In the event of ventricular fibrillation, use a weight-based energy dose of 2 to 4 J/kg body weight for monophasic or biphasic devices. For refractory ventricular fibrillation, consider increasing the dose to 4 J/kg. For ventricular tachycardia with a pulse, perform electrical cardioversion with 1 J/kg. This can be progressively increased up to 4 J/kg subsequently if needed.

2- Resuscitation in pregnancy

a. Resuscitation step

The best maternal care provides the best fetal care, so follow general principle of resuscitation when treating the pregnant woman.

- To accommodate the increase in blood and plasma volume that develops during the pregnancy, make sure that the volume of resuscitation fluids increases by 50% above that required by the non-pregnant patient.
- Place 2 large-bore IVs above the diaphragm level and provide rapid infusion of isotonic saline or ringer lactate. Volume must be adequately replaced before considering vasopressor, especially in pregnancy. Select the vasopressor by desired effects in the mother and least harmful effects on the fetus.
- Place the patient to full left tilt position.



b. Airways changes affecting intubation.

In the pregnant patient, the incidence of Mallampati class III airways increase making intubation more difficult associated with weight gain in pregnancy, this contributes to the likelihood of a difficult airways.

Adjunctive airways equipment and patient preparation:

- Smaller sized endotracheal tubes
- A gum elastic bougie
- A short laryngoscope handle, and a stylet readily available.
- Pre-oxygenation (>95%)
- Pace the patient to supine position manually displace the uterus to the left. Elevate the head and the shoulder with a pillow.

c. CPR and defibrillation in pregnancy

Cardiopulmonary arrest in pregnancy is broken down in 2 categories: Before and after fetal viability. Typically, the onset of fetal viability varies between 22 and 26 weeks. By 20 weeks the uterus fundus is palpable at the umbilicus; Then from the 20 weeks to 32 weeks, the fundus height (in centimeters) approximates the gestation age. If the fundus height is at or below the umbilicus, resuscitation effort should focus on the mother with no modification of CPR. If the uterus fundus is palpable above the umbilicus, one person should provide manual left lateral displacement of the uterus while another is performing CPR.

According to current advance life support guidelines, Perform defibrillation at recommended adult dose.



Manual left uterine displacement by the one-handed technique from the right of the patient during adult resuscitation. [Reproduced with permission from Zelop CM, Einav S, Mhyre JM, et al: Cardiac arrest during pregnancy: ongoing clinical conundrum, *Am J Obstet Gynecol*. 2018 Jan 2. pii: S0002-9378(17)32806-5. Copyright Elsevier.]

d. Pregnancy related cause of maternal cardiopulmonary arrest

Pregnancy-Related Causes of Maternal Cardiopulmonary Arrest

Obstetric complications

- Hemorrhage (17.2%)
  - Uterine atony
  - Placental abruption
  - Placenta previa, accreta, increta, or percreta
  - Disseminated intravascular coagulopathy
- Severe pregnancy-induced hypertension (15.7%)
- Amniotic fluid embolism
- Idiopathic peripartum cardiomyopathy (8.3%)
- Iatrogenic events
- Failed intubation
- Pulmonary aspiration
- Intravascular local anesthetic overdose (1.6%)
- Drug error, overdose, or allergy
- Hypermagnesemia

Pulmonary embolism (19.6%)

- Thrombus
- Air
- Fat

Stroke (5%)

Trauma

- Homicide
- Suicide
- Motor vehicle accident

Infection or sepsis (12.6%)

Other (19.2%) (cardiovascular, pulmonary, and neurologic comorbidities)

e. Medication in pregnancy

Medications Used During Resuscitation: Considerations in Pregnancy		
Drug	**Indications**	**Pregnancy Risk Category**
Epinephrine	Potentially beneficial in all forms of cardiac arrest	Category C. Teratogenic in animals in large doses; may induce uteroplacental vasoconstriction and fetal anoxia.
Lidocaine	Ventricular ectopy, tachycardia, and fibrillation	Category B. Use during pregnancy is not well studied; crosses the placenta, but in therapeutic doses has no teratogenic effect on the fetus; may cause fetal bradycardia.
Atropine	Symptomatic bradycardia	Category C. Crosses placenta but results in no fetal abnormalities; can cause fetal tachycardia.
Sodium bicarbonate	Cardiac arrest unresponsive to other measures; documented preexisting metabolic acidosis	Category C. No studies of risk. Use for hyperkalemia and selected toxic overdoses.
Calcium chloride or gluconate	Cardiac arrest due to hyperkalemia, or as antidote to magnesium toxicity (a potential complication when giving high doses of magnesium for eclampsia)	
Dopamine	Hemodynamically significant hypotension in the absence of hypovolemia	Category C. No teratogenic effects in animals, but sufficient studies in humans are lacking; use only when clearly indicated.
Dobutamine	Short-term inotropic support of patients with depressed myocardial contractility	Category B. Not teratogenic in animal studies.
Norepinephrine	Vasopressor for septic shock after adequate volume replacement	Category C. No animal reproductive studies done. Crosses the placenta.
Amiodarone	Ventricular fibrillation, tachycardia, and supraventricular tachycardia	Category D. Is part of Advanced Cardiac Life Support algorithm in pregnancy; use if benefit outweighs risk; serious fetal adverse effects of congenital goiter and hypothyroidism.
Adenosine	Supraventricular tachycardia	Class C. Multiple case reports of the safe use of adenosine to treat maternal and fetal supraventricular tachycardia.
Magnesium sulfate	Torsades de pointes; prevention or treatment of seizures in severe preeclampsia or eclampsia	Class D. Crosses the placenta, and levels in fetus are similar to the mother. Neonatal neurologic depression may occur with respiratory depression, muscle weakness, and loss of reflexes. Continuous maternal use for >5 days may cause fetal hypocalcemia or bone abnormalities.
Ephedrine	Hypotension related to spinal anesthesia or unresponsive to fluids	Class C. Multiple reports of use during anesthesia-related hypotension in pregnancy. Maintains uterine blood flow. May cause dose-dependent increase in fetal acidosis, tachycardia, and abnormal variability in fetal heart rate (indicative of fetal stress), or an increase in metabolic activity.
Phenylephrine	Hypotension related to spinal anesthesia or unresponsive to fluids	Class C. Superior to ephedrine for management of hypotension after spinal anesthesia with a decrease in fetal acidosis.[14]
Vasopressin	No longer recommended for cardiac arrest	Class C. There are no controlled data in human pregnancy.

IX. Evolution and prognosis

Survival rates vary significantly; favorable factors include:

- Early and effective bystander-initiated CPR. The American Heart Association (AHA) estimates that the survival rate for cardiac arrest is estimated to be around 50% in cases, where the CPR is administered within 3–5 min. However, this survival decreases by 7–10% with each minute that defibrillation is delayed.
- Witnessed arrest.
- In-hospital location (particularly a monitored unit)
- Initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT)
- Early defibrillation of VF or VT
- Post resuscitative care, including circulatory support and access to cardiac catheterization.

**** Out hospital cardiac arrest (60%-80%)

X. Complications

- Neurologic dysfunction
- Brain injury
- Disorder of consciousness
- Neurocognitive deficits
- Changes in quality of life

XI. PREVENTION AND RECOMMENDATION

Lifestyle Changes to Prevent a Heart Attack

- Stop smoking and limit alcohol.
- Choose good nutrition: Vitamin, mineral, fiber, low calories.
- Control LDL cholesterol level (<70 mg/dL) and Triglyceride level at the normal value is considered good for your heart health.
- Control your blood pressure regularly.
- Manage diabetes.
- Exercise regularly and weight control
- Get enough sleep and reduce stress.

XII. REFERENCES

1- https://www.sfcardio.fr/sites/default/files/2019-11/2015-2e_Ref_Cardio_ch25_arret_cardio_circulatoire.pdf
2- http://www.ce-mir.fr/UserFiles/File/national/livre-referentiel/livre-referentiel-cemir-2021/22-ch13-159-176-9782294769580.pdf
3- https://www.urgences-sante.qc.ca/wp-content/uploads/2014/03/Module-5-Arr%C3%AAt-cardiorespiratoire-r%C3%A9animation.pdf
4- https://www.sfmu.org/upload/consensus/ce_acr.pdf
5- https://www.editions-ellipses.fr/PDF/9782340028906_extrait.pdf
6- http://abilitatipracticecluj.ro/pdf/franc/MU_fr_01.pdf
7- https://www.ncbi.nlm.nih.gov/books/NBK563231/#:~:text=Cardiopulmonary%20arrest%20(CPA)%20is%20the,by%20a%20primary%20cardiac%20event.
8- https://www.moh.gov.my/moh/resources/Arkib/Basic%20Life%20Support%20Training%20Manualnew.pdf
9- https://www.msdmanuals.com/professional/critical-care-medicine/cardiac-arrest-and-cpr/cardiac-arrest
10- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6482460/
11- https://www.sciencedirect.com/science/article/pii/S0735675723006605#:~:text=Cardiac%20arrest%20(CA)%20is%20a,%2C%20and%20hypothermia%20%5B2%5D.
12- https://nhcps.com/wp-content/uploads/2020/01/2021_ACLS_Handbook.pdf
13- www.TintinalliEM.com

ACUTE METABOLIC COMPLICATION OF DIABETES MELLITUS, HYPEROSMOLAR HYPERGLYCEMIA STATE

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I. DEFINITION

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS, also known as hyperosmotic hyperglycemic nonketotic state [HHNK]) are two of the most serious acute complications of diabetes. DKA is characterized by ketoacidosis and hyperglycemia, while HHS usually has more severe hyperglycemia but no ketoacidosis. Each represents an extreme in the spectrum of hyperglycemia.

II. EPIDEMIOLOGY

Diabetes prevalence has increased significantly worldwide, leading to a higher incidence of diabetes-related complications. This trend is observed across all regions, with low- and middle-income countries experiencing the most rapid rise. Common acute complications include diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). These conditions are more prevalent in type 1 diabetes but can also occur in type 2 diabetes under certain conditions.

III. ETIOLOGY

- Hyperosmolar state precipitated by factors that:
  - Impair peripheral insulin action
  - Increase endogenous or exogenous glucose
  - Decrease patient's ability to replace fluid loss
- Infection (esp. pneumonia and UTI) most common precipitating factor
- Other precipitating causes include:
  - Inadequate therapy/medication omission
  - Sepsis
  - Medications/drugs:
    - Diuretics
    - β-blockers
    - Calcium channel blockers
    - Atypical antipsychotics
    - Corticosteroids
    - Sympathomimetics
    - Phenytoin
    - Cimetidine
    - Amphetamines
    - Ethanol
  - Myocardial infarction
  - CVA
  - Renal failure

- Heat stroke
- Pancreatitis
- Appendicitis
- Intestinal obstruction
- Endocrine disorders
- Pregnancy
- Trauma
- Burns

IV. PATHOPHYSIOLOGY

The pathophysiology that gives rise to HHS requires that three interrelated elements be present: insulin deficiency, renal impairment, and cognitive impairment.

- Relative insulin deficiency is the fundamental defect in HHS. Patients have sufficient insulin to inhibit ketone body formation but not enough to prevent hyperglucagonemia, glycogenolysis, and gluconeogenesis. The resulting hyperglycemia induces osmotic diuresis, with resultant fluid and electrolyte losses.
- typical patients with HHS are old. Their renal blood flow and GFR are reduced, and they cannot readily excrete a glucose load. When they become hyperglycemic, the glucose is neither metabolized nor excreted. It remains in the extracellular fluid space. The resulting increase in osmolality, together with the decreased GFR, causes still less glucose to be excreted.
- Hyperglycemia leading to hyperosmolality normally activates thirst. The combination of mild diabetes and azotemia does not lead to HHS unless the affected individual does not drink sufficient water to prevent hyperosmolality.

Together, these three factors produce dehydration and the hyperosmolar hyperglycemic state. The severe dehydration that occurs is due to the osmotic diuresis of glucose in the absence of compensatory free water intake. Dehydration, in turn, leads to hemoconcentration, setting the stage for severe prerenal azotemia, thrombosis, and shock.

Moreover, hyperglycemic crises are proinflammatory states that lead to generation of reactive oxygen species and oxidative stress. Proinflammatory factors returned to near-normal levels within 24 hours of insulin therapy and resolution of hyperglycemia.

V. DIAGNOSIS

1) Clinic

- History
  - Progression of signs and symptoms typically occur over days to weeks
  - Polyuria/polydipsia/weight loss
  - Dizziness/weakness/fatigue
  - Decline in mental state
  - Blurred vision
  - Leg cramps
- Physical Exam
  - Dehydration
  - Tachycardia
  - Sunken eyes
  - Hypotension

- Orthostasis
- Dry mucous membranes
- Decreased skin turgor
- Collapsed neck veins
- Coma/lethargy/drowsiness
- Decreased urinary output – late finding
- Seizures/focal neurologic deficits
- Concurrent precipitating medical illness

2) Investigation

- Diagnostic criteria:
  - Serum glucose ≥600 mg/dL (usually >1,000 mg/dL)
  - Minimal ketosis
  - pH ≥7.30, HCO_3 ≥15 mEq/L
  - Effective serum osmolality >320 mOsm/kg:

  Serum osmolality = 2 × Na^+ + glucose in mg/dL/18

  BUN not included because it is freely permeable between fluid compartments
- Lab
  - Broad testing indicated to evaluate hyperosmolar syndrome and identify precipitating causes
  - Electrolytes:
  - K+ may be elevated even in the presence of total body deficit owing to shift from intracellular space to extracellular space
  - Mild anion gap metabolic acidosis owing to lactic acid, β-hydroxybutyric acid, or renal insufficiency

  Sodium corrected for hyperglycemia:

  Corrected [Na+] = [Na+] + 0.016 × [(glucose in mg/dL) – 100]
  - BUN, creatinine:
  - Venous blood gas (VBG) or arterial blood gas (ABG
  - Serum ketones, β-hydroxybutyrate, and lactate level if pH <7.3 or significantly elevated anion gap to evaluate mixed acid–base disorder
  - Serum osmolarity
  - CBC, blood culture
  - Lipase: 3× upper limit of normal is diagnostic for pancreatitis
  - Urinalysis: Check for ketones/glucose, UTI
  - Magnesium, calcium, phosphate
- Imaging
  - CXR to evaluate for possible underlying pneumonia
  - Head CT: When indicated for altered mental status or with focal neurologic deficit

VI. DIFFERENTIAL DIAGNOSIS

- If acidosis or significant anion gap present, must determine cause (i.e., ketosis, DKA, lactic acidosis, [hypoperfusion, sepsis, or postictal], or other causes of metabolic acidosis)
- Alcoholic and fasting ketoacidosis
- Anion gap acidosis

- Metabolic encephalopathy
- Mixed disorder of HHS and DKA present in up to 33% of patients
- Differentiate HHS from DKA

DKA	HHS
Precipitant factors	
Noncompliance with insulin treatment	Noncompliance with treatment
Infection	Infection
New -onset (type1) diabetes	New-onset (type2) diabetes
other	Other (corticoids, excess diuretics, etc..)
Course of illness	
Rapid (in general < 24hs)	Insidious (days)
Clinical finding	
Polyuria, polydipsia, dehydration, hypovolemia	Polyuria, dehydration, hypovolemia
Nausea, vomiting, abdominal pain	Depressed mental status up to coma
Fruity odor of breath, Kussmaul respiration	
Diagnostic laboratory Criteria	
Blood glucose > 200-500 mg/dL*	Blood glucose > 540-600 mg/dL*
AND elevated ketones in blood or urine	AND serum osmolality > 320mmol/kg
AND metabolic acidosis (pH <7.3 and HCO3 < 18 mmol/L)	No significant ketosis No metabolic acidosis
Concomitant Laboratory Abnormalities	
Elevated anion gap	Variable anion gap
Low C-peptide	Normal C-peptide
	Acute kidney injury

* For conversion of blood glucose concentrations in mg/dL to mmol/L, divide by 18. The numbers are the highest reported blood glucose cutoff for both diabetic ketoacidosis and hyperosmolar hyperglycemic state. In patients at risk—taking sodium-glucose co-transporter 2 (SGLT2) inhibitors, pregnancy, excessive alcohol use, decreased caloric intake, chronic liver disease—ketoacidosis may develop in the absence of elevated blood glucose concentrations (euglycemic diabetic ketoacidosis).

VII. MANAGEMENT

The best treatment for HHS is prevention.

1) Objectives
- correction of the fluid and electrolyte abnormalities that are typically present and
- the administration of insulin
- find and treat the triggering cause

2) Critical Signs
- Shock
- Coma
- Hypokalemia
- Very high serum osmolarity

3) Mortality Risk factors
- Prognosis is worse for elderly patients and
- patients in whom coma and hypotension are found.

4) Outpatient management
   - Check glycemia, give water to drink if possible.
   - HHS is an acute condition and may be life threatening, patient should be checked and treat in hospital.

5) First-line treatment
   Initial Stabilization/Therapy: ABCs:
   - Secure airway in comatose patients
   - Cardiac monitor and 18G IV
   - Naloxone, thiamine, and blood glucose for Altered mental status, when suspect the corresponding cause.
   - Restore hemodynamic stability with IV fluids 0.9% NS 1–2 L over the first hour.

- Frequent reassessment of volume and mental status

Serum levels of Na^+, K^+, $PO4^-$ do not accurately reflect the total body solute deficits or the intracellular environment. Repeat electrolyte and glucose levels hourly.

- Search for a precipitating event. Mortality/morbidity of HHS usually secondary to inciting cause
- Fluids:
  - Begin resuscitation with 0.9% NS 1–2 L over 1–2 hr to restore intravascular volume and achieve hemodynamic stability
  - Fluid loss avg 20–25% body weight or 100–200 mL/kg
  - Calculate total body water (TBW) deficit using corrected serum sodium:

  Total Body Water deficit = 0.6 × weight (kg) × (1 – 140/corrected Na^+)
  - Average fluid deficit is 8–10 L
  - Replace 50% of the fluid deficit over the next 12 hr
  - After initial resuscitation use NSS if serum sodium is low, 1/2 NS if serum sodium is elevated/normal or patient is hyperosmolar.
  - Add D5 to fluid to when serum glucose is < 250 mg/dL
- Potassium:
  - Anticipate hypokalemia:

  Total body deficit of ~5–10 mEq/kg body weight (replace over 3 d)
  - Begin potassium repletion after urine output is established. Do not start in anuric patients or if initial K^+ level is >5 mEq/L
  - 1g Kcl = 13.4 mEq K + 13.4mEqCl = 27mEq
  - If the initial K^+ is normal (4–5 mEq/L), give 20–30 mEq KCl in the first L of fluids, then give 20 mEq/hr
  - If the initial K^+ is low (3–4 mEq/L), give 40 mEq in first L
  - If serum K^+ is <3 mEq/L hold insulin and give 10–20 mEq/hr until K^+ >3.3, then add 40 mEq to each liter
  - Follow repeat serum K^+ levels q1–2h and adjust treatment accordingly
- Insulin:
  - No role in the early resuscitation

- Earlier use of insulin may cause rapid correction of hyperglycemia with collapse of the intravascular space, hypotension, and shock or hypokalemia precipitating dysrhythmias
- Some patients will not require insulin
- Use insulin as sole therapy in patients with fluid overload (i.e., acute renal failure)
- Begin only after achieving hemodynamic stability and evaluating for hypokalemia:
- Do not use unless serum K+ >3.3 mEq/L
- SC/IM insulin not recommended due to erratic absorption
- Titrate drip to optimally decrease serum glucose by 50–90 mg/dL/hr. More rapid correction places the patient at risk for developing cerebral edema
- Decrease drip rate by 1/2 when serum glucose < 250 mg/dL
- Adjust insulin drip to maintain serum glucose between 150–200 mg/dL
- Insulin: Begin with 0.05–0.1 U/kg/hr; modify after assessing clinical response

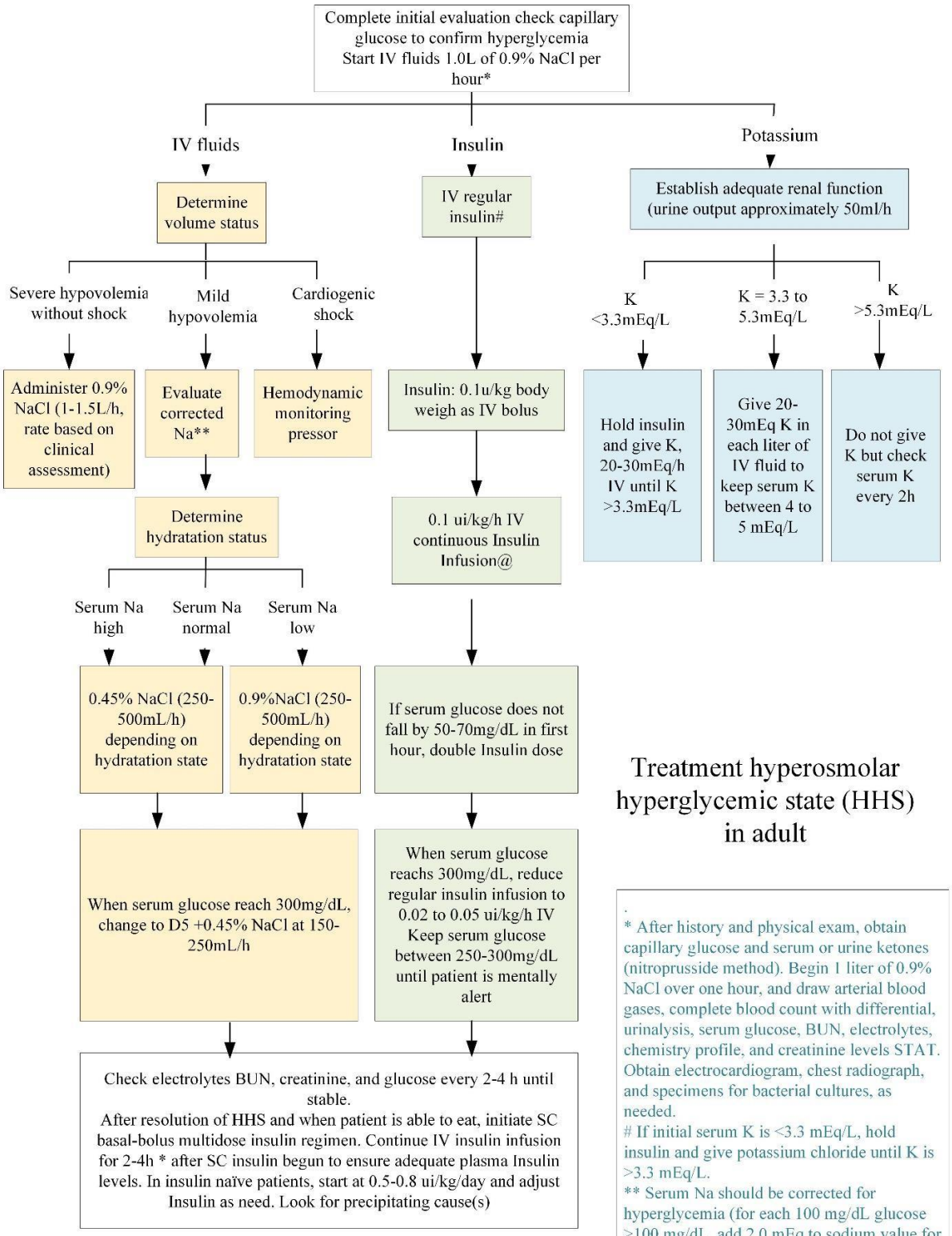
- Phosphate:
  - Routine replacement not recommended
  - If serum levels <1 mg/dL, give 20–30 mmol potassium phosphate over 24 hr
  - Monitor serum calcium levels closely
  - Potassium phosphate IV:
    - Phosphorous serum level <0.5 mg/dL: 0.5 mmol/kg IV infused over 4–6 h
    - phosphorous serum level 0.5–1 mg/dL: 0.25 mmol/kg IV infused over 4–6 h
  - Potassium phosphate PO:
    - Phosphorus 250 mg per tablet and potassium 1.1 mEq per tablet
- Magnesium:
  - 0.35 mEq/kg magnesium in fluids for first 3–4 hr (2.5–3 g $MgSO_4$ in 70 kg patient). Caution in ARF.
  - $MgSO_4$ (magnesium sulfate): 50% (5 g/10 mL; dilute to at least 20% before IV use)
- Anticoagulation:
  - Arterial thrombosis may complicate hyperosmolar state: Consider SC heparin as prophylaxis
  - Remain vigilant to detect thrombotic complications (e.g., MI, pulmonary embolus, mesenteric ischemia).

6) Treatment adjustments

Insulin used without concomitant vigorous fluid replacement increases the risk of shock.

7) Algorithm:

Management of hyperosmolar hyperglycemic state (HHS) in adult



HHS diagnostic criteria: Serum glucose >600 mg/dL, arterial pH >7.3, serum bicarbonate >15 mEq/L, and minimal ketonuria and ketonemia. Normal laboratory values vary; check local lab normal ranges for all electrolytes.

Treatment hyperosmolar hyperglycemic state (HHS) in adult

.
* After history and physical exam, obtain capillary glucose and serum or urine ketones (nitroprusside method). Begin 1 liter of 0.9% NaCl over one hour, and draw arterial blood gases, complete blood count with differential, urinalysis, serum glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT. Obtain electrocardiogram, chest radiograph, and specimens for bacterial cultures, as needed.
# If initial serum K is <3.3 mEq/L, hold insulin and give potassium chloride until K is >3.3 mEq/L.
** Serum Na should be corrected for hyperglycemia (for each 100 mg/dL glucose >100 mg/dL, add 2.0 mEq to sodium value for corrected serum sodium value).
@ An alternative IV insulin regimen is to give a continuous intravenous infusion of regular insulin at 0.14 units/kg per hour; at this dose, an initial intravenous bolus is not necessary.

VIII. SPECIAL CASES

- Geriatric Considerations: Most commonly seen in elderly type II diabetics who experience a stressful illness that precipitates worsening hyperglycemia and reduced renal function
- In the elderly, 30–40% of cases are associated with the initial presentation of diabetes
- Pediatric Considerations: Hyperosmolar hyperglycemic states (HHS) rare in pediatric patients.

IX. EVOLUTION AND PROGNOSIS

Overall mortality for HHS is estimated at 5-20% [7] and is usually due to the underlying illness that caused the hyperglycemic crisis. The prognosis is worse for elderly patients and patients in whom coma and hypotension are found. This is in contrast to the mortality rate of DKA, which is estimated to be about 1-5%.

X. Complications

- Hypotension (insulin shifts glucose from interstitial compartment to intracellular accompanied by water may precipitate hypotension and shock)
- Cerebral edema (Rapid reduction of glucose concentration is a major contributor to the development of cerebral edema.
- Non cardiogenic pulmonary edema.

XI. PREVENTION AND RECOMMENDATION

- For diabetic patient, the elderly, the chronically ill, and institutionalized populations are at increased risk for HHS. Any living situation or comorbidity that prevents adequate hydration, including for example immobility, advanced age, debility, dementia, agitation, impaired thirst response, restricted access to water, and restraint use, place these patients at risk.
- Patient education focused on encouraging adherence to blood glucose monitoring and compliance with prescribed medications coupled with adequate follow-up to establish a durable diabetes management regimen.
- Sick days management (many factors lead to hypoglycemia, or hyperglycemia)
- Review with nursing home staff the importance of adequate fluid intake and close monitoring of hydration status in patients with diabetes.
- Avoid medications that interfere with effectiveness of insulin

XII. REFERENCES

1. Matthew T. Robinson, Catherine D. Parker Hyperosmolar syndrome, in 5mn Emergency Consult Unbound Medicine 2000-2024 online platform, Wolters Kluwer Health Lippincott Williams & Wilkins.
2. Lilly, Craig M.; Irwin, Richard S.; Boyle, Walter A.; Kelly, William F.. Irwin and Rippe's Intensive Care Medicine (p. 6376). Wolters Kluwer Health. Kindle Edition.
3. Jan Gunst, Greet Van den Berghe, Diabetic ketoacidosis and hyperosmolar hyperglycemic state, in Jean-Louis Vincent, MD, PhD Textbook of Critical Care, 8th edition 2023, Elsevier p. 1086-91

TRAUMATISM IN ADULT

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I. DEFINITION

Traumatism = A morbid condition of a system owing to an injury or a wound.

Traumatic injuries can range from minor isolated wounds to complex injuries involving multiple organ systems. All trauma patients require a systematic evaluation to maximize outcomes and reduce the risk of undiscovered injuries. Life-threatening injuries must be immediately stabilized before moving along the primary survey. A primary survey should be repeated whenever the patients' status deteriorates.

II. EPIDEMIOLOGY

According to the World Health Organization (WHO), road traffic injuries accounted for 1.25 million deaths in 2014, and trauma is expected to rise to the third leading cause of disability worldwide by 2030[1]. Over 45 million people globally sustain moderate to severe disability each year due to trauma[2]. Outside areas of armed conflict, penetrating injuries are responsible for fewer than 15 percent of traumatic deaths worldwide. Approximately half of traumatic deaths result from central nervous system (CNS) injury, while a third result from exsanguination.

III. ETIOLOGY

Variety of causes including:

- Penetrating trauma
- Motor vehicle and motorcycle accidents
- Falls from height.
- Assault (including domestic violence)
- Mass-casualty events (including terrorism)
- Burns

High-risk patients: Extremes of age, pregnancy, bleeding disorders (including potent antiplatelet or anticoagulant use), GCS <14, abnormal vital signs, dangerous mechanism.

IV. PATHOPHYSIOLOGY

Particular mechanisms predispose patients to specific injuries.

Certain high-risk blunt mechanisms, have been associated with greater morbidity and mortality including:

- pedestrians struck by automobiles,
- motorcycle accident.
- severe motor vehicle accidents, and

[1] Global Status on Road Safety 2015, World Health Organization, http://www.who.int/violence_injury_prevention/road_safety_status/2015/ (Accessed on April 04, 2016)

[2] World Health Organization. Global burden of disease. www.who.int/healthinfo/global_burden_disease/en/ (Accessed on May 01, 2010)

- falls greater than 6m.

Any hypotensive trauma patient is at risk for development of hemorrhagic shock, a common cause of postinjury death.

Table 1: Classification of the degree of hemorrhage

Classification of hemorrhage based on Estimated blood loss at initial presentation.				
	Class I	**Class II**	**Class III**	**Class IV**
Blood loss (ml)*	Up to 750	750 - 1500	1500 – 2000	> 2000
Blood loss (% blood volume)	Up to 15	15 – 30	30 – 40	40
Pulse rate (beats/min)	< 100	100 – 120	120 - 140	> 140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (SBP-DBP)	Normal or increased	Decreased	Decreased	Decreased

* Assumes a 70kg patient with a pre-injury circulating blood volume of 5L

V. DIAGNOSIS

In general, severely injured patients (especially those with unstable vital signs) with a potential need for acute surgical intervention should be transported immediately to the nearest major trauma center.

Triage to major trauma center per EMS/SAMU protocol.

A primary survey should be performed at the scene and upon ED arrival.

a. Clinic and investigations

The protocol Advanced Trauma Life Support (ATLS) provides a standardized approach to trauma including rapid assessment and treatment. This protocol consists of following steps:

- Preparation
- Triage
- Primary survey (ABCDEs)
    - Resuscitation
    - Adjuncts to primary survey & resuscitation (eFAST, blood type, Ht…)
- Secondary survey (Head to toe Evaluation)
    - Adjuncts to secondary survey (Xray, CT scan.)
- Continued post resuscitation monitoring and reevaluation
- Definitive care (to OR, or ICU.)

The primary and secondary surveys should be repeated frequently.

In the actual clinical situation, many of these activities occur in parallel or simultaneously.

Signs and Symptoms

Primary survey (ABCDE):

Airway (with cervical spine precautions):

- Assess and stabilize the airway before moving to the next step in the primary survey.
- Maintain C-spine precautions throughout
- Indicators of airway patency: Clear speech or effectively/silently moving air
- Indicators of airway obstruction: Gurgling, stridor, snoring, choking, or no air movement

Breathing:
- Assess and stabilize breathing before moving to the next step in the primary survey.
- Indicators of effective breathing: Symmetric chest wall rise/fall, equal bilateral breath sounds, normal resp rate, and O2 saturation.
- Indicators of ineffective breathing: Asymmetric or minimal chest movement, unequal breath sounds, abnormal resp rate or O2 saturation
- Tension pneumothorax: Suggested by unilateral decreased breath sounds, tracheal shift (to opposite side), hyper expansion, hyperresonance to percussion, subcutaneous air, hypoxia, and/or hemodynamic compromise
- Hemothorax: Suggested by decreased breath sounds and/or dullness to percussion

Circulation:
- Assess and stabilize circulation before moving to the next step in the primary survey.
- Assess HR, BP, pulse quality, and end-organ (e.g., mentation, capillary refill, urine output); when abnormal, assume internal hemorrhage.

Disability:
- Assess and stabilize disability before moving to the next step in the primary survey.
- Assess level of consciousness, gross motor and sensory function, pupillary size/reactivity
- Glasgow Coma Scale is commonly used; score of ≤8 indicates severe head injury/coma.
- Spinal cord injuries: Grossly assess for lateralization of motor/sensory deficits.
- Assess brainstem function via pupillary size and reactivity to light.

Exposure:
- Undress completely, then warm passively

Secondary survey:
- Performed after the primary survey.
- Complete physical exam from head to toe
- "Finger in every orifice"

History

Key features: Initial clinical presentation, mechanism of injury, suspected injuries, and treatment rendered should be elicited from EMS/SAMU personnel, family, and bystanders.
Motor vehicles collision (MVCs): Note approximate speed of all vehicles, impact point, location of patient in vehicle, seatbelt use, passenger space intrusion, steering column damage, or extrication by EMS/SAMU.
AMPLE history: Allergies, medical/surgical issues, past medical, last oral, events leading up to trauma. (Discuss tetanus status if stable)

Physical Exam
- See Signs and Symptoms
- Stabilize simultaneously during assessment.

Essential Workup

- Primary and secondary surveys
- Critically ill patients: Activate trauma team, rapid transfusion and lab/imaging standby.
- Point of care (POC) US (e-FAST)

- Portable radiographs include AP chest, AP pelvis, and lateral cervical spine.
- Computed tomography: Only when hemodynamically stable or adequately stabilized.
- Use evidence-based clinical decision rules (e.g., NEXUS, Canadian) to avoid unnecessary imaging.

Diagnostic Tests and Interpretation

Lab

- POC Hgb serially if hemorrhagic shock
- POC glucose if altered mental status.
- Blood type, CBC, coagulations, blood gas, lactate, renal function, lipase, and Urine analysis for major trauma patients
- Pregnancy test in all females of childbearing age
- Consider cardiac enzymes to rule out cardiac injury.

Imaging

- Significant chest trauma requires objective evaluation of the lungs, heart, and great vessels with e-FAST, CXR, CT, angiography, and/or thoracotomy.
- Blunt abdominal trauma requires objective evaluation using e-FAST followed by abdominal CT or exploratory-laparotomy:
    - If free fluid on e-FAST
    - Hemodynamically stable: CT with IV contrast
    - Hemodynamically unstable: Exploratory lap

For head trauma, CT is recommended if prolonged loss of consciousness, amnesia, persistent altered level of consciousness, or severe head ach or vomiting.

For cervical spine fractures: CT is highly sensitive.

Pan CT scan, (head, neck, chest, abdomen/pelvis in a single pass with IV contrast) lower missed injury rate but significant radiation exposure

- Suspected spine injuries (with neuro deficits): emergent MRI
- Extremity injuries:
    - Plain films identify most fractures (aside from scaphoid, hip, tibial plateau, talus, etc.)
    - Suspected vascular injury: Duplex US or CT angiography.

VI. DIFFERENTIAL DIAGNOSIS

Consider medical conditions leading to trauma (e.g., stroke, seizures, dysrhythmias, and suicide attempt)

VII. MANAGEMENT

1- Objectives

Rapid assessment, rapid treatment to maintain vital signs. Treat as early as possible the derangement that may threaten the victim life. Not left behind or overlook any lesion incurred by trauma. Get the definitive treatment early.

2- Critical signs

Trauma with unstable vital signs, altered mental status, combined head-chest trauma, head trauma plus other bleeding lesion. Spinal trauma with neurological signs or cervical spinal lesion.

3- Mortality risk factor

Mechanism of trauma (pedestrian hit by car, high speed motor vehicle accident, fallen from height > 6m, blast injury, penetrating wound, high velocity projectile or fragments etc) Multiple lesions, age extremities, victims were under anticoagulant treatment, medical condition of victims.

4- Out-patient management

Any patient of remarkable trauma or accidents should be assessed in ER. A presumed minor head injury or minor chest trauma may overlook a progressively develop severe lesions.

5- First line treatment

a. Initial Stabilization/Therapy

- Primary survey: Immediately stabilize any serious injuries once identified:
    - Airway (with cervical spine precautions):
        - Use jaw thrust, suction, oropharyngeal vs. nasopharyngeal airways, and/or McGill forceps.
        - Rapid sequence intubation: the preferred technique in major trauma; consider ketamine or etomidate to minimize peri-intubation hypotension.
        - Video laryngoscopy may allow endotracheal intubation with minimal impact on traumatic brain or unstable cervical spine injuries.
        - Failed airway: Extra glottic device (e.g., laryngeal mask airway) or cricothyroidotomy.
    - Breathing:
        - 100% oxygen and respiratory monitoring
        - Pre-oxygenation: 8 deep breaths or 3 min of tidal volume
        - Tension pneumothorax: (Diagnosed clinically) emergently decompress with needle thoracostomy followed by tube thoracostomy.
        - Hemothorax: Tube thoracostomy (28F) is usually indicated, if massive hemothorax consider autotransfusion and thoracotomy in the OR.
        - Open chest wounds: Cover with a 3-sided adherent dressing and consider tube thoracostomy.
        - Flail segment, pulmonary contusion, burns: Treat respiratory distress with mechanical ventilation (use low tidal volume + PEEP for lung protection)
    - Circulation:
        - Place on a cardiac monitor.
        - Obtain IV access (ideally 2 large-bore peripheral IVs; alternatives include intraosseous lines, central lines, or venous cut down)
        - Control external bleeding with direct pressure or tourniquets temporarily.
        - Crystalloid fluid bolus (10–20 cc/kg) is controversial (e.g., allow permissive hypotension)
        - Replace lost blood with blood products in 1:1:1 ratio of PRBC, FFP, and platelets. (CE, plasma frais congelé, plaquette)
        - Treat unstable pelvic fractures with pelvic binding.
        - Consider giving tranexamic acid (TXA) to all patients with hemorrhagic shock, as part of a massive transfusion protocol.
        - Pericardial tamponade:
            - Stable: Emergent pericardiocentesis window

        - Unstable; thoracotomy
    - Penetrating chest trauma and witnessed arrest: Consider thoracotomy (if an available surgeon); see "algorithm" below.
- Disability:
    - If Glasgow Coma Scale score of ≤ 8 + head injury: Treat elevated intracranial pressure with mannitol or hypertonic saline, controlled ventilation (ideal PCO_2 30–35 mm Hg), and elevating head to 30 degrees (while maintaining spine immobilization)
    - Intracranial bleeding or spinal cord injury: Obtain neurosurgical consultation; high-dose steroids are generally not recommended.

b. Emergency department Treatment/Procedures

Emergency department Treatment/Procedures

- Definitive treatment may require emergent surgery or interventional radiology.
- Prompt stabilization, early recognition of the need for operative intervention, and appropriate surgical consultation are paramount.
- Re-evaluation is key to identify occult/delayed injuries.

Medication

- Dictated by need for specific interventions.
- TXA (Tranexamic acid) must be given before transfer/arrival to a trauma center in order to meet the time requirement of early administration. The dose is 1 gram of tranexamic acid IV bolus over 10 minutes, followed by 1 gram IV over 8 hours.
- Consider short-acting, hemodynamically neutral medications.
- Consider prophylactic antibiotics in penetrating trauma.
- Ensure an updated tetanus status.

c. Disposition

Admission Criteria

- Many major trauma patients are routinely admitted for observation, monitoring, and re-evaluation.
- Patients with significant injuries or hemodynamic instability should be admitted to the OR/ICU.
- Patients requiring frequent assessments should be admitted to a monitored setting.

6- Treatment adjustment _Pearls and pitfalls

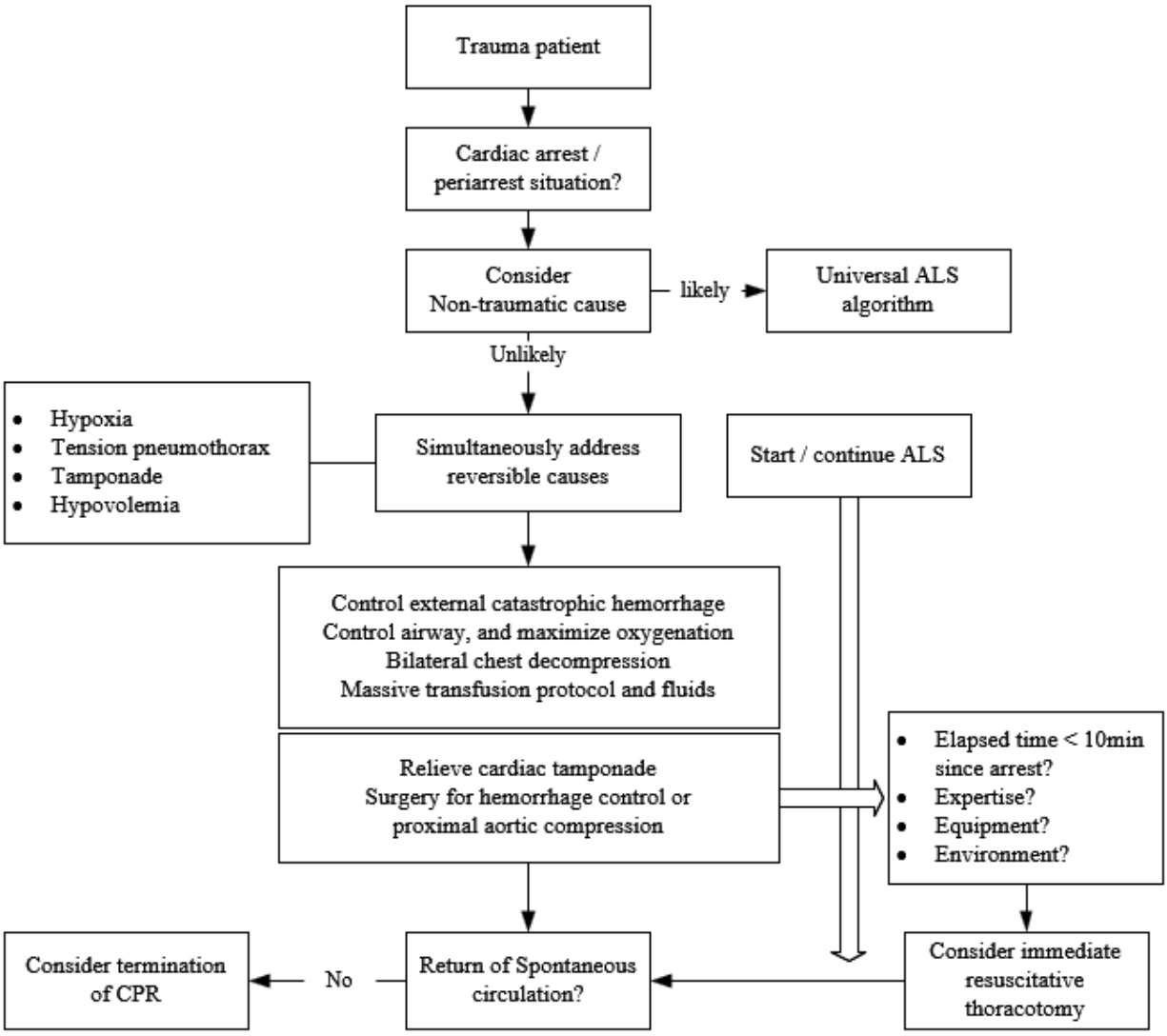
- In general, severely injured patients (especially those with unstable vital signs) with a potential need for acute surgical intervention should be transported immediately to the nearest major trauma center.
- The ABCs of trauma remain the standard approach to the initial assessment and treatment in major trauma.
- Life-threatening injuries must be immediately stabilized before moving along the primary survey.
- A primary survey should be repeated whenever the patients' status deteriorates.
- A high level of suspicion for occult injuries should be maintained, with a low threshold for observation and/or advanced imaging.
- Ensure an updated tetanus status.

7- Algorithm

Unless obvious signs of death are present in the field, providers in most emergency medical systems continue to transport patients without pulse or respiration to a hospital once cardiopulmonary resuscitation has been initiated.

For patients in traumatic arrest upon arrival to the ED, a critical decision must be made regarding the appropriate level of intervention and, specifically, the use of emergent thoracotomy.

The strongest recommendation for performing ED thoracotomy can be made for patients with penetrating chest trauma with witnessed signs of life during transport to or in the ED and at least cardiac electrical activity upon arrival. There were no survivors among patients with blunt trauma and no respiration or pulse in the field. ED thoracotomy for this group is not indicated (including in the presence of myocardial electrical activity).



Decision making algorithm, peri-arrest situation and trauma

ALS= advanced life support

Adapted from Truhlar AJ, Deakin, CD, Soae J, et al: European Resuscitation Council Guidelines for Resuscitation 2015. Section 4. Cardiac arrest in special circumstances. Resuscitation 95: 148-201, 2015.

VIII. SPECIAL CASES

- **Elder patients**

Assume that older patients involved in trauma have sustained a significant injury, even if they appear well. The paradox of elder trauma patients is that their physiology and medical interventions can both mask and exacerbate the severity of injuries. Medications are but one example: beta blockers may mask the effects of shock by suppressing tachycardia, while warfarin and other anticoagulants increase the risk of severe hemorrhage.

- **Victims of crime**

Clinical evaluation and treatment of injuries is the foremost responsibility of the clinician caring for a trauma patient. When possible, caretakers should consider and act on the need to preserve potential evidence if the trauma may be connected to a crime. As examples, placing removed clothing into paper bags, avoiding cutting through holes in clothing created by penetrating injuries, and careful documentation of injuries may all be significant.

IX. EVOLUTION AND PROGNOSIS

There are notable disparities in mortality rates for injured patients around the world. For example, one study looked at the mortality rates for all seriously injured adults (injury severity score of 9 or more) in three cities, in countries at different economic levels. The mortality rate (including both pre-hospital and in hospital deaths) rose from 35% in a high-income setting to 55% in a middle-income setting, to 63% in a low-income setting. Considering only patients who survive to reach the hospital, a similar study demonstrated a six-fold increase in mortality for patients with injuries of moderate severity (injury severity score of 15–24). Such mortality increased from 6% in a hospital in a high-income country to 36% in a rural area of a low-income country.

In addition to an excess mortality, there is a tremendous burden of disability from extremity injuries in many developing countries. By comparison, head and spinal cord injuries contribute a greater percentage of disability in high income countries. Much of the disability from extremity injuries in developing countries should be eminently preventable through inexpensive improvements in orthopedic care and rehabilitation.

X. COMPLICATIONS

Complications of trauma management may arise from some special situations.
Common pitfalls and ways to avoid them:
Esophageal intubations —

Between 0.5 and 6 percent of prehospital intubations are esophageal due to airway difficulty or displacement during transport. Verify the position of all endotracheal tubes either by direct visualization or use of an end-tidal carbon dioxide (ETCO2) detector.
Hemorrhagic shock —

Approximately 30 percent of the circulating blood volume may be lost before the onset of hypotension. A transient response to one or more fluid boluses means the patient likely has ongoing hemorrhage and is in a persistent state of shock. A high index of suspicion should be maintained and an aggressive search for the source of ongoing hemorrhage is warranted.
Cardiac tamponade —

Assume that elevated jugular venous pressure (JVP) in a trauma patient is caused by pericardial tamponade. However, hypovolemic patients with tamponade may not have elevated JVP. Perform the FAST exam early in the circulation evaluation of the unstable patient and begin by looking at the heart.
Thoracoabdominal injury —

Assume that any penetrating wound of the thorax or abdomen involves both compartments until proven otherwise.
Penetrating bowel injury —

During the initial resuscitation, injuries caused by low velocity penetrating wounds (typically stab wounds) are easily missed by ultrasound, because there is too little intraperitoneal

blood to be detected, and by CT, because there is inadequate tissue destruction. For stab wounds, high clinical suspicion may warrant further evaluation by laparoscopy, laparotomy, or diagnostic peritoneal tap despite initially negative imaging studies. Alternatively, a trauma surgeon may opt to perform serial observations of patients with abdominal stab wounds (and some extraperitoneal gunshot wounds) over a 12- to 24-hour period.

Gunshot wounds typically require therapeutic laparotomy and should be distinguished from the aforementioned stab wounds – these high velocity injuries are associated with a much greater morbidity and mortality than their low velocity counterparts.

Open book pelvic fractures —

The unstable pelvis should not be manipulated multiple times; additional manipulation exacerbates hemorrhage. Once suspected, open or unstable pelvic fractures should be stabilized using a pelvic binder, or a sheet if no binder is available. If the patient is hemodynamically stable, computed tomography (CT) imaging is obtained. The unstable patient requires either surgery or angiography.

Ocular injuries —

Periorbital swelling and ecchymosis do not preclude performing an ocular examination. Patients with such findings are at higher risk of ocular injury. In addition, injuries such as a globe rupture or retro-orbital hematoma must be diagnosed quickly in order to maximize the opportunity to salvage vision.

XI. PREVENTION AND RECOMMENDATION

Improved safety standards and programs to minimize injury from vehicular-related events (motor vehicle, motorcycle, bicycle, pedestrian), working places, falls, violence, sports, and recreation provide best prevention against Traumatic injuries.

Wear helmet while riding two wheelers.

Do have access to seat belts and air bags while driving. Take good care of children to avoid injuries.

Do not drive under the influence of alcohol and drugs.

Maintain safe living areas for seniors.

XII. REFERENCES

1. Jorge Fernandez, Sam L. Frenkel, Peter L. Steinwald. Trauma multiple, In 5min Emergency consult, (2024) Unbound Medicine electronic platform, Editor: Wolters Kluwer Health Lippincott Williams & Wilkins
2. Mock C, Lormand JD, Goosen J, Joshipura M, Peden M.Guidelines for essential trauma care. Geneva, World Health Organization, 2004
3. Peter A. Cameron Barry J. Knapp William Teeter. Trauma in adult. In: Judith E. Tintinalli, Editor-in-Chief Emergency Medicine. A comprehensive Study Guide, 9th edition, Mc Graw Hill; 2020 p. 1669-76
4. Global Status on Road Safety 2015, World Health Organization, http://www.who.int/violence_injury_prevention/road_safety_status/2015/ (Accessed on April 04, 2016)
5. World Health Organization. Global burden of disease. www.who.int/healthinfo/global_burden_disease/en/ (Accessed on May 01, 2010)

INITIAL MANAGEMENT OF HEAD TRAUMA

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I. DEFINITION

Head trauma is a broad term describing an external trauma to the craniofacial area of the body from blunt, penetrating, blast, rotational, or acceleration-deceleration forces. Traumatic brain injury (TBI) is often categorized into mild (Glasgow Coma Scale score, 13–15), moderate (GCS score, 9–12), and severe (GCS score, 3–8), but this actually represents a spectrum of injury. Patients with a presentation GCS score of 13–15 who are stable or improving are unlikely to have CT scan findings that warrant intervention

II. EPIDEMIOLOGY

The most common principal mechanisms of injury for all age groups includes falls, being struck by or against an object, and motor-vehicle crashes in the civilian population. Gunshot wounds (GSWs) to the head are particularly lethal; the overall mortality rate is estimated to be 90%, with 70% of deaths occurring at the scene. TBIs in Cambodia are on the rise, 34% occur during 5-9pm and 40% during the weekend; while the vast majority is 74% occur as the result of road traffic accidents of which 81% are motorcycle related. Skull fracture is the most common diagnosis, where frontal lobe hematomas most commonly involved, resulting the ratio of subdural to epidural is 1:1.05[1].

III. ETIOLOGY

Direct injury. Direct head trauma occurs when the head is struck, or its motion is suddenly arrested, by an object. The resulting damage to the skull and brain depends on the consistency, mass, surface area, and velocity of the object striking the head. Direct injury can also be caused by compression of the head.

Indirect injury. In indirect brain injury, the cranial contents are set into motion by forces other than the direct contact of the skull with an object. A common example is an acceleration- deceleration injury in which no direct mechanical impact is sustained, but the cranial contents are set into vigorous motion. As the bridging subdural vessels are strained, subdural hematomas (SDHs) may result.

Besides these two patterns of head injuries, there are more causes such as: penetrant head trauma, scalp wounds, skull fracture (linear fractures, depressed fractures and basilar fractures), extra-axial injury (epidural hematoma, subdural hematoma, traumatic subarachnoid hemorrhage, subdural hygroma) and intra-axial injury (diffuse axonal injury, cerebral contusion, intracerebral hematoma and intracerebellar hematoma).

IV. PATHOPHYSIOLOGY

Cerebral hemodynamics and increased intracranial pressure

[1] Reference: https://pubmed.ncbi.nlm.nih.gov/30790736/

The brain has an extremely high metabolic rate, accounting for approximately 20% of the entire oxygen consumption of the body and requiring approximately 15% of total cardiac output. Hypertension, alkalosis, and hypocarbia promote cerebral vasoconstriction, whereas hypotension, acidosis, and hypercarbia cause cerebral vasodilation. Cerebral Perfusion Pressure (CPP) defines by: CCP = MAP – ICP

If CPP falls below 40 mm Hg, autoregulation is lost and cerebral blood flow (CBF) declines, resulting in tissue ischemia and altered cerebral metabolism. Avoidance of hypotension or elevation in ICP in the head- injured patient helps ensure that CPP can be maintained. The recommended target CPP value is between 60 and 70 mm Hg.

Cushing reflex

Progressive hypertension associated with bradycardia and diminished respiratory effort is a specific response to acute, potentially lethal increases in ICP. This response is called Cushing reflex or Cushing phenomenon, and its occurrence indicates that the ICP has reached life- threatening levels. However, only one- third of cases of life- threatening increased ICP manifest the full triad of hypertension, bradycardia, and respiratory irregularity

V. DIAGNOSIS

Physical examination:

In the setting of head trauma and suspected brain injury, management should be guided by the principles of trauma resuscitation. A primary survey focusing on airway, breathing, and hemorrhage control should be performed expeditiously. After immediate life threats are adequately addressed, a secondary survey should evaluate for underlying head injury, brain injury, and neurologic compromise.

Acute Neurologic Examination:

The goals of the acute neurologic assessment of head trauma patients include detection of life- threatening injuries and identification of neurologic changes in the immediate post-trauma period. An efficient neurologic examination in the emergency setting includes evaluation of mental status, GCS score, pupillary size and responsiveness, and motor strength and symmetry.

Table 1: Glasgow Coma Scale

Glasgow Coma Scale		
Response	Score	Significance
Eyes opening		
Spontaneously	4	Reticular activating system intact; patient may not be aware
To verbal command	3	Opens eyes when told to do so
To pain	2	Opens eyes in response to pain
No eyes opening	1	Does not open eyes to any stimuli
Verbal Stimuli		
Oriented, converses	5	Relatively intact CNS, aware of self and environment
Disoriented, converses	4	Well- articulated, organized, but disoriented
Inappropriate words	3	Random exclamatory words
Incomprehensible	2	Moaning, no recognizable words
No verbal response	1	

		No response or intubated
Motor response		
Obeys verbal commands	6	Readily moves limbs when told to
Localizes to painful stimuli	5	Moves limb in an effort to remove painful stimuli
Flexion withdrawal	4	Pulls away from pain in flexion
Abnormal flexion	3	Decorticate rigidity
Extension	2	Decerebrate rigidity
No motor response	1	Hypotonia, flaccid—suggests loss of medullary function or concomitant spinal cord injury

Mild TBI: GCS of 13-15, Moderate TBI: GCS of 9-12 and Severe TBI: GCS of 3-8

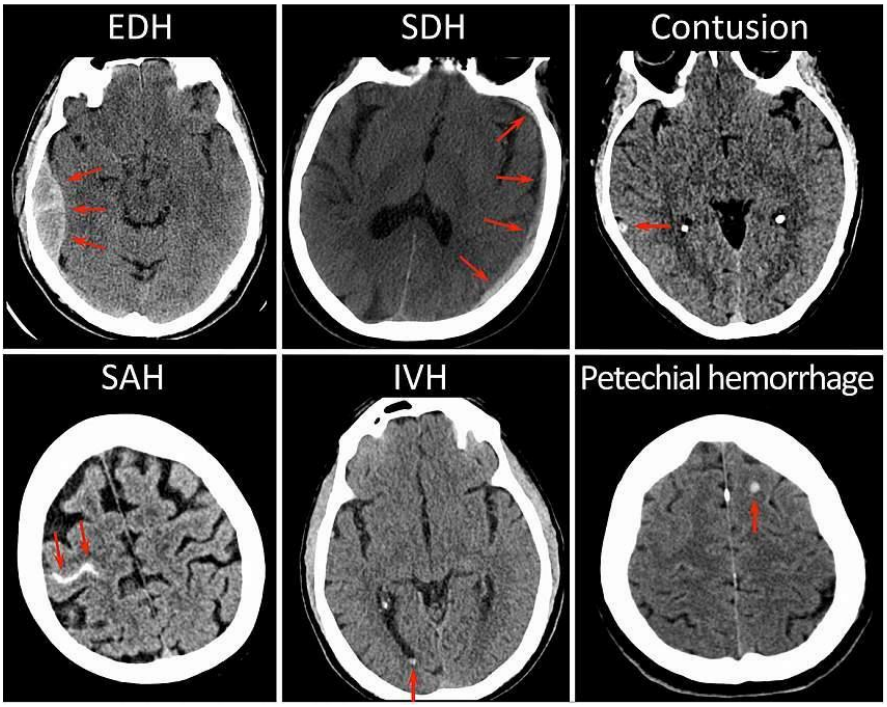
Investigations

Laboratory tests: Routine laboratory tests are generally not needed for patients with isolated mild TBI in the acute setting, except for a bedside glucose test in patients with altered mental status and determination of the blood alcohol level in patients suspected of alcohol intoxication and head trauma. Suspicion of systemic pathology as the cause of the head trauma, such as when a diabetic patient sustains an moto vehicle collision (MVC) after losing consciousness from hypoglycemia, warrants directed testing for culprit conditions. Coagulation studies are indicated in patients with coagulopathies (e.g., hemophilia, Von Willebrand disease), suspected liver disease, and those on anticoagulants.

Neuroimaging

Skull radiography: skull radiography after head trauma has long been replaced by cranial CT, which is the cornerstone of imaging for acute head trauma. Skull radiographs for adults with either mild or severe TBI are not recommended.

Computed tomography: Noncontrast CT of the head is the diagnostic standard for identifying intracranial injury in the ED. This scan delineates acute intra- axial and extra-axial bleeding, cerebral swelling, ischemic infarction caused by hypoxia after trauma, evidence of increased ICP, and pneumocephalus. It is sensitive for demonstrating mass effect, ventricular size and configuration, bone injuries, and acute hemorrhage, regardless of location (i.e., parenchymal, subarachnoid, subdural, or epidural spaces).



VI. DIFFERENTIAL DIAGNOSIS

In the context of trauma, conditions presenting with an altered loss of consciousness (LOC) include seizures, intoxication with alcohol or drugs, and systemic trauma resulting in hypoxemia or hypoperfusion. Sedatives or motor function may be altered by neuromuscular blocking agents administered prior to ED arrival. Head trauma may result in confounding injuries to other parts of the head or neck, including skull or facial bone fractures, cervical spine or spinal cord injuries, eye injuries, otolaryngeal injuries, and damage to blood vessels within the neck. LOC can be also caused by stroke, spontaneous acute subdural hematoma, cerebral aneurysms, brain metastasis, hydrocephalus, or Alzheimer disease.

With age, the brain atrophies and creates more space within the cranial vault for blood to accumulate, so older adults can have significant hemorrhage and not show signs of deterioration.

VII. MANAGEMENT

Out- of- Hospital Care

The out- of- hospital management of the head- injured patient should focus on preventing or minimizing secondary brain injury specifically on the major systemic insults of hypotension, hypoxia and hypocarbia. Interventions should be aimed at maintenance of oxygenation and prevention of hypocarbia through appropriate airway management, supplemental oxygen as needed, and controlled ventilation. Hypotension should be avoided through directed fluid resuscitation and control of hemorrhage.

Emergency Department Management

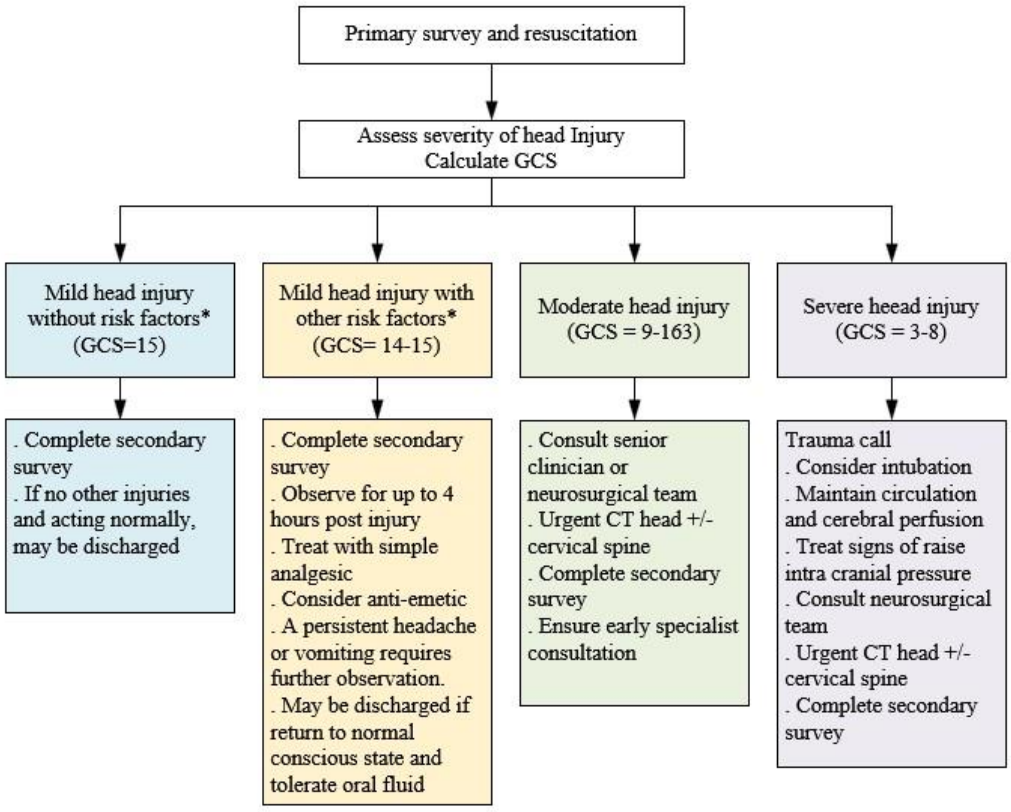
Airway: The airway should be secured early to protect against aspiration and prevent secondary brain injury as a result of hypoxia or hypercarbia.

Hypotension: Systemic hypotension has profound implications for neurologic outcomes. As such, fluids or blood transfusion should be delivered to maintain a blood pressure as close to normal as possible, with a SBP of at least 110 mm Hg for those 15 to 49 and over 70 years of age, and at least **100 mm Hg** for those 50 to 69 years old.
Brain- directed osmotic therapies should be reserved for patients with signs of transtentorial herniation or progressive neurologic deterioration not attributable to extracranial causes. If there are signs of impending herniation syndrome, such as deepening coma, a newly asymmetric pupil, or other substantially diminishing neurologic parameters, osmotic diuretics, such as mannitol is recommended.

Hyperventilation: hyperventilation was recommended as a method to reduce ICP. However, this reduction in ICP is accomplished by reducing CBF, which is important in meeting the brain's metabolic demands. A low Paco2, and the resulting lower CBF, may result in cerebral ischemia, whereas high Paco2 levels can result in cerebral hyperemia and high ICP. Normal ventilation is currently the goal for severe TBI patients in the absence of cerebral herniation, and Paco2 should be maintained in the normal range of 35 to 45 mm Hg.

Cranial decompression: In patients with impending herniation who do not respond to first-line therapies, cranial decompression may temporarily reverse or arrest the herniation syndrome.

Algorithm



(*) Risk factors:

- Severe headache
- Persistent altered mental status/acting abnormally
- Abnormal neurology
- Suspected child abuse
- Palpable skull fracture
- Signs of base of skull fracture
- Non-frontal scalp hematoma (occipital, parietal or temporal) in child <2 years
- Severe mechanism
- Post-traumatic seizure
- Loss of consciousness
- Persistent vomiting
- Known bleeding disorder/anticoagulation
- Ventriculoperitoneal shunt
- Neurodevelopmental disability

(Adapted from: https://www.rch.org.au/clinicalguide/guideline_index/Head_injury/)

VIII. SPECIAL CASES

Mild Traumatic Brain Injury and Sports- Related Concussion: Athletes with a concussive head injury should be immediately removed from play and not return until they have been evaluated by a health care provider with expertise in concussion management. There should be a gradual stepwise increase in physical activity. Anticoagulated patients: there is a higher incidence of intracranial bleeding in TBI patients on anticoagulants following head trauma, with an incidence of up to 22% in patients. patients taking anticoagulation with intracranial lesions should be managed with reversal of anticoagulation like vitamin K or fresh frozen plasma, where patient with a negative initial head CT scan do not need to have their anticoagulation reversed.

Head trauma in older adult: older patients have increased morbidity and mortality from TBI and have higher rates of intracranial injuries following head trauma The presence of comorbid medical conditions, use of anticoagulants, preexisting cognitive deficits, polypharmacy, alcohol consumption, and unique physiology of the aging brain make it challenging for the emergency clinician to detect brain injury.

IX. EVOLUTION AND PROGNOSIS

The ultimate survival and neurologic outcome of the brain-injured patient depends on the extent of TBI occurring at the time of injury (primary injury) and the subsequent effects of systemic insults (secondary injuries), such as those caused by hypotension and hypoxia. Thus, clinical care of patients with TBI emphasizes early management to minimize the occurrence of secondary brain injury. Emergency clinicians can influence the incidence and severity of primary brain injury through injury prevention programs.

X. COMPLICATIONS

The complications of head trauma are divided into two main outcomes:

Central Nervous System Infections: meningitis after basilar fractures (caused by variety of microbes but early meningitis within 3 days injury of CSF usually caused by Pneumococci), brain abscess (after penetrant injury) and cranial osteomyelitis.

Medical complications: Disseminated intravascular coagulation, respiratory complication and cardiac dysfunction.

XI. PREVENTION AND RECOMMENDATION

All patients with moderate to severe head trauma require imaging to determine the extent and nature of the brain injury and necessity of neurosurgical intervention. Neurosurgical consultation should be obtained as soon as possible to help direct the patient's subsequent management.

In patients with persistent symptoms of headache, confusion, or memory difficulties, delayed MRI may define lesions in the regions related to cognition that cannot be seen on CT. Although not useful in the emergency setting, MRI has prognostic value during subsequent care and assists in directing the future rehabilitation of these patients

XII. REFERENCES

1. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic brain injury- related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. MMWR Surveill Summ. 2017;66:1–16.
2. Greer N, Sayer N, Koeller E, Velasquez T, Wilt TJ. Outcomes associated with blast versus nonblast- related traumatic brain injury in US military service members and veterans: a systematic review. J Head Trauma Rehabil. 2018;33:E16–E29.
3. Miller SC, Whitehead CR, Otte CN, et al. Risk for broad- spectrum neuropsychiatric disorders after mild traumatic brain injury in a cohort of US Air Force personnel. Occup Environ Med. 2015.
4. Reginelli A, Pinto A, Russo A, et al. Sharp penetrating wounds: spectrum of imaging findings and legal aspects in the emergency setting. Radiol Med. 2015.
5. Galvagno Jr SM, Nahmias JT, Young DA. Advanced trauma life support((R)) update 2019: management and applications for adults and special populations. Anesthesiol Clin. 2019;37:13–32.
6. Joseph B, Pandit V, Aziz H, et al. Mild traumatic brain injury defined by Glasgow Coma Scale: is it really mild? Brain Inj. 2015;29:11–16.
7. Stippler M, Liu J, Motiei- Langroudi R, Voronovich Z, Yonas H, Davis RB. Complicated mild traumatic brain injury and the need for imaging surveillance. World Neurosurg. 2017;105:265–269.
8. O'Keeffe E, Kelly E, Liu Y, et al. Dynamic blood- brain barrier regulation in mild traumatic brain injury. J Neurotrauma. 2019.
9. Yoo RE, Choi SH, Oh BM, et al. Quantitative dynamic contrast- enhanced MR imaging shows widespread blood- brain barrier disruption in mild traumatic brain injury patients with post- concussion syndrome. Eur Radiol. 2019;29:1308–1317.
10. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017;80:6– 15.

INITIAL MANAGEMENT OF CHEST TRAUMA

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I. INTRODUCTION

Chest trauma is any form of injury to the chest including ribs, heart and lungs, great vessels, trachea and esophagus. Chest injuries are potentially life-threatening because of immediate disturbances of cardiorespiratory physiology, tension pneumothorax, cardiac tamponade, airway obstruction, and uncontrolled hemorrhage. Care of severe thoracic trauma is multidisciplinary in nature, involving trauma surgeons, cardiothoracic surgeons, and intensivists. Improved understanding of underlying physiologic mechanisms, newer imaging modalities, minimally invasive approaches, and pharmacologic therapies have contributed to decreasing morbidity and mortality in patients with thoracic injuries.

II. EPIDEMIOLOGY

Chest trauma is a major cause of death and disability in Asia. In 2019, an estimated 1.2 million people died from chest trauma worldwide, and Asia accounted for 40% of these deaths. The most common causes of chest trauma in Asia are road traffic accidents, falls, and assaults.

Approximately 75% of patients with thoracic trauma require only simple tube thoracostomy and volume resuscitation, and the initial care and disposition of these patients is usually performed by emergency clinicians.

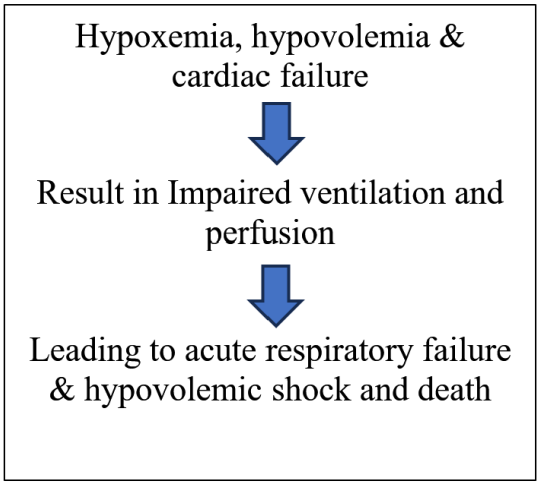
III. ETIOLOGY

It is either blunt or penetrating. Blunt chest trauma results from sudden compression or positive pressure inflicted to chest wall. Penetrating trauma occurs when a foreign object penetrates to the chest wall. Injury location and type dictates both assessment and management.

IV. PATHOPHYSIOLOGY

Life-threatening injuries are often resulted from chest trauma throughout one or more pathologic mechanisms. There are:

- Hypoxemia from disrupting of the airway: injury to the lung parenchyma, rib cage and respiratory musculature, massive hemorrhage, collapsed lung, and pneumothorax.
- Hypovolemia from massive fluid loss from great vessels, cardiac rupture, or hemothorax.
- Cardiac failure from cardiac tamponade, cardiac contusion, or increased intra thoracic pressure.



V. DIAGNOSIS

Clinical manifestation

- **Respiratory**
  - Dyspnea, respiratory distress
  - Cough with or without hemoptysis
  - Cyanosis of mouth, face, nail beds, mucous membrane
  - Tracheal deviation
  - Audible air escaping from chest wound
  - Decreased breath sound on side of injury
  - Decreased O2 saturation
  - Frothy secretion
  - Bruising, abrasion, subcutaneous emphysema
  - Asymmetric chest movement
- **Cardiovascular**
  - Tachycardia, decreased blood pressure, narrow pulse pressure
  - Asymmetric blood pressure values in both arms
  - Distended neck vein
  - Muffled heart sound
  - Chest pain
  - Dysrhythmia

Investigation

- Assessment of hemodynamic stability and **ABC** approach (Airway, Breathing, Circulation) before proceeding the secondary survey
- **History taking** to assess time and mechanism of the injury
- **Physical examination** (head-to-toe examination) to find any signs and symptoms of chest injury:
  - Abdominal and chest tenderness
  - Chest wall bruising and swelling
  - Decreased lung sound, wheezing
  - Rapid pulse and rapid breathing
  - Chest crepitation

- Cyanosis and dyspnea

- **Imaging**
  - **Chest Radiography**: evaluate for pneumothorax, tension pneumothorax, hemothorax, chest wall fractures, and pulmonary contusion.
  - **Focused assessment sonography in trauma (FAST)** examination: evaluated for hemothorax, cardiac tamponade and will assist in diagnosis of abdominal injury.
  - **CT of chest, abdomen and pelvic** (for stable patients only): higher sensitivity than chest x-ray for detection of acute traumatic chest injuries however, obtaining a chest CT requires transportation out of the ED. Performing with IV contrast, is a rapid and reliable imaging for laceration and contusion.
  - **Pulse oximetry:** is helpful to assess adequacy of oxygenation and need for supplemental O2
  - **EKG:** An EKG may be helpful in patients with blunt chest to help elucidate a cause of the accident.
  - **CT angiography or MRI**
- **Laboratory test:** Blood testing, including ABG, does not have much utility in making the diagnosis of any of the conditions listed above**.**
  - Complete blood count (CBC)
  - Type and cross-match
  - Arterial blood gas (ABG)
  - Cardiac enzymes
  - Coagulation profile

VI. DIFFERENTIAL DIAGNOSIS

There are two classifications:
Immediate life-threatening injuries (Lethal Six) and Potential life-threatening injuries (Hidden Six)

- **Immediate life-threatening injuries (Lethal Six)**
  Fetal if they are not recognized and treated immediately
  - Airway obstruction
  - Tension pneumothorax
  - Open pneumothorax (sucking chest wound)
  - Massive hemothorax
  - Flail chest
  - Cardiac tamponade
- **Potential life-threatening injuries (Hidden Six)**
  - Cardiac contusion
  - Aortic disruption
  - Diaphragmatic rupture
  - Esophageal injury
  - Pulmonary contusion
  - Tracheobronchial injuries

VII. MANAGEMENT

All trauma patients must be managed as following protocols:

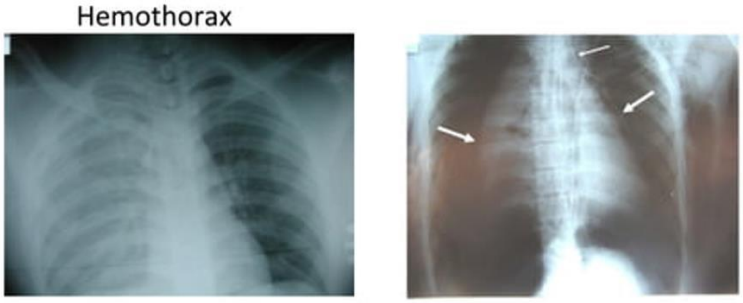
- **A** (Airway with c-spine protection): Is the patient speaking in full sentences?
- **B** (Breathing and Ventilation): Is the breathing labored? Are symmetrical, breath sounds present bilaterally?
- **C** (Circulation with hemorrhage control): Are pulses present and symmetric? How does the patient's skin appear? (cold clammy, warm well-perfused)
- **D** (Disability): What is their GCS scale? Are they moving all extremities?
- **E** (Exposure/Environmental Control): Completely expose the patient. Is rectal tone present? Is there any gross blood per rectum?

Initial intervention:

- **IV** – 2 large-bore (minimum 18 Gauge) Antecubital IV
- **O2** – Nasal cannula, Face Mask
- **Monitor:** Place the patient on a cardiac monitor.

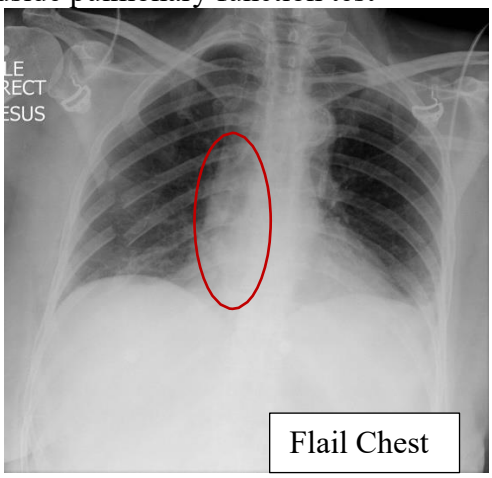
Specific management

- **Hemothorax:** is an accumulation of fluid in the pleural space after blunt or penetrating traumatic chest injury. Most commonly finding on clinical examination is the diminution or absent breath sound of affected side.
  - **Pleural tapping**: removal of pleural fluid
  - **Chest tube insertion**: to drain excess fluid
  - Oxygen support
  - Maintaining of tissue perfusion

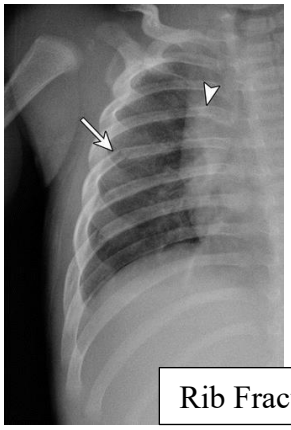


- **Flail Chest:** Loss of stability of chest wall as the result of multiple rib fractures, or combined rib and sternum fractures. It is called paradoxical movement when three of more adjacent ribs are fractured at two points
  - Stabilize the flail portion of the chest with hands
  - Apply a pressure dressing and turn the patient on the injured side
  - Analgesia
    - Ketamine: 0.1–0.3 mg/kg IV
    - Fentanyl: (Short-acting): 0.25–2 mcg/kg IV
    - Morphine: (Intermediate-acting): 0.1 mg/kg IV
    - Lidocaine: (Topical for chest tubes): <6 mg/kg SQ

- Thoracic epidural analgesia
- Intercostal nerve blocks
- others:
  - Monitored by serial chest Xray daily
  - Arterial blook gas analysis
  - Pulse oximetry
  - Bedside pulmonary function test

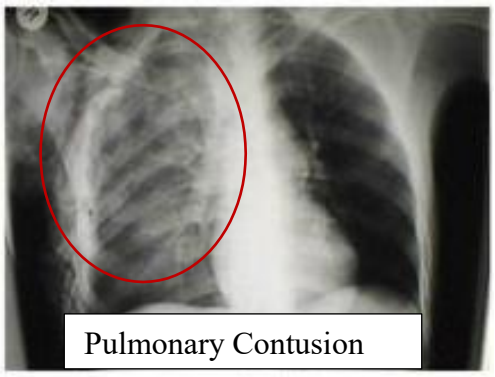


- **Rib Fracture:** is often a clinical diagnosis, with severe point tenderness, bony crepitus, ecchymosis, and muscle spasm over the rib. Simple rib fracture account for more than 50% for non-penetrating trauma which heal in 3-6 weeks.
  - To control pain
    - Intercostal nerve block
    - Ice cover over the fracture site
    - Sedation:
      - Ketamine: 1–3 mg/kg IV
      - Etomidate: 0.3 mg/kg IV
      - Midazolam: 0.05 mg/kg IV
    - Epidural analgesia
  - Avoiding excessive activity
  - Treating any associated injuries
  - **Surgical fixation:** is rarely necessary unless fragments are grossly displaced.



Rib Fracture

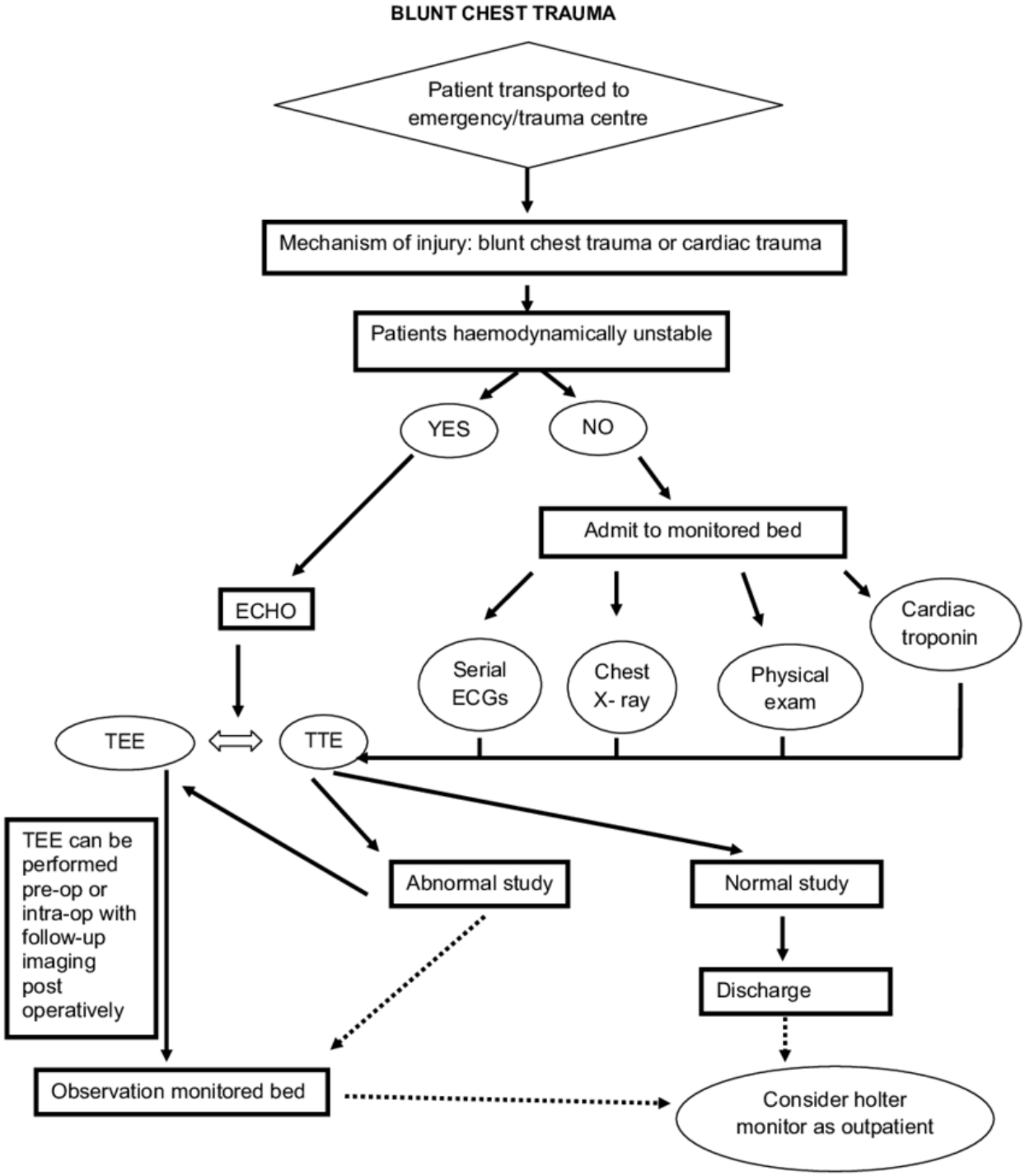
- **Pulmonary contusion**
  - Maintaining of the airway: Postural drainage, physiotherapy.
  - Providing adequate oxygenation: O2 supply, mechanical ventilation support (if required)
  - Controlling pain
  - Antibiotics to prevent pulmonary infection
  - Diuretics to reduce pulmonary edema
  - Restriction of intravenous (IV) fluids (to maintain intravascular volume within strict limits)



Pulmonary Contusion

- **Pneumothorax:** accumulation of air in the pleural space, result in 10-15% of chest trauma patients.
  - Asymptomatic patient with negative initial imaging can be safely observe for 6 hours.
  - For moderate and large pneumothorax, chest tube should be placed.
  - In patient with open pneumothorax defect should be covered immediately. Positive- pressure ventilation can then be initiated, if needed, without the fear of producing a tension pneumothorax, and the patient can be prepared for definitive surgical repair.
  - In tension pneumothorax: needle thoracostomy (2^{nd} intercostal space of mid-clavicular line) or tube thoracostomy (5^{th} intercostal space of anterior-axillary line)

Algorithm



TEE: Transesophageal echocardiography, TTE: Transthoracic echocardiogram
(Blunt chest trauma algorithm from: https://www.researchgate.net/figure/Blunt-chest-trauma-algorithm_fig1_7760949)



VIII. SPECIAL CASES

Pregnancy consideration:

- In pregnant patients, remember to use the least amount of radiation available and to shield the uterus during imaging when possible
- Take note of the differences in anatomy of the thoracic cavity in pregnant patients, as well as differences in lab values, intravascular volume, and cardiovascular physiology

Pediatric Considerations

- The rib cage is highly elastic in children and can withstand significant forces without overt signs of external trauma and can underestimate even major intrathoracic injuries
- Retrospective studies have proposed limiting chest CT in pediatric trauma to patients with a vehicle-related mechanism or an abnormal CXR

IX. EVOLUTION AND PROGNOSIS

- Chest trauma patients can present with several conditions each of which can be acutely life threatening; a majority of these conditions can be clinically diagnosed and treated during the primary survey.
- Tension pneumothorax is a clinical diagnosis, chest x rays are not indicated for making this diagnosis.
- Bedside ultrasonography can be extremely useful for diagnosing acute traumatic chest conditions.
- Only hemodynamically stable patients should be sent for advanced imaging such as CT scan.
- ED thoracotomies are reserved for patients presenting with traumatic arrest secondary to penetrating chest trauma only

X. COMPLICATION

- Chest wall injury
    - Sucking wound and open pneumothorax
    - Ribs-pain, hemothorax, flail chest, deformed chest, respiratory distress.
- Lung injury
    - Lung contusion, hemopneumothorax
    - Emphysema thoracis
- Major airway injury (surgical emphysema, massive hemothorax)
- Esophageal injury
    - Mediastinitis, sepsis, septicemia, pneumothorax

- Cardiac injury
    - Cardiac tamponnade, myocardial contusion/ laceration
- Great vessel injury
    - Hypovolemia, shock
- Terminal complication : Acute respiratory distress syndrome (ARDS)

XI. PREVENTION AND RECOMMENDATION

Chest injuries are common and often life-threatening in trauma patient. Principle aims of treatment are control of hypoxia and hypotension. So rapid treatment and identification will definitely save the life.

XII. REFERENCE

1. 10th Edition ROSEN'S Emergency Medicine Concepts and Clinical Practice
2. Harrisons Manual of Medicine, 20th Edison
3. Simon B, Ebert J, Bokhari F, et al. Management of pulmonary contusion and flail chest: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. 2012;73(5 suppl 4):S351–S361. https://doi.org/10.1097/TA.0b013e31827019fd.
4. Liang Y- S, Yu K- C, Wong C- S, Kao Y, Tiong T- Y, Tam K- W. Does surgery reduce the risk of complications among patients with multiple rib fractures? A meta- analysis. Clin Orthop Relat Res. 2019;477(1):193–205. https://doi.org/10.1097/CORR.0000000000000495.
5. https://doi.org/10.1016/j.injury.2018.01.033.
6. https://www.uptodate.com/contents/initial-evaluation-and-management-of-adults?search=blunt%20chest%20trauma&source=search result&selectedTit
7. https://www.saem.org/about-saem/academies-interest-groups-affiliates2/cdem/for-students/online-education/m4-curriculum/group-m4-trauma/chest-trama
8. Centers for Disease Control and Prevention. Accidents/unintentional injuries. Available at http://www.cdc.gov/nchs/FASTATS/acc-inj.htm.
9. Fox N, Schwartz D, Salazar JH, et al. Evaluation and management of blunt traumatic aortic injury: A practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2015;78(1):136–146.
10. Karmy-Jones R, Jurkovich GJ. Blunt chest trauma. Curr Probl Surg. 2004;41(3):211–380.
11. Lotfipour S, Kaku SK, Vaca FE, et al. Factors associated with complications in older adults with isolated blunt chest trauma. West J Emerg Med. 2009;10(2). Available at http://escholarship.org/uc/item/9922n5.

ACUTE ABDOMINAL SYNDROME

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I. DEFINITION

Acute abdominal syndrome refers to the sudden onset of severe abdominal pain, often signaling a potentially life-threatening condition. This syndrome encompasses a broad range of medical and surgical emergencies that require prompt diagnosis and intervention. The pain may arise from various abdominal organs such as the stomach, intestines, liver, pancreas, kidneys, or reproductive organs.

II. EPIDEMIOLOGY

Acute abdominal syndrome is a common presentation in emergency departments worldwide, representing a significant proportion of emergency medical and surgical admissions.
Its epidemiology varies depending on the underlying cause, age group, gender, and geographic location.

The incidence and Prevalence of acute abdominal pain accounts for approximately **5–10%** of emergency department visits globally. Appendicitis 7–10%, Cholecystitis about 3–4% and is more prevalent in middle-aged adults, particularly in women, Pancreatitis about 1–2% of cases, with a higher prevalence among individuals with gallstones or alcohol use disorder, Bowel Obstruction around 2–4% of acute abdominal emergencies, more common in older adults.

III. ETIOLOGY

1. Surgical causes:

Cause	Diagnostic clue
Appendicitis (Acute appendicitis)	Common. Laboratory parameters indicating acute inflammation usually increased, but not necessarily yet in the initial phase.
Intestinal obstruction	Surgical scars, hernias, possible malignancy. Initially undulating pain; development of strangulation: a suspicion of this is an indication for surgery.
Perforated peptic ulcer	Acute onset, peritonism. Often the first symptom of peptic ulcer disease. Pain starts in the upper abdomen
Acute cholecystitis (Cholelithiasis)	Colicky pain in the right costal arch, clear tenderness on palpation, clinical manifestations of an infection. Ultrasonography. Pain becomes constant as the cholecystitis progresses. Often the first symptom of gallstone disease.

Acute pancreatitis (Acute pancreatitis)	History of alcohol consumption. Consider gallstones as possible etiology. Urine and serum amylase may be normal in chronic or recurrent cases.
Mesenterial thrombosis	May be difficult to diagnose on the basis of clinical manifestations; often resembles strangulation. Clear peritonitis is initially absent but the patient is obviously ill. The patient usually has atrial fibrillation or some other cardiovascular disease.
Complicated diverticulitis of the colon (Diverticulitis and diverticulosis)	The most common site is the sigmoid colon. Peritonitis or abscess, clear local tenderness, low-grade fever and increased inflammation parameters. Ileus and intestinal bleeding are possible.
Volvulus	Sigma is the most common site. Symptoms of intestinal obstruction (risk for perforation!). Plain abdominal X-ray is diagnostic. Volvulus of the caecum develops more slowly.
Testis torsion	The testis is tender on palpation. Often pain and tenderness in lower abdomen. Doppler ultrasonography. In an unclear case, explorative surgery should be readily performed.

2. Gynecological causes:

Ectopic pregnancy (Ectopic pregnancy)	Pain; referred pain in shoulder. Urine pregnancy test may be negative, sensitive serum test is usually positive.
Ovarian origin	Ovulation pain, oophoritis, ruptured cyst, torsion of a cyst. The etiology of acute lower abdominal pain in a young woman is often revealed on laparoscopy.
Myoma	Torsion; necrosis; bleeding into the abdominal cavity, infection
Endometriosis (Endometriosis)	Menstrual pain

3. Non-surgical causes for acute abdomen
   - ✉ Metabolic disorders:
   - ✉ Infectious causes:
   - ✉ Referred pain:
   - ✉ Immunological disorder:
4. Other Causes

IV. PATHOPHYSIOLOGY

Acute abdominal syndrome (AAS) encompasses a variety of conditions that lead to severe abdominal pain and can arise from multiple underlying pathophysiological mechanisms. Understanding these mechanisms is essential for accurate diagnosis and management.

1. **Inflammation**
   - Appendicitis: Inflammation of the appendix due to obstruction (often by fecalith) leads to swelling, necrosis, and potential perforation.
   - Cholecystitis: Inflammation of the gallbladder typically caused by bile duct obstruction (often by gallstones) results in increased

pressure and inflammation.

2. **Mechanical Obstruction**
   Bowel Obstruction: Can be due to adhesions, hernias, or tumors, leading to distension, ischemia, and potential perforation. Increased intraluminal pressure causes pain and can lead to bowel ischemia.
3. **Ischemia**
   Mesenteric Ischemia: Reduced blood flow to the intestines (due to embolism or thrombosis) leads to ischemia and can result in tissue necrosis. Symptoms often include severe, sudden abdominal pain out of proportion to physical findings.
4. **Perforation**
   Perforated Viscus: Conditions like peptic ulcers or diverticulitis can lead to perforation, resulting in spillage of intestinal contents into the peritoneal cavity, leading to peritonitis and severe inflammation.
5. **Visceral Pain:** the abdominal organs have visceral innervation, and inflammation or injury triggers the release of mediators (like prostaglandins) that activate pain receptors. This can lead to referred pain, where the patient feels discomfort in areas not directly involved.
6. **Infection**
   Conditions like diverticulitis can lead to localized infection, resulting in abscess formation and systemic inflammatory responses. This can progress to sepsis if not addressed promptly.

V. DIAGNOSIS

1. **History**

   The history should include a complete description of the patient's pain and associated symptoms. Medical, surgical, and social history should also be sought as this may provide important information.

2. **Physical examination**

   Before the complete physical examination, take a few moments to gain the patient's trust by explaining what needs to be done, exposing only what needs to be seen, and re-covering exposed parts of the body sequentially. Provide patient privacy. Note the patient's skin (color, temperature, turgor, perfusion status), and perform a targeted heart and lung examination.

   - ✉ General examination
   - ✉ Inspection of the abdomen
   - ✉ Palpation of the abdomen
   - ✉ Palpation of the genitals
   - ✉ Auscultation of the abdomen
   - ✉ Touch per rectum

3. **Symptoms and clinical diagnostic**

Acute abdominal syndrome refers to a collection of symptoms and clinical findings associated with various conditions that cause sudden, severe abdominal pain. These conditions range from surgical emergencies like appendicitis and bowel perforation to medical conditions like pancreatitis and diverticulitis. The clinical presentation and symptoms can vary depending on the underlying cause, but some common features are shared.

✉ Severe Abdominal Pain ♦ Nausea and Vomiting ♦ Fever:

✉ Abdominal Distension: typically associated with bowel obstruction or ascites. The abdomen may feel firm and tender upon palpation.

✉ Guarding and Rebound Tenderness:

✉ Altered Bowel Habits: diarrhea or constipation can occur depending on the underlying condition. Diarrhea is common in gastroenteritis, while constipation or obstipation can suggest a bowel obstruction.

✉ Shock Symptoms (Tachycardia, Hypotension): hypovolemic shock or septic shock

 Urinary Symptoms: conditions like kidney stones or urinary tract infections can present with lower abdominal pain, sometimes accompanied by hematuria (blood in urine) or dysuria (painful urination).

 Referred Pain:

 Jaundice may accompany cholecystitis or pancreatitis, indicating possible biliary obstruction or hepatocellular damage.

4. Paraclinical examination

The choices of paraclinical examination depend on clinical setting (esp. severity of pain, rapidity of onset) and may include complete blood count, serum electrolytes, coagulation parameters, serum glucose, and biochemical tests of liver, kidney, and pancreatic function.

 Complete Blood count (CBC): Infection: Elevated white blood cell with elevated neutrophilia or with elevated lymphocyte

 Biochemistry: Elevated CRP (Infection)

 chest x-ray to determine the presence of diseases involving heart, lung, mediastinum, and pleura.

 electrocardiogram is helpful to exclude referred pain from cardiac diseases.

 plain abdominal radiographs to evaluate bowel displacement, intestinal distention, fluid and gas pattern, free peritoneal air, liver size, and abdominal calcifications.

 Abdominal ultrasonography to visualize biliary ducts, gallbladder, liver, pancreas, and kidneys. Optimal utilization of ultrasound depends on the suspected clinical diagnosis and location of pain. For nonlocalized abdominal pain, ultrasound is generally considered to be less sensitive and specific than computed tomography. For right upper quadrant pain, ultrasound of the abdomen is the sole imaging modality assigned to the highest category of appropriateness.

 CT to identify masses, abscesses, evidence of inflammation (bowel wall thickening, mesenteric “stranding,” lymphadenopathy, appendicitis), aortic aneurysm; barium contrast radiographs (barium swallow, upper GI series, small-bowel follow-through, barium enema).

 Others: upper GI endoscopy, sigmoidoscopy, or colonoscopy; cholangiography (endoscopic, percutaneous, or via MRI), angiography (direct or via CT or MRI), and radionuclide scanning, Arterial blood gas, Liver function test, Kidney function test, Amylase test.

VI. IFFERENTIAL DIAGNOSIS

Acute abdominal syndrome can arise from a wide range of medical, surgical, and gynecological conditions. A comprehensive differential diagnosis is crucial to identifying the underlying cause, as conditions can vary from benign to life-threatening.

- Appendicitis: RLQ pain, presenting with nausea, anorexia, fever, and tenderness at McBurney's point.
- Cholecystitis: RUQ pain, fever, nausea, and a positive Murphy's sign
- Pancreatitis: Epigastric or LUQ pain radiating to the back, associated with nausea, vomiting, and elevated serum lipase/amylase levels.
- Meckel's Diverticulitis: Congenital abnormality causing RLQ pain, often with bleeding or obstruction.
- Hepatitis: RUQ pain, jaundice, and malaise.
- Peptic ulcer disease: Epigastric or RUQ pain, worsened by meals, associated with nausea, and possibly melena (if ulcer bleeds).
- Liver abscess: RUQ pain with fever and malaise, often due to bacterial infection or parasitic disease (e.g., amoebiasis).
- Biliary colic: Intermittent RUQ pain due to gallstones, often postprandial (after meals).
- Ovarian Cyst Rupture or Torsion: Severe RLQ pain in females, sometimes with nausea and vomiting, and possible peritoneal signs.
- Splenic Infarction or Rupture: Acute LUQ pain, often following trauma or related to conditions like sickle cell disease or mononucleosis.
- Gastric Ulcer: Epigastric or LUQ pain, worsened by meals, possibly with hematemesis or melena.
- Diverticulitis: Inflammation of diverticula in the colon, presenting with LLQ pain, fever, and altered bowel habits (constipation or diarrhea).
- Sigmoid Volvulus: Twisting of the sigmoid colon, causing LLQ pain, distension, and constipation.
- Ovarian Pathologies (in females): Conditions like ovarian cysts or ectopic pregnancy.
- Gastroesophageal Reflux Disease (GERD): Epigastric or retrosternal burning pain, often after meals, with associated heartburn.
- Peritonitis: Generalized abdominal pain with guarding and rebound tenderness, often secondary to perforation of an organ (e.g., gastric ulcer, appendix).
- Bowel Obstruction: Diffuse crampy pain, abdominal distension, vomiting, and inability to pass gas or stools.
- Mesenteric Ischemia: Severe abdominal pain disproportionate to physical findings, commonly in elderly patients with cardiovascular disease, due to bowel ischemia.
- Renal Colic: Severe, cramping flank pain radiating to the groin, associated with hematuria, caused by kidney stones (nephrolithiasis).
- Pyelonephritis: Infection of the kidney, presenting with fever, flank pain, and dysuria.
- Cystitis: Bladder infection causing suprapubic pain, dysuria, and frequency.
- Ectopic Pregnancy: Lower abdominal pain, vaginal bleeding, and hemodynamic instability, especially in women of childbearing age.
- Pelvic Inflammatory Disease (PID): Lower abdominal pain, often bilateral, with fever and vaginal discharge, due to ascending infection from the reproductive tract.

- Abdominal Aortic Aneurysm (AAA) Rupture: Sudden, severe abdominal or back pain, with hypotension and pulsatile abdominal mass, more common in older male.

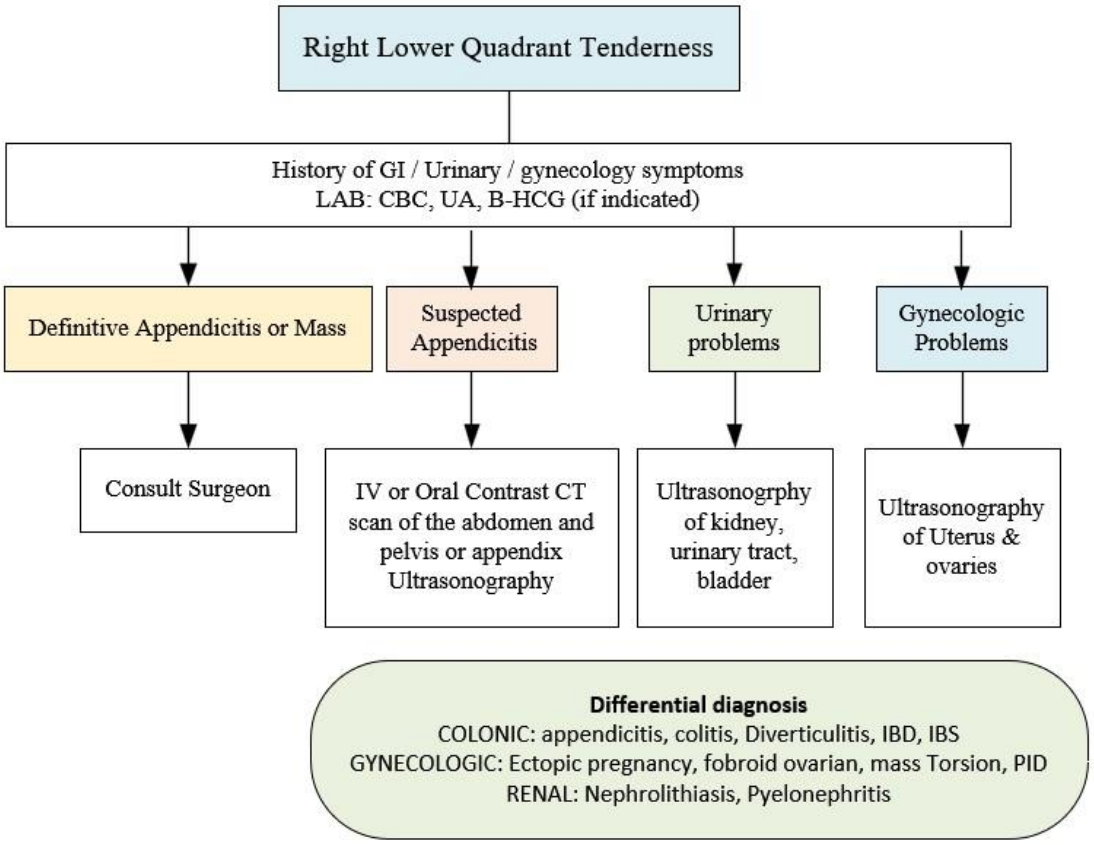
VII. ANAGEMENT

The acute abdomen consists of several intrabdominal processes that require rapid intervention in both diagnosis and treatment. An acute abdomen may present in an obvious or subtle manner, but must always be recognized. Rapid, appropriate testing and concomitant resuscitative therapy are mandatory. If the condition is even possibly surgical, early consultation with a surgeon is mandatory as well.

The management of acute abdominal syndrome (AAS) involves a systematic approach, starting from initial assessment to definitive treatment based on the underlying cause.

1. **Stabilization and monitoring of the vital signs**
   - Intravenous (IV) Fluids: To maintain hydration and electrolyte balance.
   - Broad-spectrum antibiotics
   - Pain Management: Analgesics to manage severe pain.
   - Nausea/Vomiting Management: Anti-emetics as needed.
2. **Surgical Consultation**
   - Urgent Referral: If a surgical cause is suspected (e.g., appendicitis, perforation, etc.), consult a surgeon immediately.
   - Decision for Surgery: Based on imaging results and clinical findings, determine if surgical intervention is necessary.
3. **Specific Treatment Based on Diagnosis**
   - Appendicitis: Appendectomy (surgical removal of the appendix).
   - Cholecystitis: Cholecystectomy (surgical removal of the gallbladder), possibly after stabilization.
   - Bowel Obstruction: Surgery or conservative management, depending on the cause (e.g., adhesions may be treated surgically, while some cases may resolve with conservative measures).
   - Diverticulitis: May require antibiotics and dietary modifications, or surgery if complications arise.
4. **Monitoring and Follow-Up**
   - Continuous monitoring of vital signs and symptoms.
   - Re-evaluation of laboratory tests and imaging if the patient's condition does not improve.

Algorithm: Diagnosis of Right Lower quadrant tenderness:



IBS: irritable bowel syndrome, IBD: Inflammatory bowel disease, PID: Pelvic inflammatory disease
UA: Urine analysis, BHCG: Beta Human Chorionic Gonadotropin

VIII. SPECIAL CASES

1. **Mesenteric Ischemia**

Patient has Severe, sudden-onset diffuse abdominal pain with Nausea, vomiting, diarrhea, or constipation, shock (hypotension, tachycardia), metabolic acidosis (lactic acidosis), or sepsis. The laboratory test finds the elevated white blood cell (WBC) count, elevated lactatemia and metabolic acidosis. Plain abdominal x-ray (late diagnosis) present pneumatosis intestinalis. CT angiography (CTA) show the vascular occlusion or bowel wall thickening, and identifying bowel infarction. The management: IV fluids to correct hypotension and hypoperfusion, nasogastric tube, pain relief, broads spectrum antibiotic, surgical intervention, anticoagulation and/or vasodilator.

2. **Ectopic Pregnancy**

The female patient has sudden unilateral and lower abdominal pain, amenorrhea 7 weeks, Vaginal bleeding, tachycardia, hypotension, pallor, dizziness and abdominal tenderness. Beta HCG positive. The Transvaginal ultrasound does not find an intrauterine pregnancy and find the free fluids in the pelvis. Management: IV fluids and blood transfusion if necessary and Immediate surgical intervention: Laparoscopy or laparotomy.

3. **Intussusception**

The child has severe and crampy abdominal pain, Stool mixed with mucus and blood, bilious vomiting, asthenia, dry mouth. Palpable abdominal finds the mass as "sausage-shaped" in the right upper quadrant. Abdominal X-ray shows signs of bowel obstruction

and Abdominal ultrasound finds the donut sign on transverse. Management: IV fluids to correct hypovolemia and surgical intervention.

4. **Necrotizing Enterocolitis (NEC)**

The child, 15 days, has Vomiting, abdominal distension, and bloody stools, discolor abdomen, Lethargy. Abdominal X-ray finds pneumatosis intestinalis with free air under the diaphragm. Blood tests present the elevated white blood cells, metabolic acidosis, and thrombocytopenia. Management: stop all enteral feeds, initiate parenteral nutrition (IV fluids), Nasogastric decompression, Broad-spectrum antibiotics, and surgical intervention.

IX. EVOLUTION AND PROGNOSIS

1. Evolution:

Acute abdominal syndrome (AAS) typically progresses in a series of stages, influenced by the underlying cause. With appropriate management (surgical or conservative), symptoms typically improve. Timely intervention is crucial to avoid complications.

2. Prognosis

The prognosis of patients depends on the cause.

The prognosis of AAS varies widely based on the underlying cause and the timeliness of treatment.

X. COMPLICATIONS

If left untreated, an acute abdomen may result in the following:

- Sepsis - Fistula - Death
- Necrosis and/or gangrene of bowel.

XI. REVENTION AND RECOMMENDATION

Acute abdomen has many different possible causes, and most of them aren't preventable.

All patients with an acute abdomen need to be seen by a surgeon. If the patient is stable, imaging studies can be obtained. If the patient is unstable, immediate surgical intervention may be necessary. Early recognition and intervention are essential in managing acute abdominal syndrome. Given its potentially life-threatening causes, timely diagnosis through clinical evaluation and appropriate imaging is critical. Treatment must be tailored to the specific condition, with surgical and non-surgical options available depending on the diagnosis. Multidisciplinary care and close monitoring are often required to ensure favorable patient outcomes.

XII. EFERENCES

1. Longstreth, G. F., & Lichter, D. S. (2019). Acute abdominal pain. UpToDate. Retrieved from www.uptodate.com
2. Lewis, S., & Dirksen, S. (2022). *Medical-Surgical Nursing: Assessment and Management of Clinical Problems*. 11th ed. Elsevier.
3. Li PH, Tee YS, Fu CY, Liao CH, Wang SY, Hsu YP, Yeh CN, Wu EH. The Role of Noncontrast CT in the Evaluation of Surgical Abdomen Patients. Am Surg. 2018 Jun 01;84(6):1015-1021. [PubMed]
4. Nakashima T, Miyamoto K, Shimokawa T, Kato S, Hayakawa M. The Association Between Sequential Organ Failure Assessment Scores and Mortality in Patients With Sepsis During the First Week: The JSEPTIC DIC Study. J Intensive Care Med. 2020 Jul;35(7):656-662. [PubMed]

5. Pucher PH, Carter NC, Knight BC, Toh S, Tucker V, Mercer SJ. Impact of laparoscopic approach in emergency major abdominal surgery: single-centre analysis of 748 consecutive cases. Ann R Coll Surg Engl. 2018 Apr;100(4):279-284. [PMC free article] [PubMed]
6. Geng WZM, Fuller M, Osborne B, Thoirs K. The value of the erect abdominal radiograph for the diagnosis of mechanical bowel obstruction and paralytic ileus in adults presenting with acute abdominal pain. J Med Radiat Sci. 2018 Dec;65(4):259-266. [PMC free article] [PubMed]
7. Mohammed MF, Elbanna KY, Mohammed AME, Murray N, Azzumea F, Almazied G, Nicolaou S. Practical Applications of Dual-Energy Computed Tomography in the Acute Abdomen. Radiol Clin North Am. 2018 Jul;56(4):549-563. [PubMed]
8. Brunicardi, F. Charles, et al. *Schwartz's Principles of Surgery*. 11th ed. McGraw-Hill, 2019.
9. Doherty, Gerard M. *Current Diagnosis and Treatment: Surgery*. McGraw-Hill, 2021.
10. Stenson, T. A., et al. "Acute Abdominal Pain: A Review." *American Family Physician*, 2020.
11. Williams, J. R., et al. The Diagnostic Approach to Acute Abdominal Pain. *BMJ*, 2021.
12. American College of Gastroenterology. "Guidelines for the Management of Acute Abdomen." *American Journal of Gastroenterology*, 2022.
13. American College of Surgeons. "Guidelines for Management of Acute Abdomen." Available at: ACS Website
14. American College of Gastroenterology. "Guidelines for the Management of Acute Abdomen." *American Journal of Gastroenterology*, 2022.
15. Mark, L., & Williams, R. (2022). *Acute abdominal syndrome: Diagnosis and management*. Journal of Emergency Medicine, 45(2), 123-135.
16. Smith, J., & Taylor, B. (2020). *Evaluation of acute abdominal pain in adults*. New England Journal of Medicine, 382(4), 329-339.

HYPERKALEMIA

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I. DEFINITION

Hyperkalemia is a common electrolyte disorder defined as a plasma potassium (K) concentration >5.5 mEq/L (>5 mmol/L).

Hyperkalemia depresses cardiac conduction and can lead to fatal arrhythmias.

II. EPIDEMIOLOGY

Incidence

Incidence is higher in patients of older age, male sex, worse kidney function, comorbidities and use of renin angiotensin-aldosterone system inhibitors.

Prevalence

1–10% of hospitalized patients

2–3% in general population but as high as 50% in patients with CKD

III. ETIOLOGY

- Increased load: either endogenous from tissue release or exogenous from a high intake, usually in association with decreased excretion or chronic kidney disease (CKD)
- Decreased excretion: due to decreased glomerular filtration rate (GFR) or impaired aldosterone secretion
- Cellular redistribution: shifts from intracellular space (majority of K is intracellular) to extracellular space
- Pseudohyperkalemia: related to red cell lysis during collection or transport of blood sample, thrombocytosis, or leukocytosis

IV. PHYSIOPATHOLOGY

- Pseudohyperkalemia
    - Hemolysis of red cells in phlebotomy tube (the most common.)
    - Thrombolysis; thrombocytosis
    - Leukocytosis (reverse pseudohyperkalemia)
    - Hereditary spherocytosis
    - Infectious mononucleosis
    - Traumatic venipuncture or fist clenching during phlebotomy (spurious result)
    - Familial pseudohyperkalemia
- Increased K intake
    - Bananas, potatoes, melons, citrus juice, avocados, red meat, nuts, and dried fruits
    - Salt substitutes given to chronic kidney patients
    - Clay ingestion
- Transcellular shift (redistribution)
    - Metabolic acidosis
    - Insulin deficiency

- Hyperglycemia (diabetic ketoacidosis or hyperosmolar hyperglycemic state)
- Tissue damage (rhabdomyolysis, tumor lysis syndrome, burns, trauma)
- Cocaine abuse
- Exercise with heavy sweating

- Impaired K excretion
  - Renal insufficiency/failure
  - Addison disease
  - Mineralocorticoid deficiency
  - Primary hyporeninemia, primary hypoaldosteronism
  - Type IV renal tubular acidosis (hyporeninemic hypoaldosteronism)
  - Obstructive uropathy
  - Cirrhosis
  - Congestive heart failure (CHF)
  - Sickle cell disease
  - Amyloidosis
  - Gordon syndrome
  - Systemic lupus erythematosus
- Medication-induced (numerous)
- Genetics

  Associated with some inherited diseases and conditions
  - Familial hyperkalemic periodic paralysis
  - Congenital adrenal hyperplasia

Cellular Effects of Hyperkalemia:

Elevated extracellular potassium levels decrease the resting membrane potential, making cells less negative (closer to the threshold potential). This reduced difference between resting and threshold potentials leads to:

- ✉ Increased excitability of cells initially, causing symptoms like muscle twitching, cramping, and weakness.
- ✉ Prolonged depolarization can eventually lead to cell dysfunction, as the cells become less responsive to stimuli due to inactivation of sodium channels.
- ✉ In cardiac tissue, this can cause life-threatening arrhythmias, such as ventricular fibrillation, as well as asystole (cardiac arrest), due to the altered action potential propagation.

V. Diagnosis

Serum K level greater than the normal range (3.5 to 5.0 mEq/L); patients may be asymptomatic until >6 mEq/L.

History

- Neuromuscular cramps, myalgias, muscle weakness or paralysis
- Abdominal pain
- Palpitations
- Numbness
- Arrhythmia or cardiac arrest

Physical Exam

- Decreased deep tendon reflexes
- Muscle weakness or flaccid paralysis of extremities

Diagnostic Tests & Interpretation

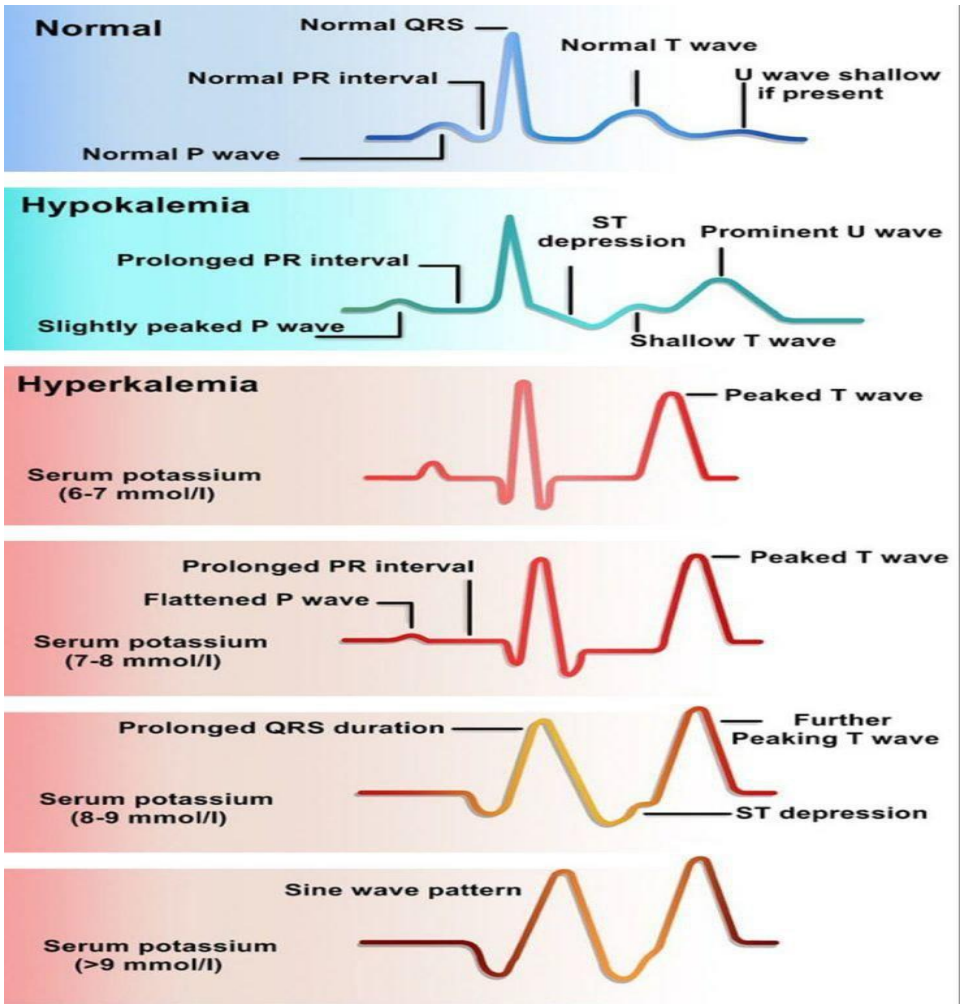
- Serum electrolytes
- Renal function: BUN, creatinine

- Urinalysis: K, creatinine, osmoles (to calculate fractional excretion of K and transtubular K gradient; both assess renal handling of K)
- Disorders that may alter lab results
- Acidemia: K shifts from the intracellular to extracellular space
- Insulin deficiency
- Hemolysis of sample
- Cortisol, aldosterone, and renin levels to check for mineralocorticoid deficiency when other causes are ruled out

Diagnostic Procedures/Other

ECG abnormalities usually occur when K ≥7 mEq/L.

- Peaked T wave with shortened QT interval in precordial leads (most common, usually earliest ECG change; however, neither sensitive nor specific)
- Lengthening of PR interval, loss of P wave, widened QRS
- Sine wave at very high K >8 mEq/L
- Can eventually lead to arrhythmias including bradycardia, ventricular fibrillation, and asystole



VI. DIFFERENTIAL DIAGNOSIS

- Acute tubular necrosis
- Digitalis toxicity
- Hypocalcemia
- Tumor lysis syndrome
- Congenital adrenal hyperplasia
- Burn injuries
- Metabolic acidosis
- Rhabdomyolysis

VII. MANAGEMENT

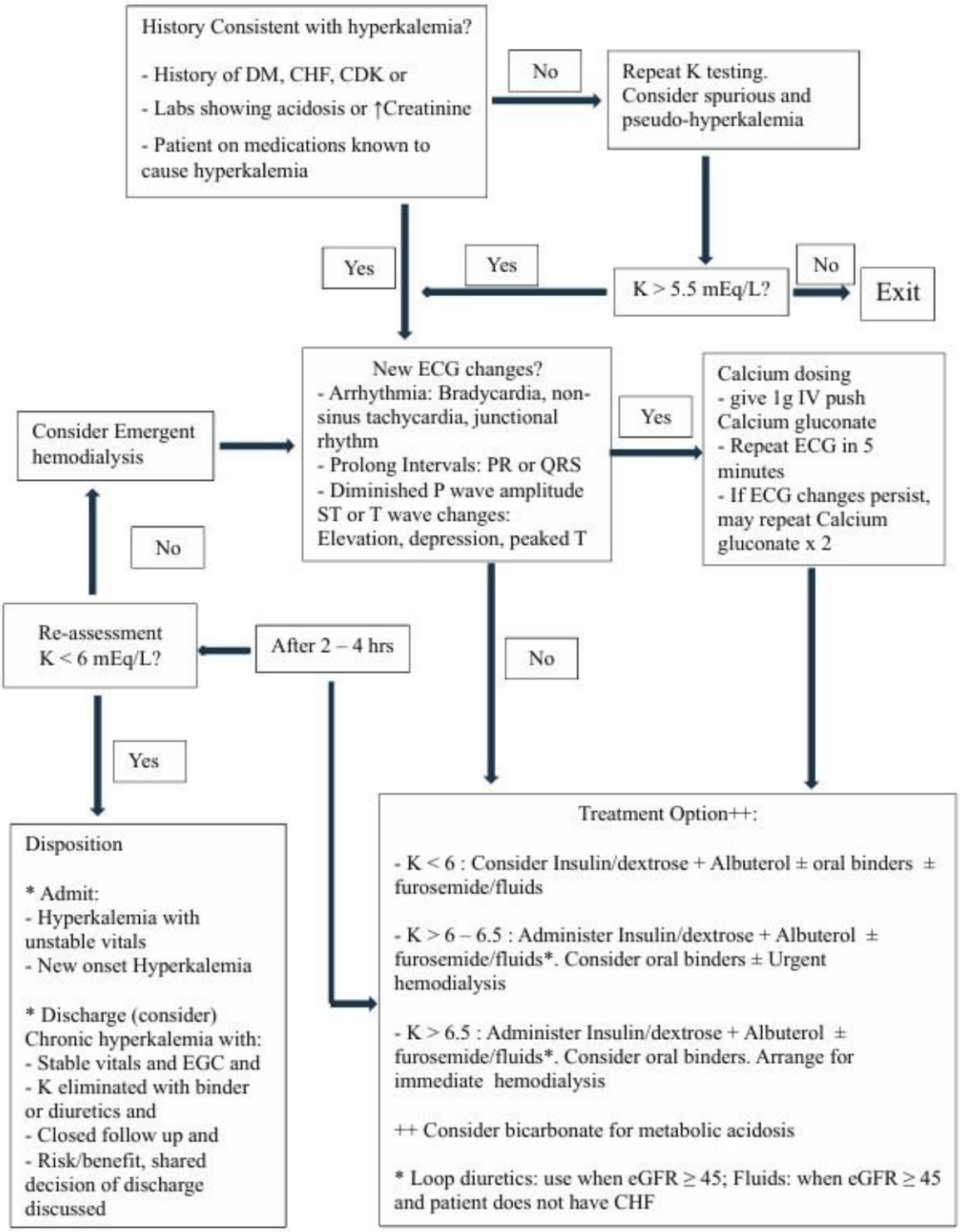
1. Objectives
    a. Prevent or treat the life-threatening effects of hyperkalemia (arrhythmia)
    b. Lower the kalemia to a near normal range
    c. Treat the possible reversible triggering or underlining causes
    d. Prevent the recurrence hyperkalemia if the underlining cause was unable to eliminate
2. Critical signs
    a. Kalemia 6 mEq/L or higher
    b. Arrythmia
    c. Acidosis
3. Mortality risk factor
    - Renal Failure: an inability to excrete potassium effectively.
    - Diabetes Mellitus: Complications that increase the risk of hyperkalemia.
    - Adrenal Disease: Addison's disease can affect potassium regulation.
    - Use of Certain Medications: Medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and potassium-sparing diuretics can increase the risk
4. Out-patient management
    - Discontinue any medications that may increase K (e.g., K-sparing diuretics, exogenous K)
    - Mild hyperkalemia (5.0–5.9 mEq/L): asymptomatic and can be managed with dietary modifications and medication adjustments.
5. First line treatment

- Stabilize myocardial membranes
    - initial treatment with calcium gluconate IV 1,000 mg (10 mL of 10% solution) over 2 to 3 minutes
    - With constant cardiac monitoring. Can repeat after 5 minutes if needed
    - Effect begins within minutes, but only lasts 30 to 60 minutes and should be used in conjunction with definitive therapies.
    - Can also use calcium chloride (3 times as concentrated; however, central or deep vein administration is necessary to avoid tissue necrosis.)
- If suspected, stop offending agent and address any reversible causes.
- Drive extracellular K into cells.
    - Nebulized albuterol (at 10 to 20 mg/4 mL saline >10 minutes—4 to 8 times bronchodilation dose) and other β-agonists have an additive effect with insulin and glucose.
    - Dextrose 50% 1 bottle 50mL (if plasma glucose <250 mg/dL) and insulin 10 U IV may drive K intracellularly but does not decrease total body K and may result in hypoglycemia (close monitoring advised, especially 1 to 2 hours postinjection).
    - Sodium bicarbonate not routinely recommended but some possible benefits in severe metabolic acidosis.

- Remove excess K from body.
    - Cation exchange resins definitive treatment but require several doses and best used with rapidly acting transient therapies above and when dialysis not readily available.
        - Patiromer calcium (Veltassa): 8.4 g PO daily (dose may vary 4.2 to 16.8 g BID in studies). This requires ~7 to 24 hours to lower K. This may be repeated q12h, if necessary.
        - Sodium zirconium cyclosilicate (Lokelma): 10 mg PO TID for up to 48 hours.
        - Sodium polystyrene sulfonate (Kayexalate): 15 g PO or 30 g rectally. This requires 1 to 4 hours to lower K. This may be repeated q6h, if necessary. Enema has faster effect than PO.
    - Loop diuretics (furosemide): 40 mg IV q12h or continuous infusion; may need to give isotonic fluids as well if patient is euvolemic or hypovolemic prior to furosemide (Lasix)
    - Hemodialysis is the definitive therapy when other measures are not effective. This may be required particularly when conditions, such as digitalis toxicity, rhabdomyolysis, ESRD, severe CKD, or acute kidney injury, are present; should watch for post-dialysis rebound.
    - Little clinical evidence for the use of diuretics (loop and thiazides), however, can be considered for control of chronic hyperkalemia.
- Chronic hyperkalemia treatment
    - Review medication and discontinue those that can be contributing to hyperkalemia.
    - Dietary counseling of K-rich food
    - Diuretic therapy using thiazide and loop diuretics
    - Potassium binder medication can be used. Caution should be taken if Kayexalate is considered:
        - Sodium polystyrene sulfonate (Kayexalate) provides a sodium load that may exacerbate fluid overload in patients with cardiac or renal failure.
        - Avoid sodium polystyrene sulfonate use in patients who are postoperative or with a bowel obstruction or ileus due to high risk of intestinal necrosis

6. Treatment adjustment
   Mineralocorticoid replacement
   If the patient does not have a contraindication (greater than stage 1 HTN, volume overload, history of heart failure) to mineralocorticoid administration then Consider a trial of fludrocortisone 0.1 mg daily × 3 to 5 days (in patients with moderately advanced CKD, consider maintaining or increasing diuretics in tandem with the assistance of nephrology consulting service).

7. Algorithm
   Management of Adults with Hyperkalemia (K> 5.5 mEq/L)
   *All disposition and treatment recommendations should account for local standards of care and should not supersede the clinical judgement of the treating physician



K: Serum potassium. DM: diabetes mellitus. CHF: Congestive Heart Failure. CKD: Chronic Kidney Disease

VIII. SPECIAL CASES

1. Tumor Lysis Syndrome (TLS): Hyperkalemia occurs in patients undergoing treatment for cancers like leukemia or lymphoma, where massive tumor cell destruction releases intracellular contents (including potassium) into the bloodstream. This causes hyperkalemia, hyperphosphatemia, hypocalcemia, and acute kidney injury. Prophylactic measures (e.g., hydration, allopurinol, or rasburicase) are used to prevent TLS, and acute treatment follows the same principle.

2. Digitalis (Digoxin) Toxicity: Excessive digoxin (digitalis) use can impair cellular potassium homeostasis, leading to hyperkalemia. Digoxin toxicity can also lead to life-threatening cardiac arrhythmias, which are exacerbated by elevated potassium levels. Hyperkalemia in the context of digoxin toxicity is managed with digoxin-specific antibody fragments (Digibind), along with conventional hyperkalemia treatments like insulin/glucose or dialysis in severe cases. @> Rapid administration of calcium in patients with suspected digitalis toxicity may result in fatal dysrhythmia. In the case of digoxin-specific antibody fragments is non-available and myocardial membrane stabilization is need; Calcium should be administered slowly over 20 to 30 minutes in 5% dextrose with extreme caution.

IX. Evolution and prognosis

Evolution of Hyperkalemia:

1. Acute Hyperkalemia (acute kidney injury, rhabdomyolysis, trauma, or massive hemolysis), the evolution is rapid and if not treated promptly, acute hyperkalemia can lead to ventricular fibrillation, asystole, or death.
2. Chronic Hyperkalemia can evolve more gradually due to impaired renal excretion. If untreated, chronic hyperkalemia can contribute to worsening renal function, recurrent hospitalizations due to cardiovascular issues, or the need for dialysis.

Prognosis of Hyperkalemia:

The prognosis of hyperkalemia depends on several factors, including the underlying cause, the speed at which potassium levels rise, and the effectiveness of treatment:

- Mild to Moderate Hyperkalemia (Potassium 5.0–6.4 mEq/L): patients have a good prognosis if the underlying cause is treated.
- Severe Hyperkalemia (Potassium >6.5 mEq/L): the prognosis depends on how quickly treatment is initiated to stabilize the cardiac membrane and lower serum potassium levels. With timely intervention, patients often recover fully.

X. COMPLICATION

- Cardiac arrhythmias,
- Muscle weakness and paralysis,
- Respiratory failure,
- Metabolic acidosis,
- Acute or chronic kidney injury,
- Neurological effects (confusion, seizures, coma),
- Worsening of heart failure and diabetes

XI. PREVENTION AND RECOMMENDATION

Prevention of hyperkalemia involves a combination of dietary management, careful medication use, and regular monitoring, especially in high-risk populations. The goal is

- to maintain normal serum potassium levels and
- addressing underlying conditions that may predispose individuals to hyperkalemia.

In nonhospitalized patients at risk of hyperkalemia with known chronic kidney disease (CKD), heart failure, or diabetes:

- Routinely monitor blood levels (potassium concentration) 2-4 times per year depending on level of kidney function and degree of proteinuria.
- If also taking renin-angiotensin aldosterone system blockers (RAAS), monitor kidney function.
- In patients starting an angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB) assess creatinine and electrolytes prior to initiation of ACE inhibitors and ARBs and 1-2 weeks after initiation and every dose titration.

XII. REFERENCES

1. Weiner, I. D., & Wingo, C. S. (1998). Hyperkalemia: A common clinical problem. Journal of the American Society of Nephrology, 9(8), 1535-1543.
2. Mount, D. B. (2015). Hyperkalemia: Causes, symptoms, and treatments. New England Journal of Medicine, 373(2), 178-179.
3. Einhorn, L. M., Zhan, M., Hsu, V. D., Walker, L. D., Moen, M. F., Seliger, S. L., & Weir, M. R. (2009). The frequency of hyperkalemia and its significance in chronic kidney disease. Archives of Internal Medicine, 169(12), 1156-1162.
4. Kovesdy, C. P. (2014). Management of hyperkalemia in chronic kidney disease: An update. Journal of Nephrology, 27(5), 489-500.
5. Palmer, B. F. (2004). Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. New England Journal of Medicine, 351(6), 585-592.
6. Sterns, R. H., & Perazella, M. A. (2020). Hyperkalemia in the hospitalized patient. Kidney International, 97(1), 1-12.
7. Mount, D. B. (2015). Fluid and electrolyte disturbances. Harrison's Principles of Internal Medicine, 19th Edition. McGraw-Hill.
8. Palmer, B. F., & Clegg, D. J. (2017). Diagnosis and treatment of hyperkalemia. Cleveland Clinic Journal of Medicine, 84(12), 934-942.
9. Lehnhardt, A., & Kemper, M. J. (2011). Pathogenesis, diagnosis, and management of hyperkalemia. Pediatric Nephrology, 26(3), 377-384.
10. Montford, J. R., & Linas, S. (2017). How dangerous is hyperkalemia? Journal of the American Society of Nephrology, 28(11), 3155-3165.
11. Pooja Gandhi, DO, Tyler D. Sharpe, MD; Hyperkalemia, in 5minutes Clinical Consult, U-Central Unbound Medicine platform, 2024, Wolters Kluwer Health Lippincott Williams & Wilkins, Assess date Nov, 2024

HYPOKALEMIA

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I. DEFINITION

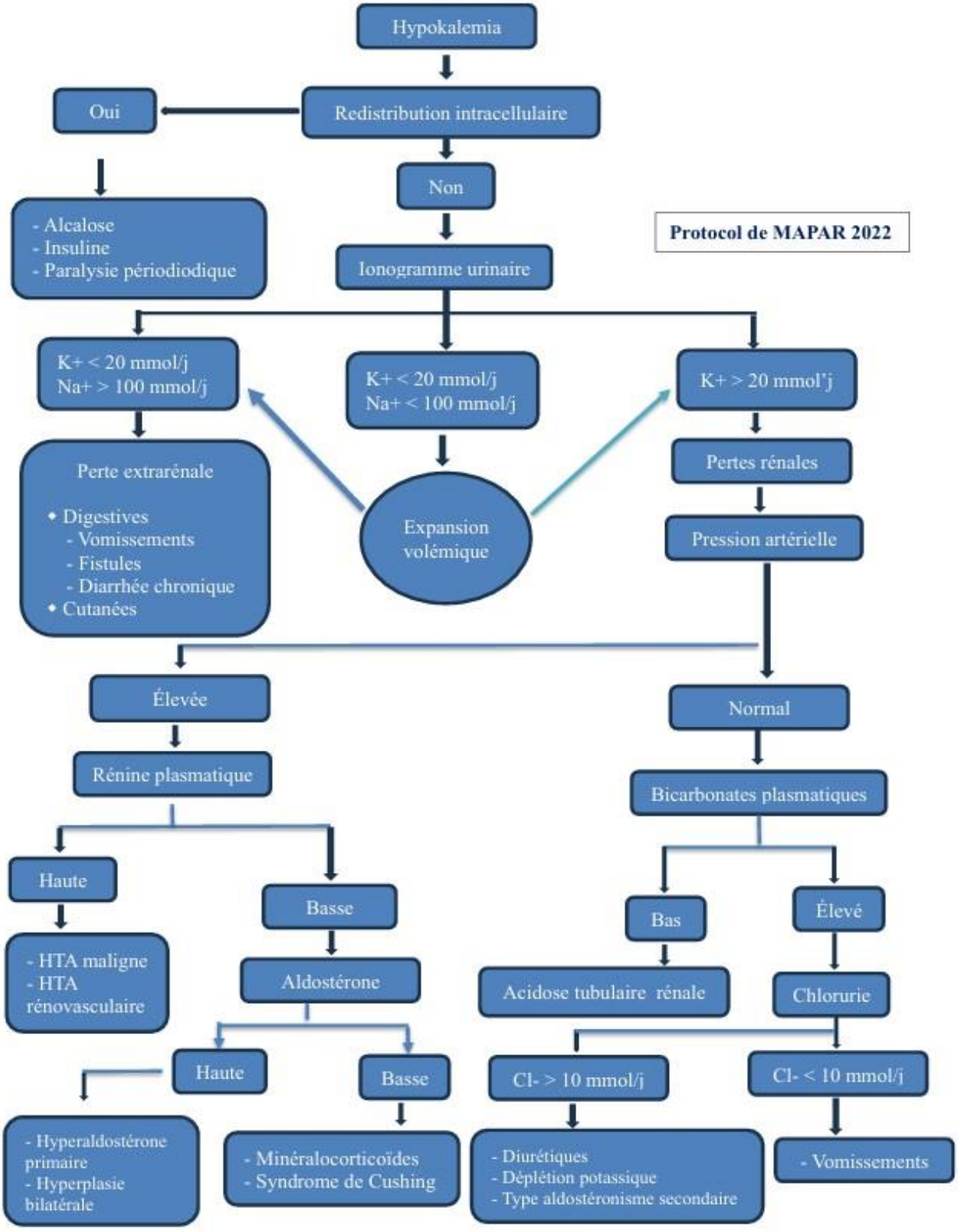
Hypokalemia is defined as a serum potassium level less than 3.5 mEq/L (3.5 mmol/L). Potassium is an essential electrolyte that plays a critical role in nerve function, muscle contraction, and maintaining normal heart rhythm. Hypokalemia can result from a variety of causes including insufficient dietary intake, increased potassium loss through the kidneys or gastrointestinal tract, or intracellular potassium shifts.

II. EPIDEMIOLOGY

Hypokalemia affects approximately 1-3% of the general population. The prevalence increases in hospitalized patients (Up to 20% of hospitalized patients may experience hypokalemia, with a higher incidence in patients in intensive care units (ICUs) due to critical illness, medications, and electrolyte imbalances), especially those receiving diuretics or other medications that promote potassium loss.

III. ETIOLOGY

- ✉ Renal losses: Diuretics (thiazides, loop), hyperaldosteronism, renal tubular acidosis, Bartter/Gitelman syndromes, hypomagnesemia. Cushing's syndrome, Liddle syndrome
- ✉ Gastrointestinal losses: Diarrhea, vomiting, nasogastric suction, laxative abuse.
- ✉ Intracellular shifts: Insulin therapy, beta-2 agonists, alkalosis, refeeding syndrome.
- ✉ Inadequate intake: Dietary deficiency, malnutrition, eating disorders.
- ✉ Miscellaneous: Hyperthyroidism, sweating.



Etiology of hypokalemia based on urinary electrolytes, Blood pressure, and serum bicarbonate.

IV. PATHOPHYSIOLOGY

1. Inadequate Potassium Intake

- Dietary Insufficiency: A diet low in potassium can lead to a decrease in serum potassium levels, particularly if combined with conditions that increase potassium loss.
- Increased Requirements: Conditions such as pregnancy, lactation, or intense physical activity can increase potassium requirements, leading to a state of deficiency if intake does not meet these needs.

2. Increased Potassium Loss

- Renal Losses
  - Diuretics: Loop and thiazide diuretics increase urinary potassium excretion by inhibiting sodium reabsorption in the renal tubules, leading to potassium loss.
  - Hyperaldosteronism: Excess production of aldosterone (primary or secondary) causes increased sodium reabsorption and potassium secretion in the renal tubules, leading to hypokalemia.
  - Renal Tubular Disorders: Conditions like renal tubular acidosis (RTA) or Bartter syndrome result in impaired potassium reabsorption in the renal tubules.
  - Post-obstructive Diuresis: After relief of urinary obstruction, there may be a significant diuresis with increased potassium loss.
- Gastrointestinal Losses
  - Vomiting: Loss of gastric acid leads to a depletion of potassium, especially if prolonged.
  - Diarrhea: Both osmotic and secretory diarrhea can cause significant potassium loss, especially in cases of chronic diarrhea.
  - Fistulas or Drainage: Intestinal or biliary fistulas can lead to losses of potassium through the gastrointestinal tract.

3. Shift of Potassium into Cells

- Insulin: Insulin promotes the uptake of potassium into cells, particularly after carbohydrate ingestion or in conditions of hyperinsulinemia, leading to transient hypokalemia.
- Beta-Agonists: Drugs such as albuterol can stimulate the Na+/K+ ATPase pump, promoting the uptake of potassium into cells and causing a drop in serum potassium levels.
- Metabolic Alkalosis: In states of metabolic alkalosis, the increased exchange of hydrogen ions for potassium ions leads to an intracellular shift of potassium.
- Stress or Catecholamines: Increased levels of catecholamines (due to stress or conditions like pheochromocytoma) can stimulate potassium entry into cells.

4. Total Body Potassium Deficit

- Chronic Diseases: Conditions such as chronic kidney disease, heart failure, and cirrhosis can alter potassium homeostasis, leading to both loss and shift mechanisms.
- Inadequate Replacement: In patients with increased potassium losses, failure to adequately replace potassium (either through diet or supplements) leads to a total body potassium deficit.

5. Effects of Hypokalemia on Cellular Function

- Membrane Potential Changes: Hypokalemia leads to hyperpolarization of the cell membrane, making it more difficult for cells to depolarize and fire. This affects muscle cells, neurons, and cardiac cells, leading to symptoms such as weakness, fatigue, and arrhythmias.
- Increased Sodium Reabsorption: The kidneys will attempt to compensate for low potassium by increasing sodium reabsorption, leading to increased fluid retention, which can exacerbate conditions like hypertension or heart failure.

V. DIAGNOSIS

A. Clinical History and Physical Examination

- History: Ask about symptoms like muscle weakness, cramps, fatigue, palpitations, or paralysis, dietary history and medication use.
- Physical examination:
  - Look for signs of muscle weakness, hypotension, or arrhythmias.
  - Examine for dehydration (dry mucous membranes, hypotension), which may point to GI or renal losses.
- Symptoms: Fatigue, muscle weakness, arrhythmias.

B. Serum Potassium Measurement

- Confirm hypokalemia: Serum potassium < 3.5 mEq/L.
  - Mild hypokalemia: 3.0 – 3.5 mEq/L.
  - Moderate hypokalemia: 2.5 – 3.0 mEq/L.
  - Severe hypokalemia: < 2.5 mEq/L.

C. Laboratory Investigations to Determine the Cause

- Urinary potassium excretion:
  - < 20 mEq/L: Suggests extrarenal (GI) losses.
  - > 20 mEq/L: Indicates renal potassium wasting
- Serum bicarbonate or arterial blood gas (ABG) helps identify the acid-base status
- Serum Magnesium: Hypomagnesemia often coexists with hypokalemia, especially in patients on diuretics or with chronic diarrhea.

D. Electrocardiogram (ECG)

- Flattened or inverted T waves.
- Prominent U waves.
- ST-segment depression.
- Prolonged QT interval.
- Ventricular arrhythmias in severe hypokalemia (e.g., Torsades de Pointes).

E. Further Testing Based on Suspected Cause

- Renin and Aldosterone Levels:
  - These are measured when hyperaldosteronism is suspected.
  - Primary hyperaldosteronism (Conn's syndrome) is associated with low renin and high aldosterone levels.
  - Secondary hyperaldosteronism (e.g., heart failure, cirrhosis) shows high renin and high aldosterone levels.

- Diuretic Screen: If diuretic use is suspected but not reported, a urine diuretic screen may be necessary to detect thiazide or loop diuretics.
- Urine Chloride:
  - Low urine chloride (< 20 mEq/L): Seen in hypokalemia due to vomiting.
  - High urine chloride (> 20 mEq/L): Indicates causes like diuretic use or primary hyperaldosteronism.
- Genetic Testing: In cases where inherited conditions like Bartter syndrome or Gitelman syndrome are suspected, genetic testing may be considered.

VI. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hypokalemia is vast. Notable ones include the following:

- Iatrogenic cause: chronic corticosteroid intake, insulin therapy
- Congenital conditions: Bartter syndrome, hypokalemic periodic paralysis
- Renal disorders: RTA, osmotic diuresis
- Gastrointestinal losses: laxative abuse, vomiting
- Poor intake: eating disorders, restrictive diets
- Skin losses: excessive sweating
- Redistribution: alkalosis from chronic obstructive pulmonary disease, nonanion-gap acidosis from diabetic ketoacidosis
- Concomitant electrolyte imbalances: hypocalcemia, hypomagnesemia.

VII. MANAGEMENT

1. Objectives

- Reduce potassium loss.
- Replenish stored potassium.
- Evaluate potential toxicities.
- Determine cause.

2. Critical Symptoms and signs

- serum potassium <2.5 mEq/L
- arrhythmias

3. Mortality Risk factors

- the elderly,
- diabetic patients,
- patients with renal insufficiency.

4. Out-patient management

- Nonemergent conditions (serum potassium >2.5 mEq/L, no cardiac manifestations) can be treated as out-patients
- Oral therapy preferred: 40 to 120 mEq/day (40 to 120 mmol/day) in divided doses
- Ensure adequate hydration (100 to 250 mL of water), better if given with or after meal.

5. First-line treatment

General Measures

- Manage underlying disease or eliminate causative factor.

- Discontinue laxative, use potassium-neutral or potassium-sparing diuretics.
- Treat diarrhea and vomiting.
- Use H2 blockers in patients with nasogastric suction.
- Control hyperglycemia if glucosuria is present.

Medication

- IV potassium only when oral administration is not feasible (e.g., vomiting, postoperative state).
- Dilution: Potassium must be diluted to avoid hyperkalemia and infusion-related complications. Typically, 10-20 mEq is diluted in 100-250 mL of saline or dextrose solution.
- Rate should not exceed 10 mEq/hr, and concentration should not exceed 40 mEq/L to lessen burning and discomfort at IV site and to avoid phlebitis.
- A central line is recommended for rate >10 mEq/hr; up to 40 mEq in 100 mL can be safely given via central access.
- Potassium chloride (KCl) is suitable for all forms of hypokalemia.
- Potassium bicarbonate or precursor (gluconate, acetate, or citrate) in metabolic acidosis
- Potassium phosphate in phosphate deficiency as in DKA

Precautions

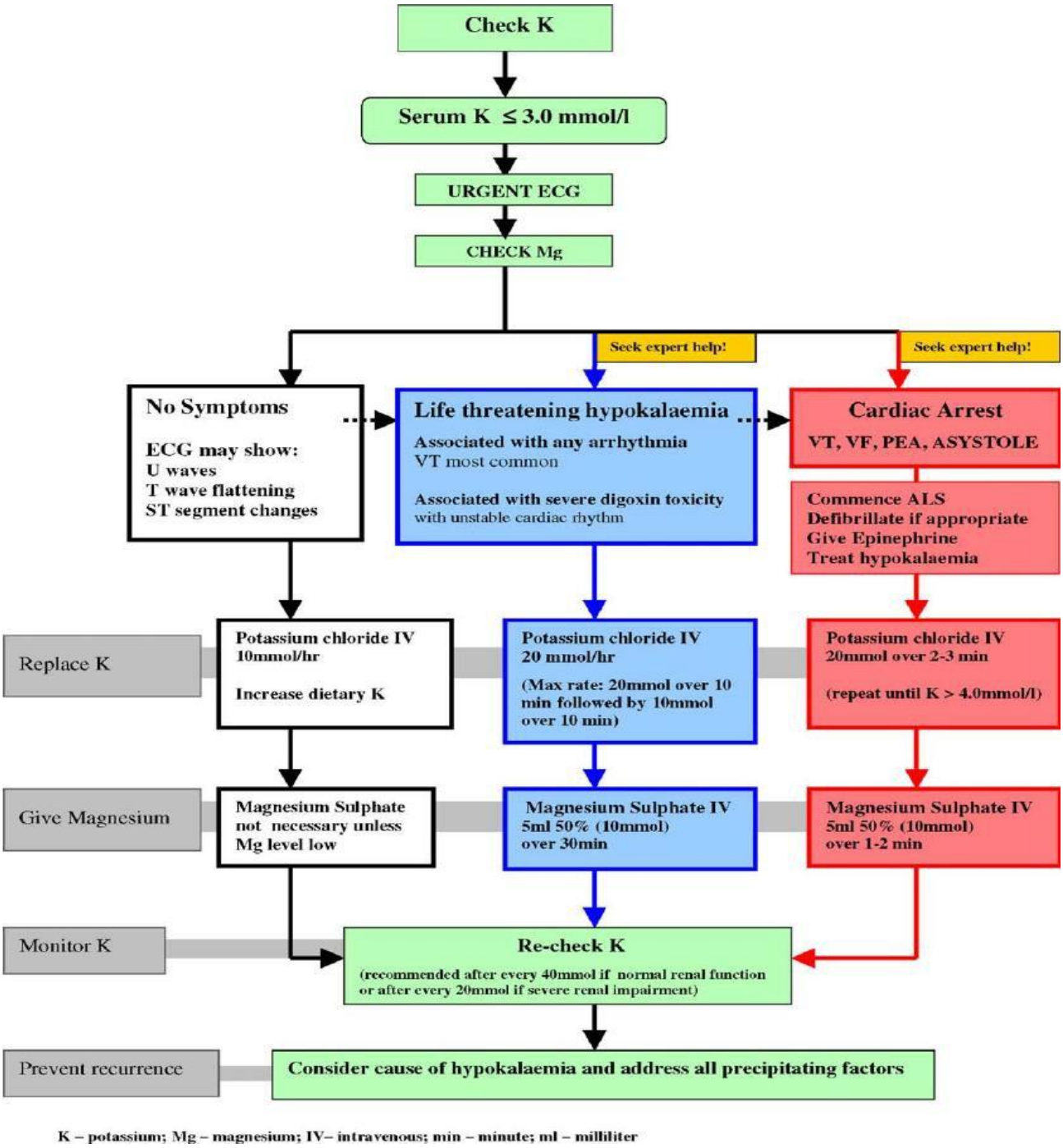
- Any form of potassium replacement carries the risk of hyperkalemia.
- Serum potassium should be checked more frequently in groups at higher risk: the elderly, diabetic patients, and patients with renal insufficiency.
- Patients receiving insulin for DKA require more timely and aggressive potassium replacement in order to account for the intracellular shift.
- Dietary potassium is almost entire coupled to phosphate, rather than chloride, and does not correct potassium loss from chloride depletion (e.g., diuretics or vomiting).
- Significant possible interactions: Concomitant administration of potassium-sparing diuretics (spironolactone, triamterene, amiloride, ACE inhibitors) magnifies risk of hyperkalemia.

6. Treatment adjustment

- Emergent situations (serum potassium <2.5 mEq/L, arrhythmias)
  - IV replacement—standard infusion rate: 10 mmol/hr; maximum infusion rate: 20 mmol/hr.
  - Central line preferred
- If patient is hypomagnesemic
  - First, give 4 mL MgSO4 50% (8 mmol) in 10 mL of NaCl 0.9% >20 minutes and then start first 40 mmol KCl infusion followed by magnesium replacement.

7. Algorithm for treatment of hypokalemia (next page).

Algorithm for treatment of hypokalemia



K – potassium; Mg – magnesium; IV– intravenous; min – minute; ml – milliliter

VIII-SPECIAL CASES

1. Hypokalemia in Diabetic Ketoacidosis (DKA)

In diabetic ketoacidosis, potassium shifts from the intracellular to the extracellular space due to insulin deficiency and hyperglycemia. Despite normal or elevated serum potassium levels on initial presentation, total body potassium is typically depleted. Potassium supplementation is generally started if the serum potassium is below 5.3 mEq/L, even if levels are within the normal range. Close monitoring of serum potassium is essential, and potassium replacement is continued until the patient is stable and potassium levels normalize.

2. Hypokalemia in Hyperaldosteronism (Conn's Syndrome)

Primary hyperaldosteronism is a condition where the adrenal glands produce too much aldosterone, leading to increased renal potassium excretion. Common symptoms include hypertension, muscle weakness, and hypokalemia with metabolic alkalosis. Treatment of the underlying condition, such as adrenalectomy in the case of adrenal adenoma or medical therapy with aldosterone antagonists (e.g., spironolactone, eplerenone). Potassium supplementation may be required initially until aldosterone levels are controlled.

3. Hypokalemia in Refeeding Syndrome

Refeeding syndrome occurs in malnourished patients when they receive high carbohydrate nutrition. It triggers the release of insulin, which causes potassium, phosphate, and magnesium to shift into cells. This can lead to severe hypokalemia, along with other electrolyte imbalances. Careful, slow refeeding with close monitoring of electrolytes, particularly potassium, phosphorus, and magnesium. Potassium supplementation is required, often in significant amounts, to prevent complications.

4. Hypokalemia in Renal Tubular Acidosis (RTA)

Type 1 RTA (distal) and Type 2 RTA (proximal) can lead to hypokalemia due to impaired acid excretion and subsequent potassium loss in urine. It's often associated with metabolic acidosis. Correction of the underlying acidosis using alkali therapy (bicarbonate or citrate) and potassium supplements. Long-term treatment with potassium citrate is often required to prevent further episodes of hypokalemia and acidosis.

5. Hypokalemia in Cushing's Syndrome

Cushing's syndrome involves excessive production of cortisol, which has mineralocorticoid activity and can lead to hypokalemia by increasing renal potassium loss. It associated features include central obesity, hypertension, and glucose intolerance. Treatment focuses on addressing the underlying cause of cortisol excess, such as adrenal or pituitary tumors. Potassium supplementation and spironolactone may be used to control hypokalemia until the condition is treated.

IX- EVOLUTION AND PROGNOSIS

The evolution and prognosis of hypokalemia depend on the severity of potassium depletion, the underlying cause, the speed of onset, and whether effective treatment is provided. Most hypokalemia will correct with replacement after 24 to 72 hours.

If the primary cause is eliminated, hypokalemia will likely resolve with no further treatment needed. Associated with higher morbidity and mortality because of cardiac arrhythmias Complication.

X- COMPLICATION

- Hyperkalemia during the course of treatment
- Increased risk of digoxin toxicity
- Increased risk of arrhythmias by increasing myocyte's resting potential and in turn its refractory period.

XI- PREVENTION AND RECOMMENDATION

Preventing hypokalemia involves a combination of dietary measures, careful medication management, and monitoring of at-risk patients. Dietary (Fruit, vegetables or legumes are rich in potassium such as Bananas, oranges, apricots, avocados, leafy greens, potatoes, tomatoes, Lentils, beans, and peas).

VIII. REFERENCES

1. Hollander-Rodriguez JC, Calvert JF. Hyperkalemia and Hypokalemia. American Family Physician. 2006. This article provides a review of the clinical presentation, epidemiology, and management of potassium disorders, including hypokalemia.
2. Palmer BF. A Physiologic-Based Approach to the Evaluation of a Patient with Hypokalemia. American Journal of Kidney Diseases. 2010.
3. Kamel KS, Halperin ML. "The complex nature of metabolic alkalosis in patients with hypokalemia." *American Journal of Kidney Diseases.* 2010;55(4):746-758. doi:10.1053/j.ajkd.2009.10.016.
4. Sica DA. "Hypokalemia: A Comprehensive Review." *American Journal of Medicine.* 2006;119(12):1041-1046. doi:10.1016/j.amjmed.2006.07.009.
5. Skogestad J, Aronsen JM. Hypokalemia-Induced Arrhythmias and Heart Failure: New Insights and Implications for Therapy. Front Physiol. 2018;9:1500.
6. Rossignon P, Soupart A. Intestinal Pseudo-Obstruction with Life-Threatening Hypokalaemia in a Patient with Adult-Onset Still's Disease. Eur J Case Rep Intern Med. 2023;10(6):003887.
7. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic Crises in Adult Patients with Diabetes. Diabetes Care. 2009.
8. Funder JW, Carey RM, Mantero F, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment. The Journal of Clinical Endocrinology & Metabolism. 2016.
9. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ. 2008.
10. Batlle D, Haque SK. Genetic Causes and Mechanisms of Distal Renal Tubular Acidosis. Nephrology Dialysis Transplantation. 2012.
11. Nieman LK, Biller BM, Findling JW, et al. The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2008.
12. Bian X, Jiang L, Ma W, Zhang M. Association of Serum Potassium Levels with In-Hospital Mortality in Critically Ill Patients. Journal of Clinical Medicine. 2018.

HYPERNATREMIA

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I. DEFINITION

Hypernatremia is a condition characterized by an elevated concentration of sodium in the blood, typically defined as a serum sodium level greater than 145 mEq/L.

II. EPIDEMIOLOGY

Hypernatremia occurs in approximately 1-3% of hospitalized patients, and 9% in ICU patients frequently linked to mechanical ventilation and diuretic use. The mortality rate from hypernatremia is high, especially among elderly patients. Hypernatremia will not develop in patients with intact thirst mechanisms who are able to access water.

III. ETIOLOGY

1. Water Loss: Hypovolemic hypernatremia:
   - Insensible Water Loss: Water loss through skin (sweating) or respiratory tract
   - Gastrointestinal Loss: Excessive loss of water via vomiting or diarrhea
   - Renal Losses: Increased urine output due to:
     - Diabetes Insipidus (DI)
     - Diuretics: Loop diuretics or osmotic diuretics
   - Hypodipsia/Adipsia
   - Burns or severe skin damage
2. Sodium Gain (Absolute Hypernatremia): Hypervolemic Hypernatremia
   - Hypertonic Saline Administration
   - Sodium Bicarbonate Administration
   - Salt Poisoning (Salt Ingestion)
   - Mineralocorticoid Excess
3. Isovolemic Hypernatremia:
   - Hypothalamic Diabetes Insipidus (DI): Head trauma, Tumor, Infection, Cerebrovascular disease, Granulomatous diseases
   - Nephrogenic Diabetes Insipidus: Congenital, Drug (Lithium), Obstructive uropathy, Chronic tubulointerstitial disease, Electrolyte disorders (hypercalcemia, potassium depletion)

Etiology of Hypernatremia in Neonates:

- Inadequate Breastfeeding (Breastfeeding-associated Hypernatremia):
- Formula Feeding Errors: Improper preparation of formula (e.g., using too little water) can lead to an excessive sodium load and dehydration in formula-fed infants.
- Excessive Insensible Water Loss:
  - preterm infants: higher surface area-to-body weight ratio
  - fever, high environmental temperature, or use of radiant warmers or phototherapy
- Diabetes Insipidus (DI):
- Excessive Sodium Intake: Hypertonic saline administration during resuscitation or inappropriate intravenous fluid therapy.

IV. PHYSIOPATHOLOGY

- Due to the powerful effect of the thirst mechanism, hypernatremia typically occurs only in patients who cannot readily access water such as infants, intubated patients, and those with altered mental status or patients with hypodipsia.
- Water loss out of proportion to salt loss is the most common cause of hypernatremia. The following conditions lead to excessive water loss:
- Transdermal loss
    - Burns or excessive sweating (e.g., fever, infants under radiant heaters, heat exposure, extreme exercise)
- Urinary loss
    - Nephrogenic diabetes insipidus (DI) (congenital or due to renal dysfunction, hypercalcemia, hypokalemia, medication-related, e.g., lithium)
    - Central Diabetes insipidus (DI) (due to head trauma, stroke, meningitis)
    - Osmotic diuresis: glucose, urea, and mannitol
    - Post-acute tubular necrosis (ATN) diuresis
- Gastrointestinal loss
    - Osmotic diarrhea: lactulose, malabsorption, and some types of infectious diarrhea
    - Enterocutaneous fistula.
    - Vomiting, NG suction
- Disorders of the thirst mechanism can result in hypernatremia due to reduced water intake (e.g., intracranial lesions, primary hypodipsia, chronic volume expansion in mineralocorticoid excess).
- Excess Na (increase in total body Na) less commonly leads to hypernatremia. The following condition may result in excessive total body Na:
    - IV infusion of hypertonic NaCl or $NaHCO_3$ during treatment of brain injury, metabolic acidosis, or hyperkalemia
    - Sea water ingestion
    - Excessive use of $NaHCO_3$ antacid
    - Incorrect infant formula preparation, tube feeding
    - Excessive Na in dialysate solutions
- With acute hypernatremia, the rapid decrease in brain volume can cause rupture of the cerebral veins, leading to focal intracerebral and subarachnoid hemorrhages and possibly irreversible neurologic damage.
- Neonates are more vulnerable to the effects of hypernatremia due to their immature kidneys and limited ability to concentrate urine.

V. DIAGNOSIS

1. Clinical History and Physical Examination:

History

- History of conditions leading to water loss or impaired thirst: nausea, vomiting, diarrhea, polyuria, fever, heat exposure, extreme exercise, brain injury
- Neurologic symptoms are common:
    - Mild: thirst, anorexia
    - Moderate: altered mental status, myalgia, muscle weakness, twitching, lethargy, irritability
    - Severe: seizure (especially if rapid development of hypernatremia), coma
- Severity of symptoms correlate with rapidity of the increase in Na as well as the degree of hypernatremia.

- Severe symptoms are likely to occur with sudden increases in plasma Na levels or at concentrations >160 mEq/L.

Physical Exam

- Signs of water or volume loss: tachycardia, hypotension, orthostatic hypotension, dry mucous membranes, poor skin turgor
- Neurologic abnormalities: lethargy, weakness, tremor, focal deficits (in cases of intracerebral bleeding/lesion), confusion, coma, seizures

2. Laboratory tests
    - Serum Electrolytes, BUN/Creatinine, Glucose, CBC
    - Serum and Urine Osmolality:
        - Normal serum osmolality is 275-295 mOsm/kg
        - High Urine Osmolality (>800 mOsm/kg): Suggests water loss through non-renal mechanisms
        - Low Urine Osmolality (<300 mOsm/kg): Suggests inappropriate water loss through the kidneys, such as in diabetes insipidus or diuretic use.
    - Urine Sodium Concentration:
        - Low Urine Sodium (<20 mEq/L): hypovolemic hypernatremia
        - High Urine Sodium (>100 mEq/L): hypervolemic hypernatremia
    - Assessment of Volume Status:
    - Specific Tests for Underlying Causes:
        - Water Deprivation Test: in central DI: an increase in urine osmolality after administration of desmopressin (ADH analog), while in nephrogenic DI, urine osmolality remains low.
        - ADH (vasopressin) Levels.
    - Imaging (If Necessary): Chest x-ray, Brain imaging (CT or MRI)

VI. DIFFERENTIAL DIAGNOSIS

- Diabetes Insipidus
- Hyperosmotic coma
- Salt ingestion
- Hypertonic dehydration
- Hypothyroidism
- Cushing syndrome.

VII. MANAGEMENT

1. Objectives
    - The treatment of hypernatremia involves treating the underlying cause and correcting the water deficit.
    - Determine the duration of hypernatremia because speed of correction depends on symptom severity and rate of development of hypernatremia.
    - Avoid rapid correction of chronic hypernatremia to prevent development of cerebral edema (goal rate is 10 mEq/L in 24 hours).

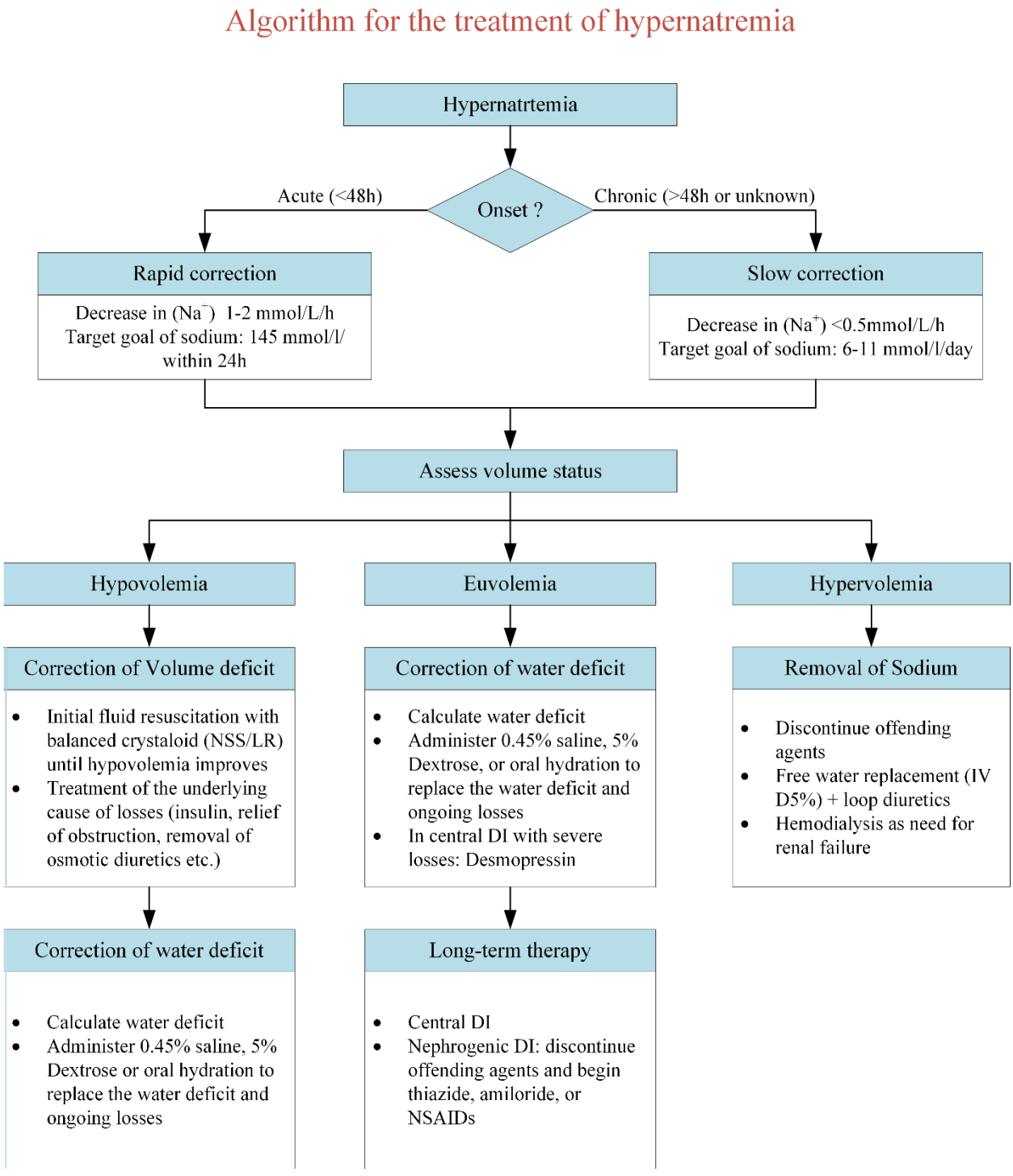
2. Critical signs
    - Serum sodium > 155mEq/L
    - Hypotension

- Neurologic abnormalities: lethargy, weakness, tremor, focal deficits (in cases of intracerebral bleeding/lesion), confusion, coma, seizures.

3. Mortality Risk factors
   - Rapid development of hypernatremia (<48h)
   - CNS thrombosis / hemorrhage, seizure
   - Chronic hypernatremia: >2 days duration has higher mortality.
   - Serum Na >180 mEq/L (>180 mmol/L): often results in residual CNS damage
4. Out-patient treatment
5. First-line treatment
   - Acute hyponatremia: relatively uncommon, may occur in acute DI, severe hyperglycemia, or salt ingestion
     - D5W infusion at 3 to 6 mL/kg/hr to lower the serum Na by 1 to 2 mEq/L/hr
     - Check serum Na every 1 to 2 hours to confirm correction at desired rate.
     - When serum Na decreases to 145 mEq/L, reduce D5W infusion to 1 mL/kg/hr until serum Na normalizes.
     - Aim to correct hypernatremia in 24 to 48 hours.
   - Chronic hypernatremia (>48 hours): Avoid rapid correction to prevent development of cerebral edema.
   - D5W infusion at 1.35 mL/kg/hr
   - Check serum Na every 4 to 6 hours to determine correction at desired rate.
   - Correct at maximum of 0.5 mEq/L/hr or 10 to 12 mEq/L/day.
   - Often need to adjust infusion rate to account for ongoing water losses
   - Hypernatremia with hypovolemia: Correct severe volume depletion with isotonic IV fluids first and then address hypernatremia:
     - Once hemodynamically stable, can correct hypovolemia and hypernatremia simultaneously with 0.45% saline as every 2 mL of this solution will provide 1 mL of saline and 1 mL of water.
     - Water Deficit (L)= Total Body Water × (Natremia (Lab) − 140)/140
     - Total body water (TBW) = 0.6 × body weight (kg) for men.
       0.5 × body weight (kg) for women.
       0.45 × body weight (kg) for elderly individuals.
   - Hypernatremia with hypervolemia: can treat hypervolemia with diuretics while simultaneously correcting hypernatremia
     - Concomitant diuretic treatment will increase urinary water losses and may necessitate increased water repletion.
   - Consider oral water repletion for mild hypernatremia.
   - Euvolemic Hypernatremia: Free Water Replacement: Give oral water if the patient can drink. If oral intake is not feasible, administer 5% dextrose in water (D5W) intravenously.
   - High infusion rates of D5W may cause hyperglycemia.
   - Hyperglycemia-induced osmotic diuresis will increase urinary water losses and necessitate increased water repletion.
6. Treatment adjustment
   - Dialysis can be considered if acute kidney injury and conventional treatment has failed.
   - May use medication in treatment of diabetes insipidus (DI)
   - Central DI

    - Desmopressin acetate (DDAVP): Use parenteral form for acute symptomatic patients and use intranasal or oral form for chronic therapy.
    - Free water replacement: may use 2.5% dextrose in water if giving large volumes of water in DI to avoid glycosuria
    - May consider sulfonylureas/thiazide diuretics for chronic but not acute treatment
- Nephrogenic DI
    - Treat with diuretics and Non-Steroid Anti-Inflammatory drugs.
    - Lithium-induced nephrogenic DI: hydrochlorothiazide 25 mg PO BID or indomethacin 50 mg PO TID, or amiloride hydrochloride 5 to 10 mg PO BID

7. Algorithm


Algorithm for the treatment of hypernatremia
Hypernatrtemia
Onset ?
Acute (<48h)
Chronic (>48h or unknown)
Rapid correction
Decrease in (Na^-) 1-2 mmol/L/h
Target goal of sodium: 145 mmol/l/ within 24h
Slow correction
Decrease in (Na^+) <0.5mmol/L/h
Target goal of sodium: 6-11 mmol/l/day
Assess volume status
Hypovolemia
Euvolemia
Hypervolemia
Correction of Volume deficit
Initial fluid resuscitation with balanced crystaloid (NSS/LR) until hypovolemia improves
Treatment of the underlying cause of losses (insulin, relief of obstruction, removal of osmotic diuretics etc.)
Correction of water deficit
Calculate water deficit
Administer 0.45% saline, 5% Dextrose, or oral hydration to replace the water deficit and ongoing losses
In central DI with severe losses: Desmopressin
Removal of Sodium
Discontinue offending agents
Free water replacement (IV D5%) + loop diuretics
Hemodialysis as need for renal failure
Correction of water deficit
Calculate water deficit
Administer 0.45% saline, 5% Dextrose or oral hydration to replace the water deficit and ongoing losses
Long-term therapy
Central DI
Nephrogenic DI: discontinue offending agents and begin thiazide, amiloride, or NSAIDs

SPECIAL CASES

- Geriatric Considerations
    - Most commonly affected group due to impaired renal concentrating ability and reduced thirst mechanism.
    - Consider neglect if underlying etiology is dehydration alone
- Pregnancy Considerations
    - May encounter transient DI of pregnancy
    - Vasopressin and desmopressin are category B drugs in pregnancy
    - Hydration status much more difficult to evaluate accurately by exam

IX. EVOLUTION AND PROGNOSIS

The progression and prognosis of hypernatremia involves several key phases, influenced by the underlying cause, the speed of development, and clinical management.

Neonates and elderly patients are at higher risk for complications, can further complicate the prognosis and recovery.

Mortality rates of 42-75% have been reported for acutely evolving hypernatremia and 10-60% for chronic hypernatremia

X. COMPLICATION

The complications of hypernatremia can be severe and life-threatening, especially in vulnerable populations such as neonates, the elderly, and individuals with underlying health conditions.

- subarachnoid or subdural hemorrhage due to the rupture of bridging veins and dural sinus thrombosis. It can lead to permanent brain damage or death.
- Rapid correction of chronic hypernatremia may cause cerebral edema, seizure, and permanent brain damage.
- ~~A~~cute kidney injury (AKI),
- Cardiovascular Issues (hypertension and increased cardiac workload),
- thromboembolic Events (the hypercoagulable state).

XI. PREVENTION AND RECOMMENDATION

- Early Breastfeeding Support (newborn)
- Treatment/prevention of underlying cause
- Properly prepare infant formula and never add salt to any commercial infant formula.
- Keep patients well hydrated.
- Frequent neurologic checks during acute correction of hypernatremia
- Daily weight, electrolytes, and blood glucose for a period immediately after correction
- Avoid rapid correction of chronic hypernatremia to prevent development of cerebral edema (goal rate is 10 mEq/L in 24 hours).
- Monitor serum Na and adjust water repletion to achieve desired rate of correction as available formulas for calculating water deficit and estimating ongoing water losses have limited accuracy.

XII. REFERENCES

1. Adrogué HJ, Madias NE. "Hypernatremia." N Engl J Med. 2000 May 18;342(20):1493-9.
2. Adrogué HJ, Madias NE. "Hyponatremia." N Engl J Med. 2000;342(21):1581-1589.
3. Lindner G, Funk GC. "Hypernatremia in critically ill patients." J Crit Care. 2013 Dec;28(6): 216.e11-20.
4. Palevsky PM, Bhagrath R, Greenberg A. "Hypernatremia in hospitalized patients." Ann Intern Med. 1996 Feb 1;124(2):197-203.
5. Sterns RH. "Disorders of plasma sodium — causes, consequences, and correction." N Engl J Med. 2015 May 14;372(1):55-65.
6. Sterns RH, Hix JK, Silver S. "Management of hypernatremia in the intensive care unit." Crit Care Clin. 2015 Oct;31(4):499-507.
7. Sterns RH. "Diagnosis of hypernatremia." UpToDate. Accessed October 2023.
8. Verbalis JG, Goldsmith SR, Greenberg A, et al. "Hyponatremia and hypernatremia: a practical guide to disorders of water balance." Am J Med. 2013 Sep;126 (9 Suppl 1)
9. Verbalis JG, Gullans SR. "Rapid correction of chronic hyponatremia produces reversible brain edema in rats." Brain Res. 1991;568(1-2):337-340.
10. Seay NW, Lehrich RW, Greenberg A. "Diagnosis and management of hypernatremia: A clinical review." BMJ. 2014 Nov 11;349
11. Maghnie M, Villa A, Aricò M, et al. "Central diabetes insipidus in children and young adults." N Engl J Med. 2000; 343: 998-1007.
12. Fleseriu M, Petersenn S, Lagrou S, et al. "Craniopharyngioma: A review of long-term outcomes." Eur J Endocrinol. 2021 Mar;184(3)
13. Gleeson H, Amin R, Maghnie M. "Diagnosis of craniopharyngioma: DI and other endocrine abnormalities." Endocrine. 2015; 50(2): 532-542.
14. Rittenhouse KJ, To T, Rogers AI. "Hypernatremia in the elderly." Am J Gastroenterol. 2006; 101(10): 2270-2273.
15. Holland-Bill L, Christiansen CF, Heide-Jørgensen U, Ulrichsen SP, Ring T, Jørgensen JO, Sørensen HT. "Hyponatremia and hypernatremia in acute internal medicine: prognostic impact in a cohort of 113,000 patients." Eur J Endocrinol. 2015; 173(1): 71-81.
16. Moritz ML, Ayus JC. "The pathophysiology and treatment of hypernatremic dehydration in children." Pediatrics. 2010; 126(5)
17. Jain S, Cheng J, Alper SL. "Hypernatremia in breastfed infants due to inadequate lactation." Arch Dis Child Fetal Neonatal Ed. 2008; 93(3)
18. Al-Dahhan J, Haycock GB, Nichol B, Chantler C. "Plasma sodium, osmolality, and vasopressin in term and preterm infants. Variations during the first week of life." Arch Dis Child. 1983 Apr; 58(4): 256-62.
19. Spitzer A, et al. "Hypernatremia in infants: a review of management." Clin Pediatr (Phila). 2012; 51(2): 121-127.
20. Bell RM, et al. "The prognosis of hypernatremia in elderly patients." J Am Geriatr Soc. 2005; 53(11): 2026-2030.

21. Siew ED, et al. "Acute kidney injury and the risk of subsequent hypernatremia in hospitalized patients." Nephrology Dialysis Transplantation. 2010; 25(4): 1286-1293.
22. Cummings E, et al. "Long-term outcomes in children with hypernatremia due to breastfeeding dificulties." Pediatrics. 2016; 137(1)
23. Thomas P, et al. "Management of hypernatremia in hospitalized patients." Am J Kidney Dis. 2009; 54(5): 834-847.

HYPONATREMIA

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I. DEFINITION

Hyponatremia, defined as a serum sodium concentration of less than 135 mmol/L, is one of the most common electrolyte disorders encountered in clinical practice. Sodium is an essential electrolyte that helps regulate water balance and is critical for proper muscle and nerve function. Normal serum sodium levels range from about 135 to 145 milliequivalents per liter (mEq/L).

II. EPIDEMIOLOGY

The prevalence in the general population is estimated at around 5 - 15%. Hyponatremia occurs in up to 15 - 30% of hospitalized patients in Intensive Care Unit (ICU). Prevalence may reach up to 20 - 30% in elderly hospitalized patients.

III. ETIOLOGY

- Hypovolemic Hyponatremia related to fluid losses (diarrhea, vomiting, diuretic use).

 Euvolemic Hyponatremia associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypothyroidism, or medications.

 Hypervolemic Hyponatremia is seen in conditions like heart failure, cirrhosis, and nephrotic syndrome where there is fluid retention.

IV. PATHOPHYSIOLOGY

1. Water Retention Mediated by Antidiuretic Hormone (ADH):

 ADH Secretion: The most common mechanism in hyponatremia involves inappropriate secretion or enhanced sensitivity to ADH (also called vasopressin). ADH promotes water reabsorption in the renal collecting ducts, reducing the excretion of free water. This leads to dilution of sodium in the blood.

 Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH): This is the classic example where excessive ADH release occurs despite normal or increased blood volume, leading to water retention and dilutional hyponatremia. SIADH can be caused by various factors such as malignancies (especially small cell lung cancer), central nervous system disorders (stroke, trauma), pulmonary diseases, and certain medications (SSRIs, antipsychotics).

2. Renal Water Handling:

 Dilutional Hyponatremia: When the kidney's ability to excrete free water is impaired (often due to the action of ADH), the excess water dilutes serum sodium levels. This is the hallmark of many cases of hyponatremia, especially euvolemic forms.

 Hypovolemic Hyponatremia: In cases where sodium and water are both lost (e.g., gastrointestinal losses, diuretic use, or adrenal insufficiency), hypovolemia (low blood volume) stimulates ADH secretion and thirst. The kidneys then conserve both water and sodium, but because more water than sodium is retained, hyponatremia occurs.

3. Volume Status and Hyponatremia:

 Hypovolemic Hyponatremia: Decreased total body water and sodium with a relatively greater loss of sodium. Conditions like dehydration, blood loss, or severe diarrhea can cause this form. The body compensates by activating ADH, leading to water retention and dilution of sodium.

 Euvolemic Hyponatremia: Characterized by a normal extracellular fluid volume but dilutional low sodium levels, as seen in SIADH.

 Hypervolemic Hyponatremia: Increased total body water and sodium, with a greater increase in water relative to sodium. This is commonly seen in conditions like heart failure, cirrhosis, and nephrotic syndrome. In these conditions, effective circulating volume is reduced, stimulating ADH release and further water retention.

4. Sodium and Osmolality Imbalance:

Hyponatremia reflects a reduction in plasma osmolality, causing water to move into cells, leading to cellular swelling. In the brain, this swelling can result in neurological symptoms ranging from mild confusion to seizures or coma. Rapid correction of hyponatremia can cause osmotic demyelination, especially in chronic cases.

Plasma Osmolality = 2Na+ + Glycemia + Blood urea (280 – 295 mOsm/L)

5. Medications:

Some medications can impair renal water excretion, leading to hyponatremia. These include diuretics (especially thiazides), antidepressants (SSRIs), antiepileptics (carbamazepine), and chemotherapy agents.

6. Thirst Mechanism:

Excessive intake of free water without adequate sodium intake can also dilute serum sodium, especially in patients with impaired renal water excretion, such as those with SIADH or heart failure.

V. DIAGNOSIS

1. Clinical History and Physical Examination: To evaluate symptoms and volume status
2. Classify by Duration:
   - Acute Hyponatremia: Onset within <48 hours, more symptomatic.
   - Chronic Hyponatremia: Develops over >48 hours, often less symptomatic but still dangerous.
3. Evaluate Serum Osmolality:
   - Low Osmolality (< 280 mOsm/kg): True hyponatremia, also called hypotonic hyponatremia.
   - Normal Osmolality (280–295 mOsm/kg): Pseudohyponatremia (e.g., due to hyperlipidemia or hyperproteinemia).
   - High Osmolality (>295 mOsm/kg): Hypertonic hyponatremia (e.g., due to hyperglycemia).
4. Determine Volume Status (Hypotonic Hyponatremia):

 Hypovolemic Hyponatremia (loss of both sodium and water):
   - Causes: Diuretics, vomiting, diarrhea, burns, Addison's disease.
   - Urine sodium <20 mEq/L (extrarenal loss) or >20 mEq/L (renal loss).

 Euvolemic Hyponatremia (normal body fluid but low sodium):
   - Causes: SIADH, hypothyroidism, adrenal insufficiency, polydipsia.
   - Urine sodium >20 mEq/L.

 Hypervolemic Hyponatremia (excess water retention):
   - Causes: Heart failure, cirrhosis, nephrotic syndrome.

- Urine sodium typically <20 mEq/L.

 Urine Sodium:
- Low (< 20 mEq/L): Extrarenal losses (GI losses, third-spacing).
- High (> 20 mEq/L): Renal causes (SIADH, diuretics, renal failure).

 Urine Osmolality:

Uosm = 1.25 x urea in mmol/L + 1.1 x Na in mmol/L + 67 x Glucose in mmol/L
- Low (< 100 mOsm/kg): Suggests polydipsia or beer potomania.
- High (> 100 mOsm/kg): Suggests SIADH or adrenal insufficiency.

5. Specific Testing for Underlying Conditions:

 Check for malignancies, pulmonary, CNS diseases, or drugs that cause SIADH.

 Adrenal and Thyroid Function: Rule out adrenal insufficiency or hypothyroidism.

6. Imaging Studies: If SIADH is suspected, imaging of the chest or brain might be necessary to rule out tumors or lung pathology.

VI. DIFFERENTIAL DIAGNOSIS

True hyponatremia is associated with hypo osmolality. Conditions causing hyperosmolar hyponatremia and iso-osmolar hyponatremia (pseudo-hyponatremia) should be differentiated first.

- Hyperglycemia
- Hyperlipidemia
- Mannitol overdose
- Hyperproteinemia

 Differential Diagnosis for Hypo-Osmolar Hyponatremia

- Gastroenteritis	- Diuretic use	- Congestive heart failure
- Liver failure	- Psychogenic polydipsia	- Adrenal crisis
- Renal causes	- SIADH	- Hypothyroidism

 Postoperative or Trauma-Related Hyponatremia: Post-surgical patients, especially neurosurgical cases, are at risk of developing SIADH.

VII. MANAGEMENT

1. Objectives
   - Classify hyponatremia according to severity, symptomatology, and type of hyponatremia associated with volemia and serum osmolarity.
   - Early treatment or prevention of cerebral edema
   - Prevent the complications neurologic secondary to rapid increase in natremia. Increase natremia not more than 10mEq/L in first 24h.
   - Treat the underlining causes.
2. Critical signs & symptoms
   - Natremia < 125 mEq/L
   - Rapid installation hyponatremia (≤48h)
   - Mental disturbance
3. Mortality risk factors
   - Cerebral edema with increase ICP
   - Seizures
   - Hypovolemic shock
   - Pathologies that induce SIADH
4. Out-patient management
   - Admission is mandatory if the patient is symptomatic or has acute hyponatremia (developing over <48 hours), which increases the risk of cerebral edema.

- Admission is advised if patient is asymptomatic and has a serum Na+ <125 mEq/dL.

5. First line therapy

General Measures

- Assess all medications that patients are taking.
- Institute seizure precautions.
- Institute fluid restriction for hypervolemic patients.
- Fluid resuscitation in hypovolemic patients.
- Indications for 3% hypertonic saline versus normal saline solution include: acute hyponatremia, symptomatic hyponatremia, association with intracranial pathology already at risk for cerebral edema.

Medication

- Treatment is tailored to etiology, degree of hyponatremia, onset, and symptomatology; some general principles apply:
- Expected change in serum Na+ with selected infusate: ΔNa

= [(infusate Na^+ + infusate K^+- serum Na^+) / (TBW + 1)] TBW

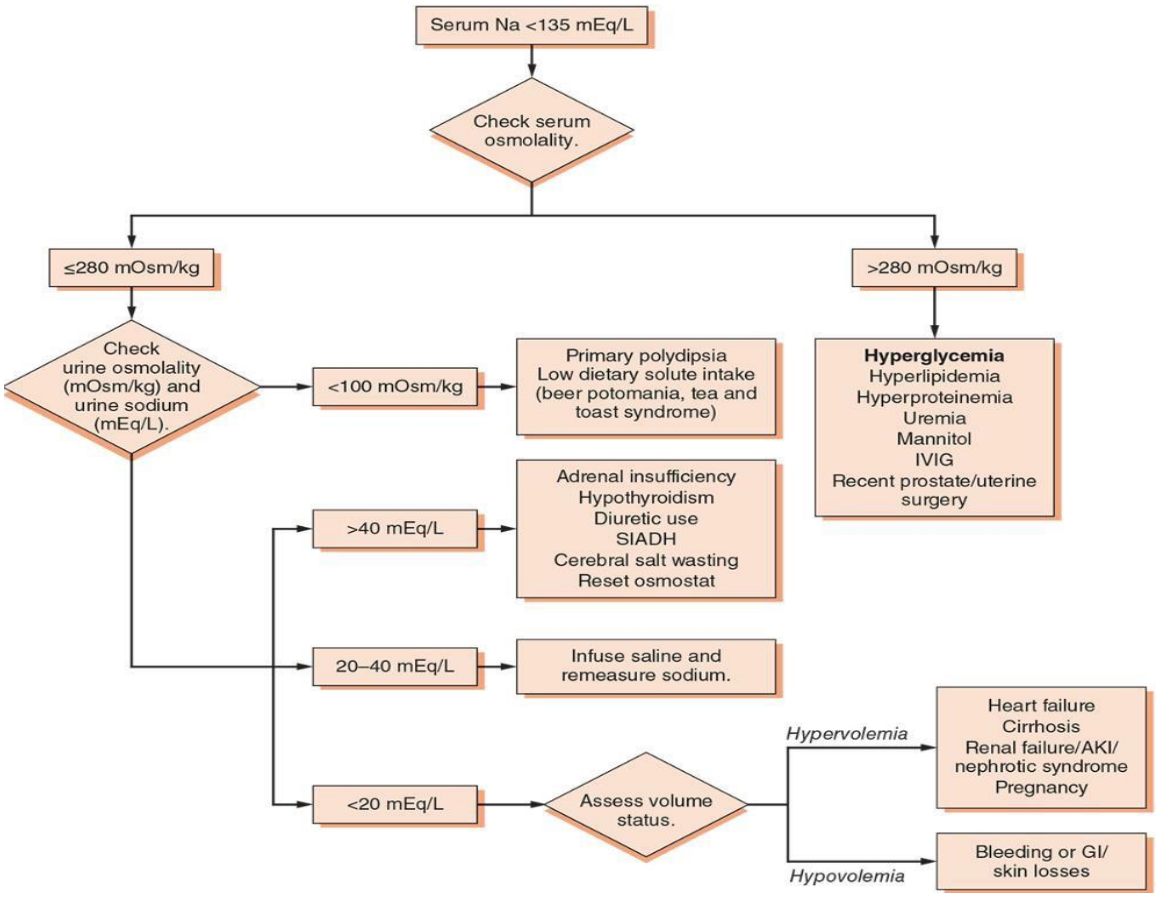
= a coefficient × weight (kg)

The coefficient for children and men: 0.6, women and elderly men: 0.5, elderly women: 0.45

- ***Asymptomatic,*** euvolemic patients can be treated with fluid restriction; etiology must be addressed.
- ***Severe hyponatremia*** (<125 mEq/L) 3% hypertonic saline should be given.
    - Done as a 100 to 150 mL bolus, with the goal of increasing the serum Na^+ 2 to 3 mEq/L. The bolus may be given twice if symptoms have not resolved.
    - Done as a continuous infusion of 3% to increase the serum Na^+ 6 to 8 mEq/L, with the goal to not exceed correction of 10 to 12 mEq/L in the first 24 hours.
    - Desmopressin can also be considered, given 1 to 2 μg every 4 to 6 hours.
    - Serum Na^+ should be checked every 2 hours. The infusion rate and fluids should be changed to isotonic saline when appropriate.
    - In patients who do not respond to the aforementioned approach, consider the use of vasopressin V2-receptor antagonists, such as tolvaptan or conivaptan. This class of medications should not be in used in patients with liver disease.
    - ***For mild to moderate hyponatremia***, use isotonic saline solution (0.9%).
    - In patients with ***severe hyponatremia (euvolemic and hypervolemic state)*** who do not respond to the aforementioned approach, consider the use of vasopressin V2-receptor antagonists, such as tolvaptan or conivaptan. This class of medications should not be in used in patients with liver disease
    - Patients with ***hypervolemic hyponatremia*** caused by cirrhosis, heart failure, or kidney disease benefit from restriction of sodium and fluids, diuretic therapy, and management of the underlying etiology.
    - Treat underlying etiology.
    - ***Chronic hyponatremia*** resulting from SIADH: demeclocycline (inhibits ADH action at the collecting duct) if fluid restriction alone is not effective
        - Contraindications: drug allergy, pregnancy, children <8 years old; caution in renal and hepatic disease

- In doses of 600 to 1,200 mg/day, the drug produces nephrogenic diabetes insipidus.
- Significant possible interactions: oral anticoagulants, oral contraceptives, penicillin

6. Treatment adjustments
   - In case of overcorrection, re-lower Na^+ concentration. Begin with infusion of 3 mL/kg of 5% dextrose in water over 1 hour. Repeat Na^+ measurement. Be cautious, dextrose infusion rates >250 to 300 mL/hr can cause significant hyperglycemia in both diabetic and nondiabetic patients and may lead to osmotic diuresis and subsequent free water loss with increased serum Na^+ concentration. Consider 2 to 4 μg IV desmopressin every 8 hours to prevent overcorrection.
   - Rapid correction of severe symptomatic hyponatremia has been associated with central pontine myelinolysis. This results in irreversible injury. Symptoms are apparent 2 to 6 days after injury and include seizure, coma, spastic paraparesis, dysarthria, and dysphagia. Patients at increased risk are those with Na^+ <105 mEq/L, alcoholism, hypokalemia, and malnutrition. MRI may not be positive until 4 weeks after symptom onset.
   - Caution: If severe, consider hypertonic saline (3% Na^+ chloride) with central line access, exercise extreme caution, and monitor serum Na^+ as frequently as every 1 to 2 hours.
7. Algorithm



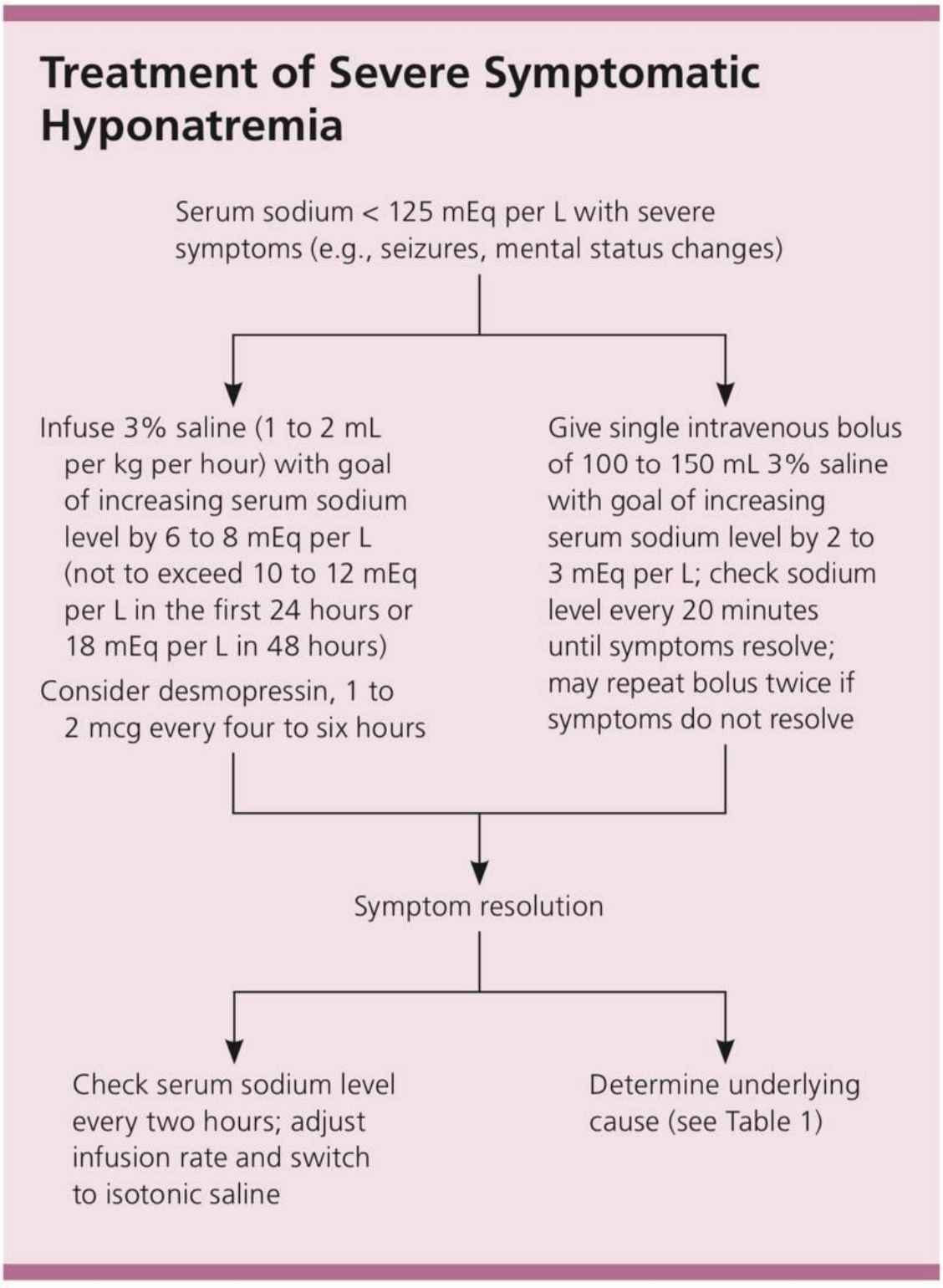


Figure 2. Algorithm for the treatment of severe symptomatic hyponatremia.

VIII. SPECIAL CASES

Geriatric Considerations

Elderly patients have a decreased renal mass placing them at risk for decreased urinary concentration and decreased response to antidiuretic hormone. Presenting symptoms may be frequent falls and gait disturbances. Clinicians should also consider the impact of comorbidities and acute disease.

Pediatric Considerations

Children are at increased risk of brain herniation from cerebral edema.

Pregnancy Considerations

Conivaptan and tolvaptan are class C drugs in pregnancy

IX. EVOLUTION AND PROGNOSIS

- In hospitalized patients, hyponatremia is associated with an elevated risk of adverse clinical outcomes and higher mortality.
- Recently, in community-dwelling, middle-aged, and elderly adults, mild hyponatremia has been shown to be an independent predictor of death.
- Associated with poor prognosis in patients with acute pulmonary embolism
- Associated with poor prognosis in patients with liver cirrhosis and those waiting for liver transplant; it is associated with significant postoperative risk and short-term graft loss.

X. COMPLICATIONS

- Occult tumor may be present if SIADH is identified.
- Hypervolemia if isotonic saline solution is used
- Osmotic demyelination (central pontine and extrapontine irreversible myelinolysis) if the Na+ is corrected too quickly.
- Hyponatremia is the cause of 30% new-onset seizures in intensive care settings.
- Can cause hyponatremic encephalopathy and brain herniation if severe and untreated, especially in young women and children.
- Chronic hyponatremia is associated with increased risk of osteoporosis, attention deficit, gait disturbances, falls, and fractures.

XI. REVENTION AND RECOMMENDATION

- Preventing hyponatremia involves identifying at-risk individuals, managing underlying conditions, and implementing strategies to maintain appropriate sodium levels to avoid complication.
- Specific recommendations vary based on the cause and severity of the condition, but the focus is on monitoring, avoiding precipitating factors, and correcting sodium imbalances cautiously.

XI. REFERENCES

1. Spasovski. Hyponatremia – Treatment Standard 2024. Nephro Dial Transplant 2024, Vol 39, No 10, October 2024, 1583 – 1592
2. Verbalis, J. G., et al. (2013). Hyponatremia treatment guidelines. *European Journal of Endocrinology*, 170(3), G1-G47
3. Verbalis, J. G., et al. (2013). Pathophysiology of hyponatremia in clinical disorders. *Nature Reviews Endocrinology*, 9(3), 173-184.

4. Sterns, R. H. (2018). "The treatment of hyponatremia." Clinical Journal of the American Society of Nephrology, 13(4), 641-649.
5. Ellison, D. H., & Berl, T. (2007). The syndrome of inappropriate antidiuresis. *New England Journal of Medicine*, 356(20), 2064-2072.
6. MICHAEL M. BRAUN, DO, Madigan Army et al. Diagnosis and Management of Sodium Disorders: Hyponatremia and Hypernatremia. Am Fam Physician 2015; 91(5): 299 – 307.
7. Sterns, R. H., et al. (2020). Treatment of hyponatremia. *New England Journal of Medicine*, 342(21), 1581-1589.
8. Schrier RW, Sharma S. Hyponatremia: Pathophysiology, classification, and approach to therapy. **Clin J Am Soc Nephrol**. 2013;8(8):1340-1349. doi:10.2215/CJN.02720612
9. Hew-Butler, T., et al. (2015). "Statement of the Third International Exercise-Associated Hyponatremia Consensus Development Conference." *Clinical Journal of Sport Medicine*, 25(4), 303-320.
10. Gheorghiade, M., et al. (2013). Hyponatremia in heart failure. *European Heart Journal*, 34(12), 845-852.
11. Harrigan, M. R. (1996). Cerebral salt wasting syndrome. *Neurosurgery Clinics of North America*, 7(4), 731-740.
12. Decaux G, Soupart A, Vassart G. Nonosmotic release of vasopressin in hyponatremia. Horm Res. 1996;45(5):163-168. doi:10.1159/000184777
13. Adrogué, H. J., & Madias, N. E. (2000). "Hyponatremia." *New England Journal of Medicine*, 342(21), 1581-1589.
14. Berl, T. (2013). "Impact of solute intake on urine flow and water excretion." *Journal of the American Society of Nephrology*, 24(6), 861-869.
15. Verbalis, J. G., et al. (2013). "The syndrome of inappropriate antidiuretic hormone secretion (SIADH)." *New England Journal of Medicine*, 356(20), 2064-2072.
16. Ghali, J. K., et al. (1992). "Hyponatremia in patients with heart failure: a marker of increased mortality." *American Journal of Cardiology*, 69(16), 1569-1572.
17. Liamis, G., Milionis, H. J., & Elisaf, M. (2013). "A review of drug-induced hyponatremia." *American Journal of Kidney Diseases*, 62(1), 67-78.
18. Anderson, R. J., et al. (2003). "Postoperative hyponatremia: A consequence of intravenous fluid administration." *Archives of Internal Medicine*, 163(4), 331-336
19. Renneboog, B., et al. (2006). "Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits." *American Journal of Medicine*, 119(1), 71.e1-71.e8.
20. on outcomes in hospitalized patients." *Kidney International*, 77(8), 744-752.
21. Summer Chavez, DO, MPH, MPM. Hyponatremia in 5min Clinical consult, U-central platform, 2024, Wolters Kluwer Health Lippincott Williams & Wilkins. Access on Nov 2024

SEPSIS AND SEPTIC SHOCK, EMPIRICAL ANTIBIOTHERAPY

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I. DEFINITION

Sepsis is defined as life-threatening organ dysfunction due to dysregulated host response to infection, and organ dysfunction is defined as an acute change in total Sequential Organ Failure Assessment (SOFA) score of 2 points or greater secondary to the infection cause.

Septic shock is a subset of sepsis with circulatory and metabolic/cellular dysfunction associated with a higher risk of mortality. In the clinical setting, septic shock is characterized by hypotension requiring vasoactive drugs to maintain a mean arterial pressure of greater than 65 mm Hg along with a serum lactate level of greater than 2 mmol/L despite adequate fluid resuscitation.

SOFA (sequential organ failure assessment) variables:

- Respiration: PaO_2/FiO_2 ratio
- Central nervous system: Glasgow Coma Scale (GCS) score
- Cardiovascular: mean arterial pressure (MAP), vasopressor administration with type and rate of infusion
- Renal: serum creatinine, urine output
- Liver: bilirubin
- Coagulation: platelet count

II. EPIDEMIOLOGY

In 2017, there were an estimated 49 million cases of sepsis and 11 million sepsis-related deaths worldwide. This accounts for approximately 20% of all annual deaths globally. Sepsis affects people of all ages, but children under 5 years old are particularly vulnerable, with an estimated 20 million cases occurring in this age group.

Regional Disparities: While sepsis is a global health concern, the burden is disproportionately higher in lower-middle-income countries (LMICs). These countries face challenges in early diagnosis, timely treatment, and access to appropriate healthcare resources, contributing to higher mortality rates.

III. ETIOLOGY

Causative organisms (most commonly bacterial)

- Gram-positive bacteria (most common): Staphylococcus sp., Streptococcus sp., Enterococcus sp.
- Gram-negative: Escherichia coli, Klebsiella sp., Proteus sp., Pseudomonas sp., and anaerobic bacteria
- Fungi: Candida sp.
- Causative organism not identified in 1 /3 of cases
- Nosocomial infections in 50% of cases

Although an infection can originate anywhere, the lung is the most common source of infection (40%), followed by the abdomen (20%), indwelling venous and arterial catheters and primary bacteremia (15%), and the urinary tract (10%).

IV. PHYSIOPATHOLOGY

Complex pathophysiology.

Multifactorial: Widespread endothelial dysfunction, complement activation, and activation of coagulation cascade led to tissue hypoperfusion, early hemodynamic changes, and organ dysfunction. An imbalance between proinflammatory and anti-inflammatory mediators leads to relative immunosuppression.

V. DIAGNOSIS

History:

Past medical, surgical, social, occupational, and travel history to identify risk factors and potential source

General symptoms

- Fever, chills, rigors, myalgias
- Mental status changes: restlessness, agitation, confusion, delirium, lethargy, stupor, coma

Specific symptoms (relative to primary source)

- **Respiratory**: cough, sputum production, dyspnea, pleuritic chest pain
- **Urinary**: dysuria, frequency, urgency, flank pain
- **Intra-abdominal**: nausea, vomiting, diarrhea, constipation, abdominal pain
- **CNS**: stiff neck, headache, photophobia, focal neurologic signs
- **Skin/soft tissue**: erythema, edema, purulent discharge

Physical Exam

- Assess vital signs: hyper-/hypothermia, tachycardia, tachypnea, hypotension.
- Signs of poor perfusion: central venous hypoxia, delayed capillary refill, cyanosis, mottled skin, altered
- mental status, oliguria/anuria
- Signs of target organ involvement

Investigation:

- Complete blood count (CBC) with differential, comprehensive metabolic profile, coagulation studies, serum lactate, arterial blood gas, urinalysis
- Peripheral blood cultures from two different sites (if possible) prior to antibiotic administration. It is important to not delay starting antibiotic therapy because positive blood cultures are not required for diagnosis; 50% of blood cultures are negative in severe sepsis/septic shock.
- Cultures from potential sites of infection, including indwelling catheters if present.
- Radiographic studies targeted at suspected source
- Common findings: leukocytosis/leukopenia, bandemia (>10%), hyperglycemia, metabolic acidosis, mild hyperbilirubinemia, hypoxemia, respiratory alkalosis, proteinuria

- Findings associated with severe disease: anemia, thrombocytopenia, coagulopathy, azotemia, hypoglycemia, acidosis.

Diagnostic Procedures/Other

- Aspiration, biopsy, and/or drainage of potentially infected body sites (pleural cavity, peritoneal cavity, biliary tree, CSF, abscess); interventional radiology techniques to aid in specimen collection as needed.
- Echocardiogram if concern for endocarditis

VI. DIFFERENTIAL DIAGNOSIS

- Bacteremia without sepsis
- Viral, rickettsial, spirochetal, and protozoal diseases
- Collagen vascular diseases, vasculitis, pancreatitis, myocardial infarction, CHF, pulmonary embolism, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), thyrotoxicosis, adrenal insufficiency, poisoning, drug reaction.

VII. MANAGEMENT

1. Objectives

The treatment of patients with septic shock has the following major goals:

- Start adequate antibiotic therapy (proper dosage and spectrum) as early as possible
- Identify the source of infection, and treat with antimicrobial therapy, surgery, or both (source control)
- Resuscitate the patient, using supportive measures to correct hypoxia, hypotension, and impaired tissue oxygenation (hypoperfusion)
- Maintain adequate organ system function by maintaining blood flow and arterial pressure, guided by cardiovascular monitoring, and interrupt the progression to multiple organ dysfunction syndrome (MODS) by appropriate antibiotics and surgical debridement, as needed

2. Critical signs

Score NEWS-2 ≥ 5 indicate possible severe sepsis

National Early Warning Score-2 (NEWS-2)

Physiological parameter	Score						
	3	2	1	0	1	2	3
Respiration rate (per min)	≤ 8		9-11	**12-20**		21-24	≥ 25
SpO2 scale-1 (%)	≤ 91	92-93	94-95	**≥ 96**			
SpO2 scale-2 (%)	≤ 83	84-85	86-87	**88-92** **≥ 93 on air**	93-94 on O2	95-96 on O2	≥ 97 on O2
Air or oxygen?		oxygen		**Air**			
Systolic BP (mmHg)	≤ 90	91-100	101-110	**111-219**			≥ 220
Pulse (per min)	≤ 40		41-50	**51-90**	91-110	111-130	≥ 131
Consciousness				**Alert**			CVPU
Temperature (°C)	≤ 35.0		35.1-36.0	**36.1-39.0**	38.1-39.0	≥ 39.1	

SpO2 scale-2 is used for patient with chronic respiratory failure (high PaCO2)

The (Quick Sequential [Sepsis-related] Organ Failure Assessment) qSOFA ≥ 2
The qSOFA score is a bedside tool used to quickly identify patients at risk of poor outcomes from sepsis. Use qSOFA alone, to screen for sepsis is not recommended.

1	Altered mental status: Glasgow Coma Scale (GCS) score < 15
2	Respiratory rate: ≥ 22 breaths per minute
3	Systolic blood pressure: ≤ 100 mm Hg

A qSOFA score of 2 or more indicates a higher risk of mortality and the need for urgent medical evaluation and intervention

3. Mortality Risk factor
   - High **P**redisposition: Elderly or immunocompromised patients.
   - Severe **I**nfection: A widespread infection or resistant infection.
   - Intense **R**esponse: High levels of inflammation markers and severe immune response.
   - Extensive **O**rgan dysfunction: Multiple organ failure (e.g., lungs, kidneys, heart).
4. Outpatient management
5. First-line treatment

- Early venous access, administration of IV fluids, and antibiotics
- Secure airway and correct hypoxemia when indicated.
- Volume resuscitation with crystalloids at 30 ml/kg within 3 hours of presentation
- Empiric antibiotic therapy targeted to suspected organism/source within 1 hour of presentation.
- Vasopressors for refractory hypotension

Targets to measure clinical response are:
    - Central venous oxyhemoglobin saturation (ScvO2) ≥ 70%
    - Central venous pressure (CVP) alone should not be used to guide resuscitation. Instead, use dynamic variables including passive leg raises, stroke volume variation, or pulse pressure variation to predict response to resuscitation.
    - MAP ≥ 65 mm Hg
    - Urine output ≥ 0.5 ml/kg/hr
- Identify and eliminate source of infection and any septic foci.
    - Early surgical consultation for acute abdomen, empyema, necrotizing fasciitis
    - interventional radiology consultation for image-guided drainage
- Transfuse pRBCs, platelets, and/or fresh frozen plasma for coagulopathic complications or in association with planned procedures.
- Transfuse pRBC if Hgb <7.0 in absence of tissue hypoperfusion, myocardial ischemia, severe hypoxemia, or acute hemorrhage.
- Only transfuses fresh frozen plasma if active hemorrhage or planned procedures.
- Prophylactic platelet transfusion if:
    - <10,000/mm^3 in the absence of bleeding,
    - <20,000/ mm^3 with significant risk of bleeding, and
    - <50,000/ mm^3 for actively bleeding patients
- Stress ulcer and deep venous thrombosis (DVT) prophylaxis
- Glucose control (≤ 180 mg/dL)

Fluid management

- Initial therapy: 30 ml/kg of crystalloids (Ringer lactate)
- Albumin administration is safe and equally effective compared to crystalloids for patients requiring large volume resuscitation

Initiate broad-spectrum antibiotic within an hour of diagnosis

Empirical antibiotherapy

Choose antibiotic based on organs-system suspected to be the primary cause of infection and the microbial epidemiology, antibiotic sensitivity data of the local institution. Follow protocolized recommendation of your hospital. In general, the antibiotic choose should be:

- Adult (Pseudomonas not suspected):
    - vancomycin (loading dose 25 mg/kg) + gram-negative coverage (3rd-generation cephalosporin, β-lactam/β-lactamase inhibitor [piperacillin/tazobactam 3.375 g IV q6h] or carbapenem)
- Adult (Pseudomonas suspected):
    - vancomycin (Recommended loading dose for complicated infections in seriously ill patients is 25 to 30 mg/kg based on actual body weight.)
    - Vancomycin (to cover MRSA) plus at least one of the following:
        - A 3rd generation Cephalosporin (e.g., ceftriaxone or cefotaxime) or
        - A combination Beta-lactam/beta-lactamase inhibitor (e.g., piperacillin-tazobactam, ticarcillin clavulanate), or
        - A Carbapenem (e.g., imipenem or meropenem)
- If pseudomonas is a possible cause, consider Vancomycin plus:
    - An Antipseudomonal cephalosporin (e.g., ceftazidime, cefepime), or

    - An Antipseudomonal carbapenem (e.g., imipenem, meropenem), or
    - An Antipseudomonal combination beta-lactam/beta-lactamase inhibitor (e.g., piperacillin tazobactam, ticarcillin-clavulanate), or
    - An Antipseudomonal Fluoroquinolone (e.g., ciprofloxacin), or
    - Monobactam (e.g., aztreonam)
- Non-immunocompromised child: 3rd-generation cephalosporin
- Neonate (<7 days old): ampicillin and gentamicin
- Alternatives to vancomycin include linezolid or daptomycin.
- If Burkholderia pseudomallei (Melioidosis) is suspected_
    - Regular contact with soil and water is a risk factor.
    - Increased risk with diabetes, COPD, alcoholism, chronic renal disease, thalassemia, malignancy, and immunosuppression.
    - Classic presentations include pneumonia and multiple abscesses. Sepsis, intra-abdominal infection, septic shock are also frequent.

  Preferred, initial IV induction phase:
    - Ceftazidime 50 mg/kg (2 g max) IV q6-8h or
    - Meropenem 25 mg/kg (1 g max) q8h
        - Dose 2g IV q 8h for adult CNS infections
    - Duration: 10-14d minimum IV minimum; however, relapse rates can exceed 5%.
- Consider narrowing antibiotic regimen at 48 to 72 hours based on culture results. Anticipate antibiotic course in general to last 7 to 10 days.

Antifungals are not routinely given. Risk factors for fungal infections include long-term antibiotic use, Total parenteral nutrition (TPN), and GI surgery.

6. Treatment adjustments

Corticosteroids and sepsis

Low dose of hydrocortisone was indicated in CIRCI_ The hypothalamic-pituitary-adrenal (HPA) axis dysfunction in critically ill patients is termed “critical illness-related corticosteroid insufficiency” (CIRCI)

- Do not administer corticosteroids to treat sepsis when shock is not present
- Steroids should not be administered to patients with septic shock unless hemodynamic stability cannot be achieved with fluid resuscitation and vasopressor agents.
- When indicated, for patients with septic shock, administer
    - hydrocortisone 200 mg/day IV in 4 divided doses or
    - as a 100-mg bolus followed by continuous infusion at 10 mg/hr (240 mg/d);
    - in patients with early severe ARDS, the optimal initial treatment regimen is continuous infusion of methylprednisolone 1 mg/kg/day
- A regimen of 7 days or longer should be used in patients with septic shock before tapering, and
- A regimen of 14 days or longer should be used in patients with early acute respiratory distress syndrome (ARDS) before tapering
- Do not use dexamethasone therapy for septic shock or ARDS

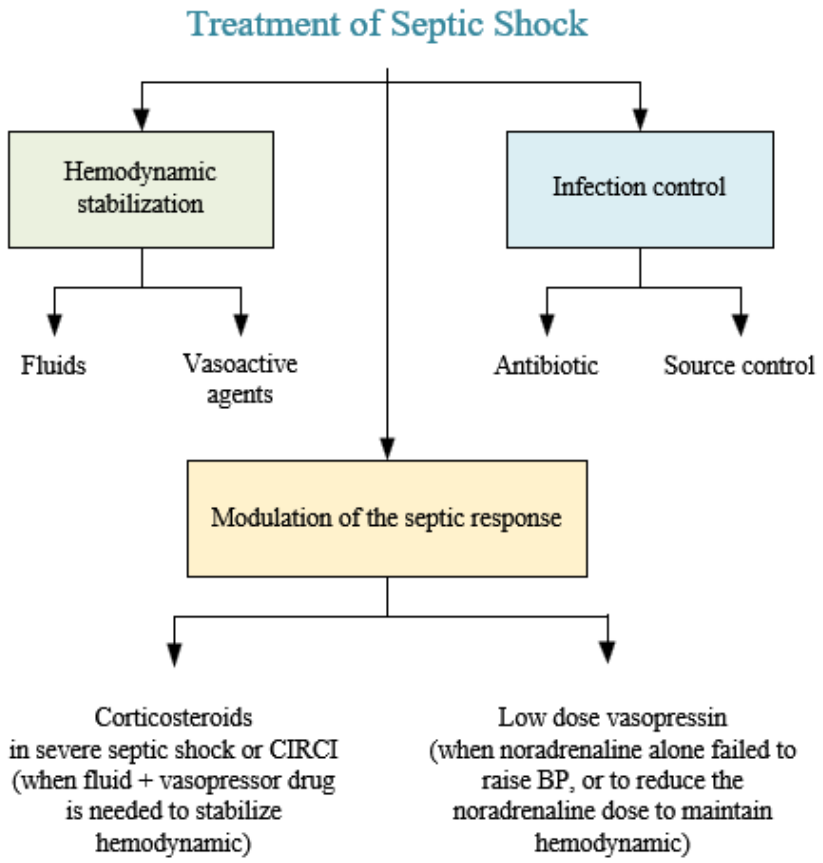
Vasopressors

- Norepinephrine 0.01 to 3.30 µg/kg/min as initial vasopressor of choice
- Vasopressin 0.03 U/min as an adjunct to norepinephrine to raise BP or decrease norepinephrine requirement.
- Low-dose dopamine for renal protection is not recommended
- lnotropic therapy with dobutamine may benefit patients with myocardial dysfunction or ongoing hypoperfusion if intravascular volume is adequate

Use of IV immunoglobulins (IVig) has no survival benefit based on high-quality studies. Intermittent hemodialysis or continuous veno-venous hemofiltration (CVVHF) for renal failure when indicated

7. Graphic:

The three aspects of Septic shock treatment



CIRCI: Critical Illness-Related Corticosteroid Insufficiency, BP: blood pressor

VIII. SPECIAL CASES

Pediatric Considerations

- Sepsis is diagnosed with suspected or proven infection in addition to meeting at least 2 SIRS criteria.
- SIRS in pediatric population requires that abnormality in temperature or WBC be present.

- Drug metabolism is reduced in children with sepsis. Monitor drug toxicity labs to prevent adverse effects.

Geriatric Considerations

Altered mental status may be presenting signs of infection.

Pregnancy Considerations

β-lactam antibiotics, macrolides, and metronidazole generally are considered safe.

IX. EVOLUTION AND PROGNOSIS

Sepsis has a high mortality rate. Estimates range from 10 to 52 percent with rates increasing linearly according to the disease severity of sepsis. Following discharge from the hospital, sepsis carries an increased risk of death as well as an increased risk of further sepsis and recurrent hospital admissions.

- Overall mortality risk ≥ 10% if the SOFA ≥ 2, approximately 40% in septic shock
- SOFA > 15 associated with >90% mortality.
- Poor prognostic factors include cirrhosis, immunosuppression (HIV/AIDS, cancer)

X. COMPLICATION

- GI hemorrhage,
- DIC,
- Hyperglycemia,
- De novo embolic foci of infection,
- ARDS,
- Multiorgan failure, death

XI. PREVENTION AND RECOMMENDATION

- **Vaccination**: pneumococcal vaccine in children and adults ≥ 65 years or immunocompromised. Hemophilus influenzae type B (infants, young children), influenza, meningococcal vaccine
- y-Globulin for hypo- or agammaglobulinemia
- Regular hand washing, sterile technique for vascular and indwelling catheter placement
- Antibiotic prophylaxis for recommended surgical procedures
- Prompt extubation for patients on mechanical ventilation as soon as clinically appropriate.

XII. REFERENCES

1. Benjamin M. Enciso, DO, Patricia Martinez Quinones, MD, Sepsis in 5-Minute Clinical Consult U-Central, Unbound Medicine platform, access date: October 2024
2. Remi Neviere, MD, Michelle Ng Gong, MD, MS, Geraldine Finlay, MD; Sepsis syndromes in adults: Epidemiology, definitions, clinical presentation, diagnosis, and prognosis in UpToDate platform Access: October 15, 2024
3. Jean-Louis Vincent, Septic shock, in Textbook of Critical Care, 8th Edition, 2024, Elsevier p. 901-07

SEVERE ACUTE RESPIRATORY INFECTION (SARI) AND INFLUENZA

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I. CASE DEFINITION

Patients with acute respiratory infection who have history of fever (or measured fever of = 38 °C), cough and onset within the last 10 days (symptoms within 10 days) and require hospitalization.

Clinical syndrome	Definition
Influenza-like infection (ILI)	Acute onset within the last 10 days following respiratory symptoms, measured fever of ≥ 38 °C and cough.
Acute respiratory infection (ARI)	Sudden onset of respiratory infection symptoms (cough, sore throat, shortness of breath, or coryza).
Severe acute respiratory infection (SARI)	Acute respiratory infection with a history of fever or measured fever of ≥ 38 °C and cough with onset within the last 10 days and requires overnight hospitalization.

II. EPIDEMIOLOGY

The pathogens that may cause SARI include a wide spectrum of community-acquired pathogens, including respiratory viruses, bacteria and other less common micro-organisms. In addition to the common viral and bacterial pathogens, an emerging respiratory virus may result in SARI and lead to a public health emergency of international concern.

Worldwide, the annual epidemics of SARI are estimated to result in 3 to 5 million cases of severe illness, and 290 000 to 650 000 respiratory deaths. This estimate does not take in account deaths from other diseases such as cardiovascular disease, which can be influenza-related. Emerging respiratory viruses include: zoonotic influenza viruses, such as avian influenza, and coronaviruses, such as MERS-CoV and SARS-CoV-2, a new subtype of influenza A virus may also have pandemic potential.

III. ETIOLOGY

Viral pathogens

Common viral pathogens

- Respiratory syncytial virus (RSV)
- Parainfluenza virus
- Rhinoviruses
- Adenovirus, enterovirus (EV-D68)
- Human metapneumovirus
- Bocavirus
- Seasonal influenza, known subtype

Less common viral pathogens

- Varicella zoster
- Measles
- Hantavirus

Virus that may constitute a public health emergency of international concern

- SARS
- SARS-CoV-2
- MERS
- New subtypes of influenza
- Other zoonotic viral infections

If immunosuppressed (i.e. people living with HIV)

- Cytomegalovirus,
- Herpes simplex viruses

Bacterial pathogens

Most common bacterial pathogens

- Streptococcus pneumoniae
- Hemophilus influenzae
- Moraxella catarrhalis
- Legionella pneumophila, non-pneumophila Legionella
- Chlamydia pneumonia
- Mycoplasma pneumoniae
- Klebsiella pneumonia
- Staphylococcus aureus

Less common, unless at risk or in high-prevalence geographic area

- Mycobacterium tuberculosis
- Burkholderia pseudomallei
- Rickettsial infections
- Coxiella burnetti (Q fever)
- Leptospira spp.
- Chlamydia psittaci
- Bortedella pertussis
- Salmonella sp.

Resistant pathogens

Risk factors for multidrug-resistant pathogens: intravenous antimicrobial therapy within < 90 days. Resistant pathogens include:

- Methicillin-resistant S. aureus (MRSA)
- Non-fermenters such as Pseudomonas aeruginosa, Acinetobacter baumannii
- Extended spectrum beta-lactamase (ESBL) producers such as E. coli, Klebsiella, Enterobacter

The rate of co-infection among these pathogens is unknown. Therefore, a positive diagnostic test for another infection does not exclude the need for other micro-organism testing.

Influenza viruses and acute severe viral syndromes

Influenza viruses are single-stranded RNA viruses of the family Orthomyxoviridae that are classified by their matrix protein composition. Three influenza types can infect humans: influenza A, influenza B, and influenza C. The influenza A virus is divided into specific subtypes based upon two major antigenic proteins on its surface: hemagglutinin (HA) [1 to 16] and

neuraminidase (NA) [1 to 9]. Influenza A can replicate in the gastrointestinal (GI) tract of some avian species without causing symptoms, but infection and symptoms may occur in other bird species, mammals, and humans. It is the only subtype with pandemic potential.
Influenza B almost exclusively infects humans. Influenza C affects humans, dogs, and pigs but seldom causes severe illness or epidemics in humans.

Depending on the origin host, humans can be infected with avian, swine and other zoonotic influenza viruses: such as avian influenza virus subtypes A(H5N1), A(H7N9) and A(H9N2), and swine influenza virus subtypes A(H1N1), A(H1N2) and A(H3N2).
Human infections are rare and primarily acquired through direct contact with infected animals or contaminated environments; all these animal influenza type A viruses are distinct from human influenza viruses and have not acquired the ability of sustained transmission among humans.
Any new influenza virus is considered to have the potential to cause a pandemic if:

- the virus has demonstrated the capacity to infect a human; and
- the haemagglutinin (HA) gene or protein is not a variant or mutated form of those – A(H1) or A(H3) – circulating widely in the human population.

IV. PATHOPHYSIOLOGY

Influenza virus has a particular predilection for respiratory epithelial cells. Infected cells undergo abrupt cessation of protein synthesis and subsequent apoptosis. Viral particles are released infecting nearby cells. Local immune cells are also infected, causing measurable deficiencies in immune function, increasing the likelihood of secondary complications. Lung histopathology of fatally infected patients reveals a diffuse alveolar filling process, with early hyaline membrane formation, and occasionally focal areas of hemorrhage. The alveolar lining is thickened, with lymphocytic infiltrates and, occasionally, early fibrosis.

V. DIAGNOSIS

Avian, swine and other zoonotic influenza virus infections in humans may cause disease ranging from mild upper respiratory tract infection (fever and cough), early sputum production and rapid progression to severe pneumonia, sepsis with shock, ARDS, and even death. Conjunctivitis, gastrointestinal symptoms, encephalitis and encephalopathy have also been reported to varying degrees depending on subtype.

Clinical presentation

Signs and symptoms of complicated ARI (SARI)

- **Respiratory distress**: fast breathing, shortness of breath, accessory muscle use, cyanosis.

– In children: central cyanosis, severe distress, grunting, severe chest indrawing or danger signs of lethargy, convulsions or inability to breastfeed or drink.

- **Cardiovascular distress**:

– Adult: low blood pressure (SBP < 100); delayed capillary refill (> 3 sec < 65 years or > 4.5 sec in older people); fast and weak pulse.
– Child: delayed capillary refill (> 3 sec); fast and weak pulse; or cool extremities or hypotension.

- **Neurologic distress**: alteration in mental status such as coma, lethargy, confusion, seizures, agitation.
- **Dehydration**:

– In children: diarrhea plus any two of the following signs: lethargy, sunken eyes, very slow skin pinch, unable to drink or drinks poorly.

- **Persistent fever** that is not responding after 3 days.

Investigation

CBC with differential (Decreased leukocyte, platelet, and lymphocyte counts are associated with increased mortality.)
Liver profile
Chemical profile
Blood culture
Chest x-ray (CXR): initial foci of consolidation. After 7 days, patchy lobar and interstitial infiltrates develop. Pleural effusions with cavitation are less common.
Lab confirmation of H5N1 is case by case:
Positive influenza A/H5 (Asian lineage) virus real-time reverse transcription-polymerase chain reaction (rRT-PCR).
Antigen detection tests: Rapid influenza diagnostic tests (RIDT) and immunofluorescence assay tests have low sensitivity to detect H5N1.

VI. DIFFERENTIAL DIAGNOSIS

- Acute respiratory distress syndrome (ARDS)
- Pneumonia
- SARI caused by different organisms

VII. MANAGEMENT

1. Objectives
   - Identify and treat severe / critical cases, as soon as possible
   - Early provide antiviral as indicated
   - Minimize spread through droplet precaution and contact precautions.
   - Supportive treatment as indicated (ventilation, fluid, vasopressor, diuretic, prone position)
   - Minimize complications of treatment (mechanical ventilation)
2. Critical Sign
   - Requires life sustaining treatment (mechanical ventilation, hemodialysis, pressor support…)
   - Acute respiratory distress Syndrome (ARDS)
   - Sepsis
   - Septic shock
   - Acute thrombosis (pulmonary thromboembolism, acute coronary syndrome, acute stroke...)

3. Mortality risk factor

Risk factors associated with severe disease:

- Age more than 60 years (increasing with age).
- Underlying noncommunicable diseases (NCDs): diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, dementia, mental disorders, chronic kidney disease, immunosuppression (including HIV), obesity and cancer.

- In pregnant or recently pregnant: women > 35 years old, obesity, with chronic medical conditions or pregnancy specific disorders (e.g. gestational diabetes and pre - eclampsia/eclampsia).
- Smoking.
- Young children (< 59 months).

4. Outpatient Management

Patient with non-complicate influenza-like infection (ILI) and non-complicate acute respiratory infection (ARI) may have supportive treatment at home. However, people who have risk factors associated with severe disease (above) should have medical check and advice.
In adults, the CURB-65 score is a validated tool that, when combined with clinical judgments can be used to predict mortality and aid in determining admission for adult patients with pneumonia.

CURB-65 score: one point for each feature present	**Total points**
Confusion	1
Urea > 7mmol/l	1
RR ≥ 30/min	1
Blood pressure (SBP < 90 or DBP ≤ 60mmHg)	1
Age ≥ 65 ys	1

- Score 0 – 1: low severity, risk of death < 3%, consider home-base care
- Score 2 – 3: Moderate severity, risk of death 3 – 15%, consider hospitalization
- Score 4 – 5: High severity, risk of death > 15%, consider ICU

Patients should be admitted to ICU based on severity of clinical condition and resource availability. In hospitals where oxygen therapy is only available in the ICU, admit all SARI patients to the ICU. In hospitals where oxygen therapy can also be delivered on wards, admit less severe SARI patients to wards but with increased monitoring.

5. First-line treatment

Give oxygen to patients who have dyspnea. Target SpO2: 94-96%

Option for oxygenation support:

Standard oxygen therapy: use nasal cannula, simple mask, venturi mask, or mask with oxygen reservoir bag.

High Flow nasal canula (HFNC): need specific machine, some ICU-ventilator have this function

Non-invasive ventilation (NIV): use ICU-ventilator, or standalone CPAP machine

Mechanical ventilation: ICU-ventilator. Patient needs to be intubated.

Antiviral drugs

- Mild to moderate cases: oseltamivir (Tamiflu) 75 mg PO BID for 5 days
- Severe cases: oseltamivir (Tamiflu) 150 mg BID for 7 to 10 days
- Postexposure prophylaxis: oseltamivir (Tamiflu) 75 mg PO once a day for 7 to 10 days
- Monitor for resistance; some H5N1 and H7N9 viruses show resistance to oseltamivir.

Almost all patients with severe influenza in the ICU will have deficits in oxygenation, leading to acute respiratory distress syndrome (ARDS) and requiring ventilatory support. Shock and renal failure are also common.

Antibacterial drugs

Secondary bacterial pneumonia was common in severe influenza. The most important adjunctive pharmacologic treatment in critically ill patients with influenza is empiric broad-spectrum antibiotics to cover possible secondary bacterial pneumonia or influenza-bacterial coinfection. Antibiotics should be selected according to local antibiograms to cover the most common pathogens involved, namely S. pneumoniae, S. aureus (including methicillin-resistant S. aureus [MRSA]), S. pyogenes, and occasionally, gram-negative bacteria.

6. Treatment adjustment

ARDS,

if PaO2/FiO2 > 200, it may response with NIV.

the severe ARDS (PaO2/FiO2 < 150, usually need mechanical ventilation. Use lung protective strategy with high PEEP. Control mode ventilation with appropriate sedation and use of neuromuscular blockade to avoid ventilatory desynchrony and high airway pressures are often needed.

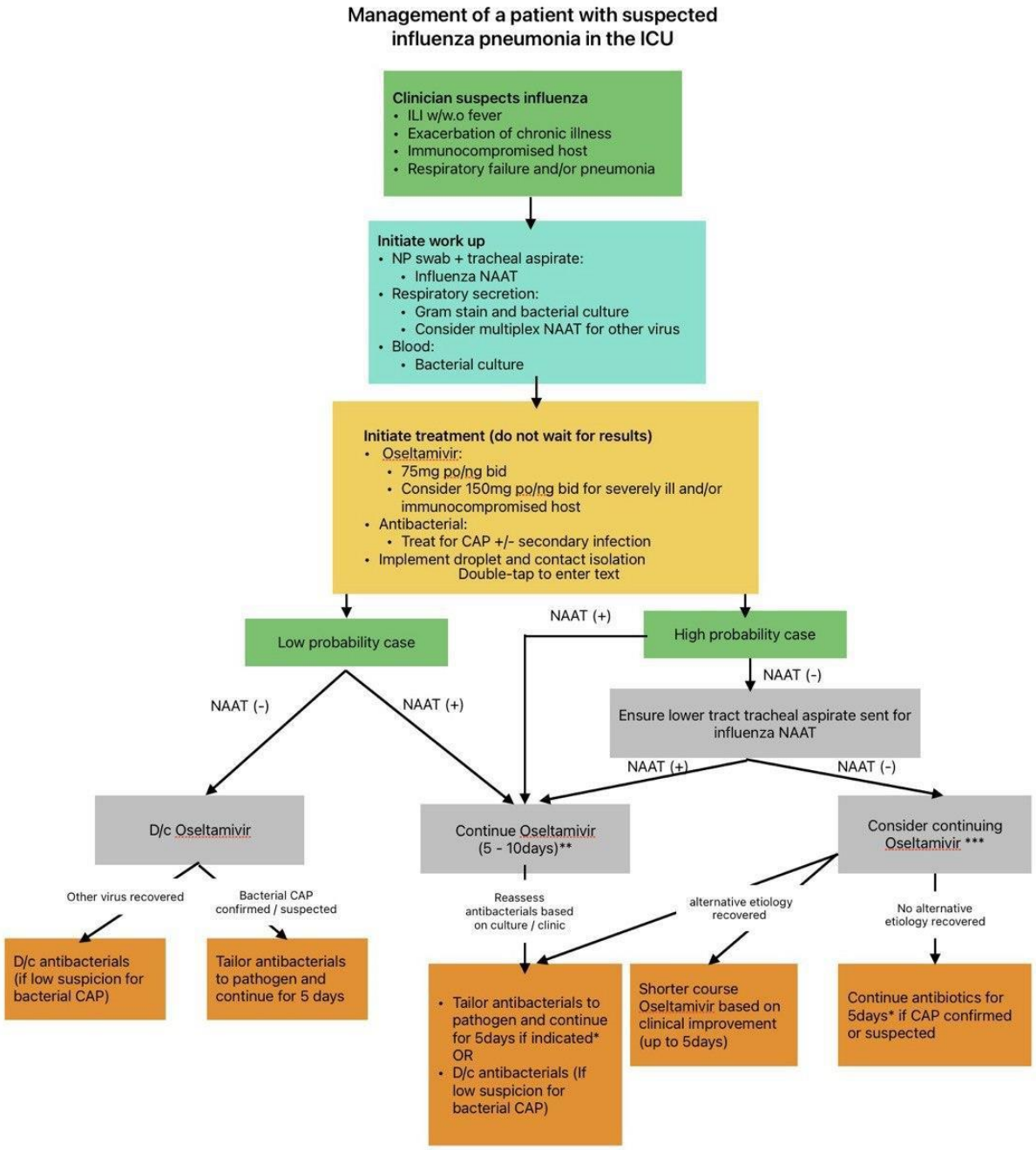
Septic shock

Septic shock is common in critically ill patients with influenza and typically results in refractory hypotension and need for moderate to high doses of vasopressors. For fluid resuscitation, the patient should receive at least 30 mL/kg of crystalloid via bolus dosing. Avoid volume overload by judicious use of diuretics.

Acute kidney injury

The development of AKI often necessitates renal replacement therapy (hemodialysis) to correct bicarbonate deficiencies to allow for increased tolerability of hypercapnia when poor lung compliance prohibits effective ventilation.

7. Algorithm
(adapted from: Textbook of Critical Care, 8TH EDITION, Jean-Louis Vincent, MD, PhD)



* A longer course may be needed if CAP is complicated by meningitis, endocarditis, or other deep-seated infection; suspected or proven MRSA or P. aeruginosa pneumonia may require a 7-day treatment course; less common specific pneumonia pathogens may require longer courses (e.g., Mycobacterium tuberculosis, Burkholderia pseudomallei).

** Because of prolonged viral shedding with primary influenza pneumonia, treatment durations longer than 5 days may be warranted, particularly for ARDS, immunocompromised, and/or severely ill patients, to a maximum of 10 days.
*** Results of most NAAT testing are highly sensitive and very highly specific. If influenza is highly suspected clinically during times of high influenza activity and NAAT results are negative, the NPV remains low, and a negative NAAT may reflect a false-negative result. If symptoms present >4 days, diagnostic yield is lower and may also result in a false-negative.
CAP, Community-acquired pneumonia; d/c; discontinue; ILI, influenza-like illness; NAAT, nucleic acid amplification test; NP, nasopharyngeal.

VIII. SPECIAL CASES

- Pediatric Considerations for antiviral
  Pediatric treatment is weight-based; safety and efficacy not established for children <1 year of age
  Oseltamivir 30 mg PO BID for 5 days ≤15 kg
  Oseltamivir 45 mg PO BID for 5 days 16 to 23 kg
  Oseltamivir 60 mg PO BID for 5 days 24 to 40 kg
  Oseltamivir 75 mg PO BID for 5 days >40 kg
- Renal impairment
  Creatinine clearance (CrCl)
  More than 61 mL/min.: Usual dose (75mg PO, BID)
  30-60 mL/min: 75 mg PO once daily or 30mg PO twice daily (or once daily for prophylaxis)
  10-30 mL/min: 30mg PO once daily (or every other day for prophylaxis)
  Dosing in hemodialysis:
  30 mg post-HD session (treatment), 30 mg every other HD session (prophylaxis)
  Dosing in CRRT: Limited data; can consider 75mg PO q 12 - 24 hours.
- Hepatic impairment: no dosage adjustment needed
- Pregnancy Considerations
  Oseltamivir is pregnancy Category C.
  Use only if potential benefits outweigh possible risk.
  Unknown secretion in breast milk

IX. EVOLUTION AND PROGNOSIS

Most hospitalized patients have risk factors. However, approximately half of hospitalized patients during pandemic years might otherwise be healthy.
Whereas most patients with influenza do not develop critical illness, 11%–19% of patients hospitalized with laboratory-confirmed influenza require treatment in the ICU. Those who develop critical illness often deteriorate rapidly, and severe illness may be protracted. For patients requiring mechanical ventilation, the mean duration is approximately 5–12 days. Many patients are difficult to oxygenate, leading to increased length of ICU stay and excess mortality. H5N1 human disease: among more than 1000 cases since 2013 in 21 countries; mortality rate of 40-61%. Mean age 16 yrs; rare deaths in people >40 yrs.

X. Complications

- Secondary bacterial pneumonia, ARDS
- Sepsis, septic shock and multiorgan dysfunction
- Myocarditis, dysrhythmia, myocardial infarction

- Acute kidney injury
- Encephalitis

XI. REVENTION AND RECOMMENDATION

Influenza is transmitted from person-to-person primarily through large-particle respiratory droplets; thus, patients with suspected influenza should be instructed to use appropriate hand hygiene, cough etiquette, and be given a face mask to wear upon entry into healthcare facilities. Patients who must be transported outside of the room should wear a mask if tolerated, or when necessary, an oxygen delivery system that limits the spread of aerosols (mask over cannula of HFNC).

Influenza vaccination is the best way to prevent or mitigate the severity of influenza illness, and in the absence of contraindications, is recommended annually, particularly those with risks for severe disease and for HCP. Vaccination and postexposure chemoprophylaxis are recommended for close contacts who are at very high risk of influenza complications.

Healthcare personnel (HCP) should apply droplet precautions by wearing standard surgical tie masks and use appropriate hand hygiene. HCPs should also consider contact precautions with gloves when anticipating contact with bodily fluids or touch with contaminated surfaces. Protective eyewear is recommended when providing direct care in close proximity to the patient. Ill HCPs with fever and respiratory symptoms should be instructed not to work until fever has dissipated for >24 hours.

XII. REFERENCES

1. Clinical care for severe acute respiratory infection: toolkit, update 2022. COVID-19 adaptation. WHO/2019-nCoV/SARI_toolkit/2022.1
2. Sylvain A. Lother, Anand Kumar, Steven M. Opal; influenza and acute viral syndromes in Textbook of Critical Care, Jean-Louis Vincent, MD, PhD, 8TH EDITION Elsevier

SNAKE BITES

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I. OVERVIEW

In Cambodia, among more than 86 known species, 17 species were known to be venomous. There are 11 species of important clinical interests. There are 2 main families of venomous snake in Cambodia. The Elapidae, has short and fixed front fang round eyes. Look from above; their head are mostly trapezoid form. This family includes cobras, king cobra, krait and sea snake, their venom contains mostly neurotoxic effect. The Viperidae has long and moveable fang, their eyes are oval, look from above; their head are mostly triangle. Some of species in this family has thermo-sensor organ. It counts pit vipers, Russell's viper. Their venom is mostly hematotoxic and myotoxic.

Common venomous snakes in Cambodia

Latin name	English name	Cambodian name
Ophiophagus hannah	King cobra	ពស់វែកឬស្សៃម
Naja kaouthia	Monocellate cobra	ពស់វែកប្របី
Naja siamensis	Indo-Chinese spitting cobra	ពស់វែកដំបូក
Bungarus flaviceps	Red headed krait	ពស់ក្រាយក្បាលក្រហម
Bungarus fasciatus	Banded krait	ពស់ក្រាយបង្គងលឿងខ្មៅ
Bungarus candidus	Malayan krait	ពស់ក្រាយបង្គងសខ្មៅ
Laticaudinae	Sea snakes	ពស់សមុទ្រ
Cryptelytrops albolabris	White-lipped green pit viper	ពស់ហនុមាន
Cryptelytrops macrops	Big eyed pit viper	ពស់ខ្យែវភ្នែកធំ
Viridovipera vogeli	Vogel's pit viper	ពស់ខ្យែវ
Daboia siamensis	Indo-Chinese Russell's viper	ពស់ស្រកាចាស់
Calloselasma rhodostoma	Malayan pit viper	ពស់ពញាក់

- Elapidae family



King cobra



Monocellate cobra



Indo-Chinese spitting cobra



Red headed krait



Banded krait



Malayan krait



Sea snake

- Viperidae family



White-lipped green pit viper



Big eyed pit viper



Vogel's pit viper



Russell's viper



Malayan vit viper

II. EPIDEMIOLOGY

It is generally recognized that the epidemiology of snakebite in the South-Est Asia Region has not been adequately studied and that the published data, based almost exclusively on hospital return to the ministry of health, therefore misleading. One reason is that many snakebite victims are treated not in hospital but by traditional healers. The incidence of snakebite varies diurnally and seasonally. It is highest during agricultural activities and seasoning rains. Male are more often bitten than female.

WHO classified venomous snakes in 2 categories:

- Category 1: Highest medical importance – highly venomous snakes which are common or widespread and cause numerous snakebites, resulting in high levels of morbidity disability or mortality
- Category 2: secondary medical importance – highly venomous snake capable of causing morbidity, morbidity, disability or death, but for which exact epidemiological or clinical data are lacking or are less frequently implicated because of their behavior, habitat preferences or occurrence in areas remote to large human, populations

Category 1	Viperidae	- white-lipped green pit viper - big eyed pit viper - Vogel's pit viper
	Elapidae	- Monocellate cobra - Indochinese spitting cobra - Malayan krait.
Category 2	Viperidae	- Malayan pit viper - Russell's viper
	Elapidae	- Banded krait - Red-headed krait, - king cobra.

III. ETIOLOGY

Most often, snake bite is an occupational disease. People get bite at work on the rice field (cobra, Malayan pit viper, Russell's viper) on rubber/palm plantation (Malayan pit viper, green pit viper). The other jobs that predisposing people to snake bite are hunting, fishing, and fishing farming, catching and handling snakes for food, displaying and performing with snakes (cobra). Sometime the bite is the result of trodden upon sleeping snake.

IV. PATHOPHYSIOLOGY

Snakebite may cause "clinical syndrome" that is specific and non-specific. The bites may accompany by a varying degree of envenoming or no envenoming at all. Clinical patterns are related to venom of causal snake.

Composition and antigenicity of snake venoms is more than 90% of snake venom (dry weight) is protein. Each venom contains more than a hundred different proteins:

- Enzymes (constituting 80-90% of viperid and 25-70% of elapid venom):
  - Snake venom metalloproteases (SVMPs) damage basement membranes, causing endothelial cell damage and spontaneous systemic bleeding.
  - Procoagulant enzymes stimulate blood clotting with formation of fibrine on blood, causing platelet aggregation, anticoagulation and hemorrhage.
  - Phospholipases A2 damage mitochondria, red blood cells, leucocytes, platelets, peripheral nerve ending, skeletal muscle, vascular endothelium and other membranes, producing presynaptic neurotoxic activity, cardiotoxicity, myotoxicity, necrosis, hypotension, hemolysis, anti-coagulation, hemorrhage, plasma leakage and auto pharmacological release of histamine and other autacoids.
  - Acetylcholinesterase may cause fasciculation.
  - Hyaluronidase: increasing permeability but can also contribute to damage cell tissue.
- Non-enzymatic polypeptide toxins: postsynaptic (□)neurotoxin and presynaptic (□) neurotoxin damage nerve ending irreparably.

- Non-toxic proteins such as growth factor.

V. DIAGNOSIS

1. Clinic presentation

Victim of snakebite may present with general nonspecific symptoms, specific symptoms for some types of snake venom, and sometimes, the consequences of disorders related to venom (anemia, renal failure, hypovolemic/cardiogenic shock, compartment syndrome…)

- Local symptoms and sign:
  - Fang marks
  - Local pain
  - Local bleeding
  - Bruising
  - Lymphangitis (raised red lines tracking up the bitten limb)
  - Lymph node enlargement
  - Inflammation (swelling, redness, heat)
  - Blistering
  - Local infection
  - Abscess formation
  - Necrosis
- Generalized(systemic) signs and symptoms
  - Syndrome related to Viperidae

Most of the species in the Viperidae family have venom that contains enzymes that interfere with blood clot and coagulation that produce hematologic disorder (i.e. ecchymosis, bleeding from the fang marks, bleeding from the cut wound, internal bleeding, increase the amount of menses…). Bleeding with or without hemolysis may be severe and lead to hemorrhagic shock and acute renal failure. Locally, pain is often severe, inflammation is important and rapidly expand, the blister may color black (Malayan pit viper, Russell's viper). Muscle tissue necrosis expand in depth and in surface with hyperkalemia and rhabdomyolysis.

  - Syndrome related to Elapidae

Most of the Elapidae snake venom contains neurotoxins that cause muscular paralysis (neurologic disorder). The death may result from respiratory muscle paralysis and respiratory arrest. The muscular group in the face is the first to be affected by neurotoxin, follow by neck and truck, when the respiratory muscle paralysis occurred. Ptosis or heavy eyelid is often the first sign of neurotoxin envenoming. Patient was looked like sleep; people has remarked that when that victim falls asleep, he will die.

All species in genres naja had neurotoxin alpha, the genre krait (Malayan krait, banded krait, red head krait, and sea snake) had neurotoxin alpha and neurotoxin beta. Disorders caused by neurotoxin beta, may be non-reversible or left neurologic sequelae after antivenom therapy. Other neurologic sign and symptoms are drowsiness, paraesthesiae, abnormalities of taste and smell, aphonia, regurgitation through the nose, difficulty in swallowing secretions, respiratory and generalized flaccid paralysis.

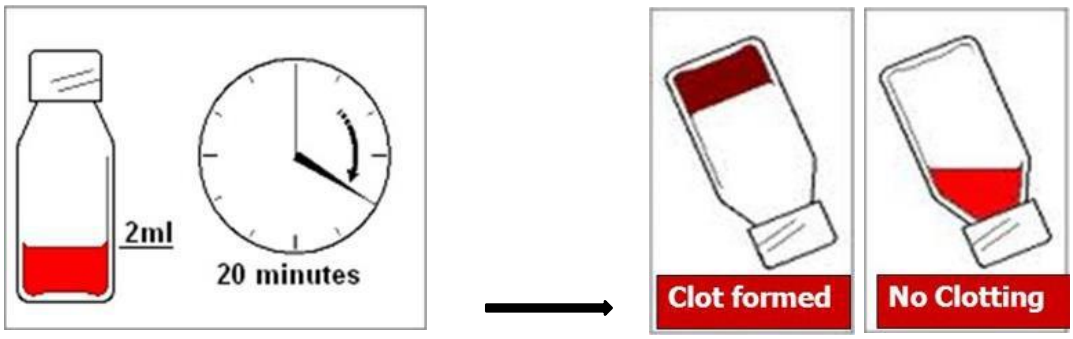
- Clinical syndrome
  - Syndrome 1: local sign (swelling etc.) with bleeding/clotting disturbances = Viperidae (all species)
  - Syndrome 2: local sign (swelling etc.) with bleeding/clotting disturbances, shock or acute kidney injury, dark brown urine bilateral ptosis, external ophthalmoplegia, fascial paralysis = Russell's viper, with conjunctival edema (chemosis) and acute pituitary insufficiency = Russell's viper and Malayan viper
  - Syndrome 3: local sign (swelling etc.) with paralysis = cobra or king cobra

- Syndrome 4: paralysis with minimal or no local sign:
  bitten on land while sleeping on the ground with/without abdominal pain = krait
  bitten in the sea = sea snake
- Syndrome 5: paralysis with dark brown urine and acute kidney injury:
  bitten on land (with bleeding/clotting disturbance) = Russell's viper
  bitten on land while sleeping indoor = krait
  bitten in the sea (no bleeding/clotting disturbance) = sea snake

2. Investigation and laboratory tests

- The 20-minute whole blood clotting test "20WBCT" or whole blood clotting test at 20 min. Positive test means that patient had been bitten by snake that mostly is in Viperidae family.
  Place 2 mL of freshly sampled venous blood in a small, new or heat cleaned, dry, glass vessel. Leave undisturbed for 20 minutes at ambient temperature. Tip the vessel once. If the blood is still liquid (unclotted) and runs out, the patient has hypofibrinogenemia ("uncoagulable blood") as a result of venom-induced consumption coagulopathy.

Clotting time using test tube method



- Other blood test help confirm envenoming: high hematocrit (plasmatic lose), anemia, low hematocrit (blood lose), acute leukocytosis (systemic envenoming), low platelet (coagulation abnormality), high potassium (rhabdomyolysis), abnormal liver function tests (systemic envenoming), respiratory acidosis (Arterial blood gas "ABG". Low function of respiratory muscle), high BUN, creatinine (acute renal failure).
- Other investigation: urine examination, chest X-ray, whole abdominal ultrasound, ECG, heart ultrasound, brain CT scan.
- Normally there is no need to wait for lab test results to start antivenom therapy, if clinical signs and symptoms are matched with envenoming or when the 20WBCT was positive.

VI. DIFFERENTIAL DIAGNOSIS

- Anaphylaxis
- Deep venous thrombosis
- Extremity vascular trauma
- Scorpion envenomation
- Septic shock
- Serum sickness
- Wasp stings
- Wound infection

VII. MANAGEMENT

1. Objective
   - Reassure the snakebite victim
   - Preserve life and prevent complication
   - Control distressing or dangerous early symptoms of envenoming
   - Arrange the transport of the patient to a place where they can receive medical care or more facility.
2. Critical sign

   Indication or criteria for antivenom treatment: antivenom treatment is recommended if and when a patient with proven or suspected snakebite develops one or more the following signs:

   a. Systemic envenoming:
   - Hemostatic abnormalities
   - Neurotoxic signs
   - Cardiovascular abnormalities
   - Acute kidney injury
   - Hemoglobin-/myoglobinuria: dark brown urine, rhabdomyolysis

   b. Local envenoming:
   - Local swelling involving more than half of the bitten limb
   - Rapid extension of swelling
   - Development of an enlarged tender lymph node draining the bitten limb.
3. Mortality risk factor

   Factors identified as distributing to a fatal outcome included
   - Availability, the right antivenom and dose of antivenom.
   - Delayed hospital treatment: transportation problem.
   - Inadequate of supported treatment: mechanic ventilation, hemodynamic treatment, renal replacement therapy.
4. Outpatient management
   - All envenomed patients should be managed in hospital
   - The traditional measure (tourniquet, cut the wound, suction on the wound, local application of ‘medicine’, burning point) are not effective and in some case, it may be dangerous.
5. First-line treatment

   A. First aid
   - Reassure the victim who may be very anxious
   - Immobilize the whole of the patient’s body by lying him/her down in a comfortable and safe position
   - Apply pressure-pad immobilization, pressure-bandage immobilization
   - Avoid any interference with the bite wound.

   B. Treatment in hospital
   - Rapid primary clinical assessment and resuscitation
   - Airway potency, respiratory movements, arterial pulse and level of consciousness must be immediately checked. Conditions that need immediate assessment and management are: shock syndrome from direct venom effect, or secondary to hypovolemia (bleeding), or by arrythmia secondary to hyperkaliemia (Rhabdomyolysis). Respiratory arrest, central acute respiratory failure (Elapidae). Sudden deterioration and systemic toxic pattern immediately after removing the tight tourniquet and compressed bandage.

C. Medication

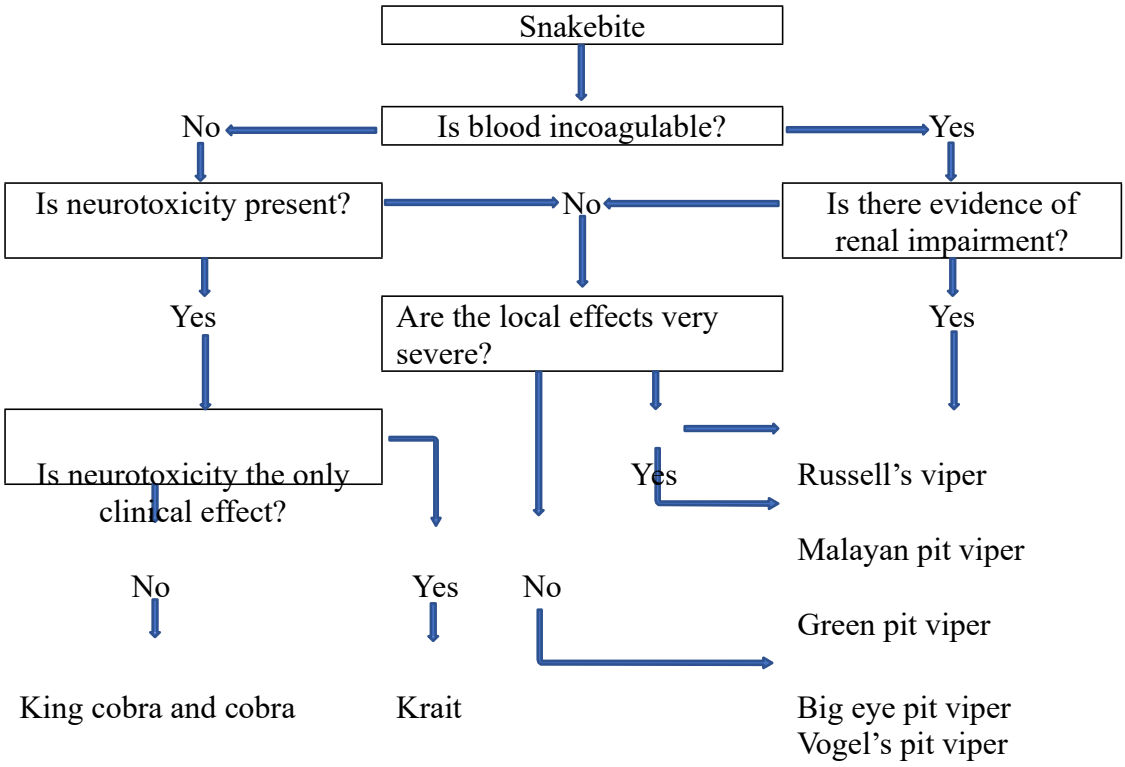
- Actually (2011), the available anti-venom are the 2 polyvalent anti venoms made in Thailand.
  - "TRC Neuro-polyvalent snake" can cover the venoms of neurotoxic Elapidae and
  - "TRC Hemato-polyvalent snake"cancover the venoms of hematotoxic Viperidae
  - Normal saline solution is added in 1 vial to make a 10mL solution. The total amount of anti-venom solution needed can be administrated in slow IV injection (max. 2mL/minute) or by IV infusion diluted in about 5mL isotonic fluids per Kg body weight (i.e. about 250mL of isotonic saline or 5% dextrose in case of an adult patient) and infuse in 30-60 minutes.
- The route of administration is intra venously
- No test needed prior to injection, but be prepared the emergency treatment of anaphylactic reactions (adrenaline, bag-valve mask, infusion set, anti-histamine, corticoid)
- The initial dose is usually empiric and varies with species and with the clinical severity
- Guide to initial dosage for some antivenoms for treating bites by medically-important snakes in South-East Asia region, based on clinical experience, rather than antivenoms' recommendation.

English name	Antivenoms	Appropriate average initial dose
King cobra	TRC* Neuro-polyvalent	10 vials
Monocellate cobra	TRC* Neuro-polyvalent	10 vials
Indo-Chinese spitting cobra	TRC* Neuro-polyvalent	10 vials
Red headed krait	TRC* Neuro-polyvalent	10 vials
Banded krait	TRC* Neuro-polyvalent	10 vials
Malayan krait	TRC* Neuro-polyvalent	10 vials
Sea snakes	TRC* Neuro-polyvalent	1-10 vials
White-lipped green pit viper	TRC* Hemato-polyvalent	3-5 vials
Big eyed pit viper	TRC* Hemato-polyvalent	3-5 vials
Vogel's pit viper	TRC* Hemato-polyvalent	3-5 vials
Indo-Chinese Russell's viper	TRC* Hemato-polyvalent	3 vials
Malayan pit viper	TRC* Hemato-polyvalent	3 vials

*Thai Red Cross, Queen Saovabha Memorial Institute,Bangkok,Thailand, www.snake-anti-venin.com/

- Children and pregnant woman must therefore be given exactly the same dose of antivenom as adult
- No absolute contraindication to antivenom treatment.

6. Treatment adjustment
   A. Antivenom treatment can be expected to neutralize free circulating venom, prevent progression of envenoming and allow recovery. However, these processes take time and the severely envenomed patient may require life support system such as reduction of pain, treatment of shock, assisted ventilation and renal dialysis until the severely damaged organs and tissue have had time to recover.
   B. Treatment of the bitten part
      - Wound management: wound dressing.
      - Bacterial infection: gentamicin with benzyl penicillin, amoxicillin or cephalosporin plus a single dose only of gentamicin plus metronidazole and tetanus prophylaxis.
      - Compartmental syndromes and fasciotomy: fasciotomy should not be contemplated until hemostatic abnormalities have been corrected, otherwise the patient may bleed to death.
7. Algorithm: Recognize species via clinicals/symptoms



VIII. SPECIAL CASES

In case antivenom reaction

- Epinephrine (Adrenaline) is given intramuscularly in an initial dose of 0,5 mg for adult, 0,01 mg/kg body weight for child, can be repeated every 5-10 minutes if the reaction persists or the symptoms become worse
- Additional treatment: inhaled short acting 2 agonist bronchodilator such as salbutamol or terbutaline, antihistamine anti-H1 blocker such as chlorphenamine maleate (adult 10mg, children 0,2 mg/Kg by intravenous injection), intravenous hydrocortisone (adult 100 mg, children 2mg/kg)

IX. EVOLUTION AND PROGNOSIS

Observation of the response to antivenom, in general the patient feel better quickly, spontaneous systemic bleeding usually stops within 15-30 minutes, blood coagulability (as measured by 20WBCT) is usually restored in 3-9 hours, in shocked patient blood pressure may increase within the first 30-60 minutes and arrythmia, bradycardia may resolve, neurotoxic envenoming may begin to improve as early as 30 minutes after antivenom but may take several times.

Criteria for giving more antivenom include a persistence or recurrence of blood incoagulability after 6 hours or of bleeding after 1-2 hours, deteriorating neurotoxic or cardiovascular signs after 1 hours.

The reversibility of toxic effect depends on time of treatment, correct choice of antivenoms, sufficient doses givens. Effects against hematologic disorder (viperidae) still exist even 1 week after bite. Toxic effects may be reserved in a few hours or few days.

X. COMPLICATION

- At the site of the bite, loss of tissue: surgical debridement, necrotic areas, amputation, malignant transformation
- Chronic kidney disease (renal failure)
- Chronic neurological deficit
- Abnormalities of electrophysiological test can persist for over 12 months following elapid bites.
- Delayed psychological morbidities: depression, anxiety, post-traumatic stress disorder (PTSD)

XI. PREVENTION AND RECOMMENDATION

- Be prepared to protect again snake bite when working in the field, sleeping, or walking in the forest.
- Community education reduces the risk of snakebite. Involve all the community workers, traditional healers, villagers. Distribute leaflets, banners, posters, video clips, displayed in hospital or clinic waiting areas and disseminate them via the radio, TV and social network.
- Be informed of signs and symptoms of envenoming and seeking medical care immediately when they got it.
- The difficulty to open the eyes (looks like sleepy) after snake bite is alarming sign of respiratory arrest, and should prompt patient to go to hospital
- Bleeding disorder, purpura, ecchymoses, can be treated medically, if left longer it may kill the patient.

XII. REFERENCES

1. Clinical practice guideline for medicine, Cambodia, 2013, snakebite, p.60-67
2. Guideline for management of snakebite, 2nd edition, 2016, WHO regional office South-Est Asia
3. David J Williams, Simon D Jensen, Mark O'Shea, editors. Snakebite management in Cambodia 2009.
4. Guideline for the management of snakebite South-East Asia region, WHO 2005, p.61
5. https://emedicine.medscape.com/article/168828-differential
6. Malaysian guideline, management of snakebite

MASSIVE BLOOD TRANSFUSION

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I. DEFINITION

Common definitions for massive transfusion in adults include:

- transfusion of ≥ 10 red blood cell (RBC) units within 24 hours or
- transfusion of > 4 RBC units in 1 hour with anticipated need for further blood product transfusion or
- replacement of > 50% of total blood volume (TBV) by blood products within 3 hours (remember that a female height 160cm has TBV = 70 x54 ~ 3780 ml)

Common definitions for massive transfusion in children and adolescents include

- transfusion of > 100% of TBV within 24 hours
- transfusion support to replace ongoing hemorrhage of > 10% TBV/minute
- replacement of > 50% TBV by blood products within 3 hours.

The general estimate TBV for pediatric patients is about 80 ml per kg of body weight. Here's a quick breakdown:

- Neonates (0-28 days): Approximately 85-90 ml per kg
- Infants (1 month to 1 year): Approximately 75-80 ml per kg
- Children (over 1 year): Approximately 70-80 ml per kg)

II. INDICATION

massive transfusion may be implemented in both trauma and non-trauma clinical settings

- Common trauma events leading to massive bleeding include:
  - penetrating trauma such as knife or gunshot wound
  - blunt trauma to chest or abdomen
  - suicide attempts
  - amputations
  - bone fractures that result in further injury to internal organs and blood vessels
  - shearing of existing injury from sudden rotation and violent extension and flexion
- Non-trauma settings for massive bleeding include
  - obstetric hemorrhage
  - gastrointestinal bleeding
  - surgical complications
  - vascular emergencies, such as ruptured abdominal aortic aneurysm

III. BLOOD PRODUCTS IN CLINICAL USE

Component	Content	Indication and dose
Whole blood (1 unit = 500 mL) *	RBCs, platelets, plasma	Rarely required. May be appropriate when massive bleeding requires transfusion of more than 5 to 7 units of RBCs (increasingly used in early trauma management).
RBCs in additive solution (1 unit = 350 mL), [pRBC]	RBCs	Anemia, bleeding. The increase in hemoglobin from 1 unit of RBCs will be approximately 1 g/dL; the increase in hematocrit will be approximately 3 percentage points.
Fresh Frozen plasma (FFP) or other plasma product (1 unit = 200 to 300 mL)	All soluble plasma proteins and clotting factors	Bleeding or expected bleeding (e.g., emergency surgery) in individuals with deficiencies of multiple coagulation factors (e.g., DIC, liver disease, massive transfusion, anticoagulation with warfarin or warfarin overdose if not corrected by vitamin K and/or PCC, depending on the clinical setting). Bleeding in individuals with isolated factor deficiencies (most often factor V) if a factor concentrates or recombinant factor is not available. Therapeutic plasma exchange in TTP (as a source of ADAMTS13). In the rare event that FFP is used to replace a clotting factor, the dose is 10 to 20 mL/kg. This dose will raise the level of any factor, including fibrinogen, by close to 30%, which is typically sufficient for hemostasis.
Cryoprecipitate, also called "cryo" (1 unit = 10 to 20 mL)	Fibrinogen; factors VIII and XIII; VWF	Bleeding patients with acquired hypofibrinogenemia, which may be due to cardiac surgery, liver transplant, postpartum hemorrhage, or trauma with massive transfusion. DIC. Uremia if DDAVP (desmopressin) is ineffective. The increase in plasma fibrinogen from 1 unit of Cryoprecipitate per 10 kg body weight will be approximately 50 mg/dL. Cryoprecipitate is generally provided in pools containing 5 units, and most patients receive 1 to 2 pools.

Platelets (derived from whole blood or apheresis) (1 unit of apheresis platelets or a 5 to 6 units pool of platelets from whole blood = 200 to 300 mL)	Platelets	The platelet count increase from 5 to 6 units of whole blood- derived platelets or 1 unit of apheresis platelets will be approximately 30,000/microL in an average-sized adult.

DIC: disseminated intravascular coagulation; FFP: Fresh Frozen Plasma; PCC: prothrombin complex concentrate; RBCs: red blood cells; TTP: thrombotic thrombocytopenic purpura; VWF: von Willebrand factor.
* 450 mL blood and 63 mL citrate-phosphate-dextrose (CPD) anticoagulant-preservative solution.

IV. EFFECTS OF MASSIVE HEMORRHAGE (OTHER THAN HYPOVOLEMIA)

Changes Occurring as a Result of Massive Hemorrhage

- the lethal triad in trauma includes coagulopathy, acidosis, and hypothermia
  - acute coagulopathy of trauma-shock
    - also known as trauma-induced coagulopathy, acute traumatic coagulopathy, acute coagulopathy of trauma, trauma-associated coagulopathy.
    - may occur within 30 minutes of severe injury - prior to red blood cell (RBC) transfusion and fluid resuscitation
    - tissue injury from trauma or surgery leads to local and subsequent systemic release of tissue factor leading to initiation of coagulation pathway and massive disseminated intravascular coagulation (DIC)
    - hypoperfusion due to massive hemorrhage leads to expression of thrombomodulin in endothelial cells and formation of thrombin-thrombomodulin complex, resulting in
      - activation of protein C, leading to inactivation of factor Va and VIIIa, and enhancement of fibrinolysis by consumption of plasminogen activator inhibitor and increase in plasmin formation
      - inactivation of thrombin-activatable inhibitor (TAFI), leading to further hyperfibrinolysis
    - The acute coagulopathy of trauma shock is a disease entity similar to or same as DIC with fibrinolytic phenotype, with possible exception that trauma-shock uniquely activates the thrombomodulin and protein C pathway.
  - acidosis
    - initial appearance may indicate tissue hypoperfusion further contributes to coagulopathy due to:
      - change in platelet shape at pH < 7.4
      - inhibition of thrombin generation at pH < 7.1
      - acceleration of fibrinolysis
  - hypothermia
    - defined as core body temperature < 35 degrees C

    - may occur in patients having trauma or elective surgery as a result of abnormal thermoregulatory control due to general anesthesia and opening of body cavities
    - effects include abnormal platelet function and coagulopathy, enzyme inhibition, and fibrinolysis
- Exacerbation of Coagulopathy as a Result of Massive Transfusion
    - dilution of clotting factors and platelets due to transfusion of red blood cell (RBC) units
    - acidosis may occur due to normal saline administration and toxicity from citrate present as anticoagulant in stored blood products
    - hypothermia as a result of administration of fluids below body temperature
    - hypocalcemia from citrate in storage solution that contributes to decrease in platelet-related activities
    - severity of coagulopathy is modified by patient-related factors including
        - age
        - comorbidities
        - inflammation
        - genetic background
        - premedication (especially oral anticoagulants)
        - pre-hospital admission fluid administration

V. EVALUATION

Findings commonly associated with bleeding patients requiring future massive transfusions include ≥ 1 or more of the following:

- INR > 1.5
- systolic blood pressure < 90 mm Hg
- hemoglobin (Hb) < 11 g/dL (< 110 g/L)
- Base deficit (BD) ≥ 6 mEq/L (≥ 6 mmol/L)
- positive focused assessment for the sonography (FAST) of trauma
- heart rate ≥ 120 beats/minute

Routine assays include hematocrit (Hct), Hb, platelet count, and assays for coagulopathy (including prothrombin time [PT], activated thromboplastin time [aPTT], INR, and fibrinogen measurement).

Viscoelastical hemostatic assays, including thromboelastography and rotational thromboelastometry, are emergency room or bedside point-of-care assays that use whole blood within minutes of collection, and therefore have shorter turn-around time compared to routine assays.

Complications of massive transfusion include transfusion-related lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion reactions, and electrolyte abnormalities

VI. MANAGEMENT

- The ultimate goal of massive transfusion is to maintain sufficient circulation and hemostasis in patients with massive hemorrhage.
- In an emergency, provide group O red blood cell (RBC) and AB plasma until patient blood type is determined and patients can receive crossmatched RBC and AB-compatible plasma.
- Massive transfusion protocol (MTP) should be implemented to optimize management and delivery of blood products.

VII. MASSIVE BLOOD TRANSFUSION (MBT) PROTOCOL

MTPs may involve predetermined ratio-driven transfusion or goal-directed transfusion protocols or combination of both, but most current MTPs use ratio-driven transfusion protocol followed by goal-directed strategy as laboratory information becomes available.

General Concepts

- massive transfusion protocol (MTP) should facilitate communication between departments and services to deliver rapid clinical care
- MTPs may involve ratio-driven transfusion or goal-directed transfusion protocols or combination of both, but most current MTPs use ratio-driven transfusion protocol
- MTPs should include
    - timing and personnel involved in the activation of MTP notification of start and stop of protocol to transfusion service and laboratory
    - definition of laboratory testing parameters used to predict need for massive transfusion blood product preparation and delivery, including predetermined transfusion packages
    - patient identification protocol to avoid ABO incompatible transfusion errors
    - other patient care needs (for example, blood warmers)
- American College of Surgeons Trauma Improvement Program (ACS TQIP) recommendations
    - during early stages of resuscitation, transfuse universal red blood cell (RBC) and plasma in a ratio between 1:1 and 2:1
    - once laboratory data are available, use goal-directed resuscitation
    - transfusion may be discontinued or downgraded to goal-oriented transfusion if bleeding is under control
- Task Force of Advanced Bleeding Care in Trauma recommendations
    - for initial management of patients with expected massive hemorrhage 1 of 2 following
    - strategies should be considered
        - fresh frozen plasma (FFP) in a plasma:RBC ratio of at least 1:2 as needed
        - Fibrinogen concentrate and RBC
    - switch to goal-directed strategy as laboratory information becomes available; goals for various blood components
        - transfuse RBC to maintain Hb > 7-9 g/dL (70-90 g/L) (ABC-T Grade 1C)
        - FFP
            - transfuse FFP to maintain prothrombin time (PT) and activated thromboplastin time (aPTT) < 1.5 × normal control or if viscoelastic hemostatic assay results suggest coagulation factor deficiency
            - avoid use of FFP in patients without major bleeding or for treatment of hypofibrinogenemia
        - administer fibrinogen or cryoprecipitate if significant bleeding associated with viscoelastic signs of functional fibrinogen deficiency or plasma fibrinogen level < 150 mg/dL (1.5 g/L)
        - transfuse platelets to maintain platelet count > 50×10^9/L or > 100×10^9/L in patients with ongoing bleeding or traumatic brain injury.
        - coagulation factor concentrates

- if used, treat based on routine laboratory coagulation testing and/or viscoelastic evidence of functional coagulation factor deficiency.
- prothrombin complex concentrate may be indicated for bleeding patients with delayed initiation of coagulation as evidenced by viscoelastic monitoring.
- consider monitoring factor FXIII activity and if deficient, supplement in patients who are bleeding

Ratio-driven Transfusion

- uses predetermined ratio of red blood cells (RBCs), plasma, and platelets
- administration of fixed ratio of RBC to plasma to platelets at 1:1:1 (initially proposed by the United State military and subsequently used in both military and civilian settings, with rationale that is more closely resembles whole blood)
- more commonly incorporated in MTPs than goal-directed transfusion
- treats coagulopathy early in resuscitation (< 6 hours of admission) while decreasing use of crystalloids and RBCs
- no delay in preparation and delivery of blood products
- may be discontinued or downgraded to goal-oriented transfusion if bleeding is under control

Goal-directed Transfusion

- uses laboratory results and clinical findings to guide blood product administration choices, volumes, and timing until target test values are achieved.
- requires use of laboratory tests that are timely and provide enough information on patient coagulation profile.
- viscoelastical hemostatic assays such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM) results may be helpful in guiding transfusion

Special Populations

Obstetric Hemorrhage

- for patients with major obstetric hemorrhage, consider ratio-driven transfusion (for example, 6:4:1 ratio of RBC to plasma to platelet units)
- hyperfibrinolysis is common; monitor closely for fibrinogen level and consider early transfusion of fibrinogen concentrate or cryoprecipitate
- tranexamic acid administration may decrease blood loss at the time of cesarean section and risk of progression to severe obstetric hemorrhage
- fibrinogen level < 200 mg/dL independently associated with severe bleeding

Pediatric Patients

- having pediatric patient-specific MTP may be beneficial but could be logistically difficult to create in institutions without free-standing children's hospital
- data on successful management of massive transfusion in children and neonates is limited, and optimal transfusion protocol is not clear.

Patients in Surgical Settings

- American Society of Anesthesiologists suggests use of MTP implemented by individual institution.

- consider that patients having cardiac surgery may have had preoperative administration of anticoagulants or antiplatelets, and on-pump heparin that may also contribute to impaired hemostasis.

Patients in Combat Settings

- administration of fixed ratio of RBC to plasma to platelet at 1:1:1 initially proposed by the United States military and continues to be used in both military and civilian settings
- administration of fresh whole blood is used in cases when apheresis platelet products are not available
    - transfusion-transmitted infections and transfusion-associated graft-versus-host disease may be a concern

Monitoring

- termination of transfusion with blood products if further transfusion is futile
- discontinuation of ratio-driven massive transfusion or downgrade to goal-oriented transfusion if either
    - surgical bleeding has been controlled
    - radiographic or physiologic indication of bleeding control after angioembolization
- discontinuation of goal-oriented blood product transfusions based on laboratory test values (including routine laboratory tests and/or viscoelastical hemostatic assays) if patient is not actively bleeding and still in the acute resuscitation phase.

Guide to Laboratory Target Values for Goal-Directed Transfusion*

Test	ABC-T target Value	ACS TQIP Target Values	Case transfusion
Hemoglobin level	≥7-9g/dL	≥ 10g/dL	RBCs
Prothrombin time	<1.5xNormal	< 18seconds	Plasma
Activated partial thromboplastin time	<1.5xNormal	< 35seconds	Plasma
Platelet count	$>50x10^9$ or $>100x10^9$ if ongoing bleeding and/or TBI	$>150x10^9$/L	Platelets
Fibrinogen level	≥150 mg/dL	> 180 mg/dL	Cryoprecipitate or fibrinogen concentrate

* ACS TQIP: American College of Surgeons Trauma Quality Improvement Program, ABC-T, Task force for Advanced Bleeding Cared in Trauma

VIII. COMPLICATIONS OF MBT

1. complications arising from rapid transfusion of large volume of fluids during massive transfusion include:
    - exacerbation of coagulopathy
    - metabolic complications—
        - complications due to citrate in blood product storage solution include
            - hypocalcemia - neonates and patients with liver disease may be at higher risk
            - acidosis_may be more sever and difficult to treat in patients with liver failure who cannot metabolize citrate to bicarbonate or process lactate
            - metabolic alkalosis occurs as a result of increase in blood pH as citrate is metabolized to bicarbonate.

        - hypomagnesemia - due to transfusion of magnesium poor solutions in addition to citrate overload
    - hyperkalemia
        - due to increase in potassium concentration as a result of red blood cell (RBC) membrane (adenosine triphosphatase) ATPase pump inactivation and hemolysis of RBCs in storage and/or irradiation
        - neonates, patients with cardiac and renal insufficiency and tissue injury at higher risk
    - hypokalemia due to
        - restoration of RBC membrane ATPase pump and potassium uptake by RBCs
        - release of aldosterone, antidiuretic hormone, and catecholamines
        - co-transfusion of low potassium solutions such as platelets, plasma, and crystalloids
    - hypothermia
        - due to rapid infusion of blood products in cold storage
        - infants and neonates at higher risk
    - transfusion-related acute lung injury (TRALI) - acute lung injury that occurs within 6 hours of transfusion and not related to other causes of acute lung injury or acute respiratory distress syndrome
    - transfusion-associated circulatory overload (TACO)
        - hydrostatic pulmonary edema
        - patients with cardiac disease and infants at higher risk
2. Other complications arising from transfusion of blood products include
        - allergic reaction
        - hemolytic transfusion reaction (acute and delayed)
        - febrile nonhemolytic transfusion reaction
        - transfusion-related immunomodulation
        - transfusion-associated graft-versus-host disease
        - posttransfusion purpura
        - infection
        - air embolism

IX. PROGNOSIS

- Mortality reported in
    - 39% of patients having ≥ 10 red blood cell (RBC) units during hospital stay (2.6% of all patients with trauma)
    - 57% of patients having ≥ 50 units of blood products in first 24 hours (0.6% of all patients with trauma)

X. REFERENCES

1. DynaMed. Massive Transfusion. EBSCO Information Services. Accessed December 27, 2024. https://www.dynamed.com/procedure/massive-transfusion
2. UpTodate. Massive Blood transfusion. Wolters Kluwer online platform. Accessed December 27, 2024. https://www.uptodate.com/contents/massive-blood-transfusion

CHAPTER II CARDIOLOGY

1. Acute coronary syndrome, ST-elevation myocardial infarction
2. Acute coronary syndrome, non-ST-elevation myocardial infarction
3. Chronic coronary syndrome
4. Emergency tachycardia
5. Emergency bradycardia
6. Pulmonary embolism
7. Acute pulmonary edema
8. Hypertension
9. Chronic heart failure
10. Aortic regurgitation
11. Aortic stenosis
12. Management of aortic aneurysms
13. Mitral regurgitation
14. Mitral stenosis
15. Management and surveillance of prosthetic valves
16. Deep venous thrombosis
17. Prevention of deep venous thrombosis
18. Infectious endocarditis
19. Pericarditis
20. Constrictive pericarditis
21. Pregnancy and heart diseases
22. Cardiovascular drugs and pregnancy
23. Cardiac evaluation before non-cardiac surgery

ACUTE CORONARY SYNDROME
ST-ELEVATION MYOCARDIAL INFARCTION(STEMI)

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I. DEFINITION

ACS is the clinical spectrum of unstable ischemic heart disease ranging from unstable angina (UA), Non-ST segment Elevation Myocardial Infarction (NSTEMI) to STEMI depending upon the degree and acuteness of coronary occlusion.

STEMI is ACS with persistent ST-segment elevation or new left bundle-branch block.

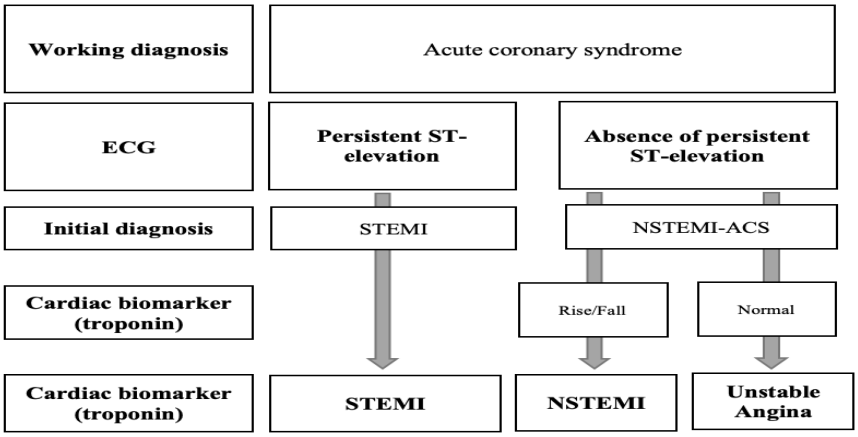


Fig. 1 Classification of acute coronary syndrome

II. EPIDEMIOLOGY

- Most recent data from WHO in 2019, ischemic heart disease (IHD) was the principal cause of death (62,22 per 100 000 population) in Cambodia.
- In Cambodia:
    - Mean age: 59,71 years
    - Female: 26,3%
    - In-hospital mortality: 11,14% (PCI: 4,7% vs non-PCI: 15,73%)
    - Primary PCI rate: 78%

III. ETIOLOGY

Acute coronary syndrome (ACS) cause by the rupture or erosion of atherosclerotic plaques in the coronary arteries, leading to the formation of blood clots that block blood flow partially or completely.

IV. PATHOPHYSIOLOGY

STEMI reflects transmural necrosis caused by acute thrombotic occlusion and longer duration of a coronary artery.

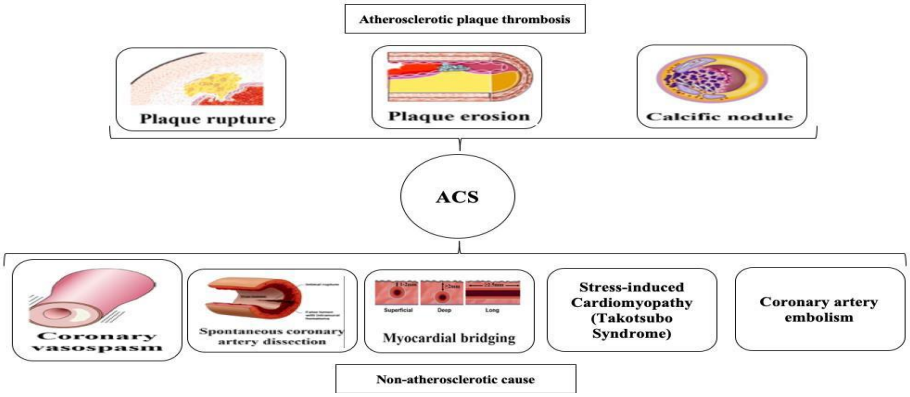


Fig. 2 Mechanism physiopathology of acute coronary syndrome

V. DIAGNOSIS

1. Clinical
   - Symptom:
     - Chest pain Ischemic-type (Angina): retro-sternal, intense, at rest, longer (>30min), irradiate to jaw and neck, trinitro-resistant.
   - Physical finding:
     - Vital sings: BP, HR, SpO2
     - Heart sounds: Third heart sound (LV dysfunction), Systolic murmur (mechanical complication)
     - Lung: rales (heart failure)

2. Investigation
   - ECG: ST segment elevation > 2mm in 2 contiguous leads or a new onset LBBB in the resting ECG
   - Cardiac Biomarkers- should not delay to wait for results for reperfusion therapy
   - Echocardiography-if available

VI. DIFFERENCIAL DIAGNOSIS

Cardiac disease	Pulmonary disease	Macrovascular disease	Digestive disease	Orthopedic disease	Other
Myocarditis	Acute pulmonary thromboembolism	Acute aortic dissection	Reflux esophagitis	Chest trauma	Anxiety attack
Pericarditis	Pneumothorax	Symptomatic aortic aneurysm	Esophageal spasm	Skeletal muscle disorder	Herpes Zoster
Acute heart failure	Bronchitis, pneumonia	Stroke	Peptic ulcer, gastritis	Costochondritis	Anemia
Hypertensive emergency	Pleurisy		Pancreatitis	Cervical disc disease	Pyrexia
Aortic stenosis			Cholecystitis gallstone	Intercostal neuralgia	Hyperthyroidism
Takotsubo syndrome				Rib fracture	
Tachyarrhythmia				Sternoclavicular arthritis	
Cardiac trauma					

Table1: Diagnosis other than cardiac ischemia for patients with chest pain

VII. MANAGEMENT

1. Objectives

"Time is muscle"- Every patient with STEMI should have the occluded artery reopened (reperfusion therapy) as soon as possible after the onset of symptoms.

Primary goal of STEMI management is to reduce the risk of death and the extent of permanent cardiac injury associated with MI.

2. Critical sign

- Shock (cool extremities, altered mental status, moist skin, weak pulse)
- Heart failure (orthopnea, jugular venous distension, pulmonary edema)
- Cardiac arrhythmia (sustained ventricular tachyarrhythmia, bradyarrhythmia)
- High bleeding risk patient (elderly, CKD with eGFR<30ml/min, cirrhosis, cancer, previous stroke, previous bleeding transfusion <6months, long-term oral anticoagulation)

3. Mortality risk factor

- **Killip classification:** Using physical examination and the development of heart failure to predict and stratify risk of mortality

Killip Class	Clinical signs	Incidence	Mortality
Class I	No clinical sings of heart failure	33% to 79%	2% to 6%
Class II	Rales or crackles in the lung, an S3 gallop, and elevated jugular venous pressure	12% to 38%	8% to 17%
Class III	Manifest acute pulmonary edema	5% to 10%	27% to 38%
Class IV	Cardiogenic shock, systolic blood pressure < 90mmHg, evidence of low cardiac output	3% to 19%	40% to 70%

- **TIMI risk Score for STEMI**: to evaluate strategy risk, in-hospital adverse events and outcome of STEMI patient. It shows strong predicted with mortality at 30 days

Risk indicator	Add to Score	Total score	30-day mortality	
			%	Odd of death
		0	**0.8**	**0.1**
Historical				
- Age >75 years	3	**1**	**1.6**	**0.3**
- 65-74 years	2			
- History of Diabetes, HTN or angina	1	**2**	**2.2**	**0.4**
Exam		**3**	**4.4**	**0.7**
- SBP < 100mmHg	3	**4**	**7.3**	**1.2**
- Heart rate > 100bpm	2			
- Killip class > 1	2	**5**	**12.4**	**2.2**
- Weight < 67kg	1			
		6	**16.1**	**3.0**
Presentation				
		7	**23.4**	**4.8**
- Anterior ST elevation or LBBB	1			
- Time to reperfusion > 4H	1	**8**	**26.8**	**5.8**
Total possible points	14	**>8**	**35.9**	**8.8**

4.Outpatient Management:

All STEMI patient is recommended to hospitalization. 5.First-line treatment

A. STEMI < 12hours:

i. Pre-hospital:

- Antalgic: Morphine 5-10mg SC or IV
- On-going chest pain: Nitroglycerine sublingually or oral spay
- Transfer with Emergency medical services (EMS) by full monitoring: oximeter, scope vital signs monitor
- Aspirin 250mg-500mg IV or PO (absence contraindicated)
- Thrombolysis: (see details in iii.a)

ii. Arrival Cardiac Care Unit (CCU):

- Strictly bed rest
- Monitoring with ECG 18 derivations
- G5% 500ml + 2gKCL/24h
- Blood test: CBC, groupage rhesus, electrolytes, glycemia, cardiac enzyme (CK-MB & Troponin T or I), Creatinine, BUN, PT, cholesterol, triglyceride
- Chest x-ray and echocardiography on bedside
- Clopidogrel 75mg: 6cp PO then 1cp daily after PCI
  - Or Ticagrelor 90mg: 2 cp then 1cp twice daily after PCI
  - Or Prasugrel 10mg: 6 cp then 1 cp daily after PCI
- Anticoagulant:
  - Heparin: 60IU/kg (max. 4000 IU) i.v bolus then continues infusion: 400IU/kg/24H (max. 24.000IU). ACT monitoring 4 after with target treatment >250ms or ACT 2 times upper normal value.
  - Or LWMH: Enoxaparin: 1mg(100IU)/Kg s.c, 2 times/day
- Nitroglycerine: if present LV dysfunction signs (stop if SBP < 100mmHg)
- Betablocker: for all patient if no contraindication
- ACE-Is/ARBs: for all patient if no contraindication
- High dose Statins: for all patient if no contraindication

iii. Reperfusion strategies:

a. Timing to determine choice of reperfusion:

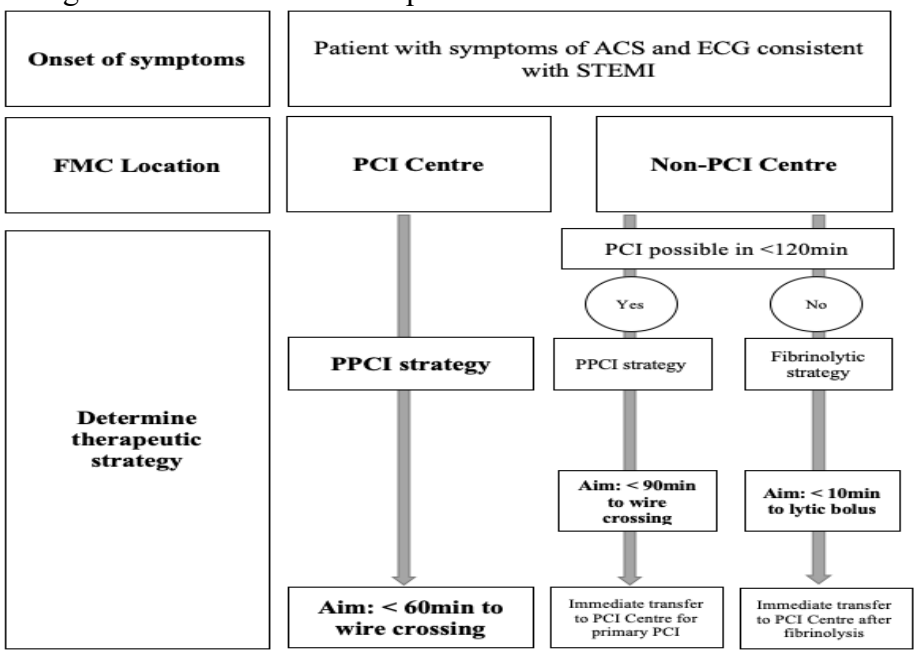


Fig. 3 Timing of choosing reperfusion treatment

b. Indication Primary PCI:
"Every STEMI <12h patients need emergency transfer to be performed primary PCI"

- STEMI < 12hours
- STEMI post-thrombolysis
- STEMI with shock state or post cardiac arrest and return of spontaneous circulation
- STEMI with contraindication thrombolysis

c. Indication Thrombolysis:

c.1. Indication:

- STEMI < 12hours with
  - Door to Balloon time > 120min if transferred from non-PCI center
  - Door to Balloon time > 90min in PCI center
  - No contraindications to thrombolysis

c.2. Choice of Fibrinolysis Agents:

- Streptokinase: 1,5M IU in 90min
- rt-PA: Actilyse: 15mg i.v bolus then 0.75mg/kg in 30min then 0.5mg/kg in 60min
- Tenectaplase: Metalyse: i.v bolus unique in 10s

Body weight	Single IV bolus over 5 s	Volume TNK to be administered
<60 kg	30 mg	6
60 to < 70 kg	35 mg	7
70 to <80 kg	40 mg	8
80 to <90 kg	45 mg	9
>90 kg	50 mg	10
In patient > 75years of age, the dose should be reduced by 50%		

c.3. Contrindication to Thrombolysis:

Absolute

- Previous intracranial hemorrhage or stroke of unknown origin at any time
- Ischemic stroke in the preceding 6 months
- Central nervous system damage or neoplasms, or arteriovenous malformation
- Recent major trauma/ surgery/head injury (within the preceding month)
- Gastrointestinal bleeding within the past month
- Known bleeding disorder (excluding menstrual)
- Aortic dissection
- Non-compressible punctures in the past 24h (e.g. liver biopsy, lumbar puncture)

Relative

- Transient ischemic attack in the preceding 6 months
- Oral anticoagulant therapy
- Pregnancy or within 1-week post-partum
- Refractory hypertension (systolic blood pressure > 180mmHg and/or diastolic blood pressure >110mmHg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer
- Prolonged or traumatic resuscitation

c.4. Results of Thrombolysis :

Successful Fibrinolysis	Failed Fibrinolysis
- Resolution chest pain - Early return ST elevation > 50% within 60-90min of initiation of fibrinolysis - Early peaking of CK-MB levels - Restoration +/- maintenance of hemodynamic +/- electrical stability	- Contiuing chest pain - Persistent hyper-acute ECG changes (<50% resolution of ST elevation) - Hemodynamic and electrical instability
Pharmaco-invasive therapy-Elective PCI (3-24hours)	**Rescue PCI-Very early(1-2hours)**

B. STEMI > 12hours:

i. Hospitalization in Cardiac Care Unit (CCU):

- Strictly bed rest
- Monitoring with ECG 18 derivations
- G5% 500ml + 2gKCL/24h
- Blood test: CBC, groupage rhesus, electrolytes, glycemia, cardiac enzyme (CK-MB & Troponin T or I), Creatinine, BUN, PT, cholesterol, triglyceride
- Chest x-ray and echocardiography on bedside
- Aspirin 250mg i.v or PO
- Anticoagulant:
    - Heparin: 400IU/kg/24H (max. 24.000IU) continues i.v, ACT monitoring 4 after with target treatment >250ms or ACT 2 times upper normal value.
    - Or LWMH: Enoxaparin: 1mg(100IU)/Kg s.c, 2 times/day
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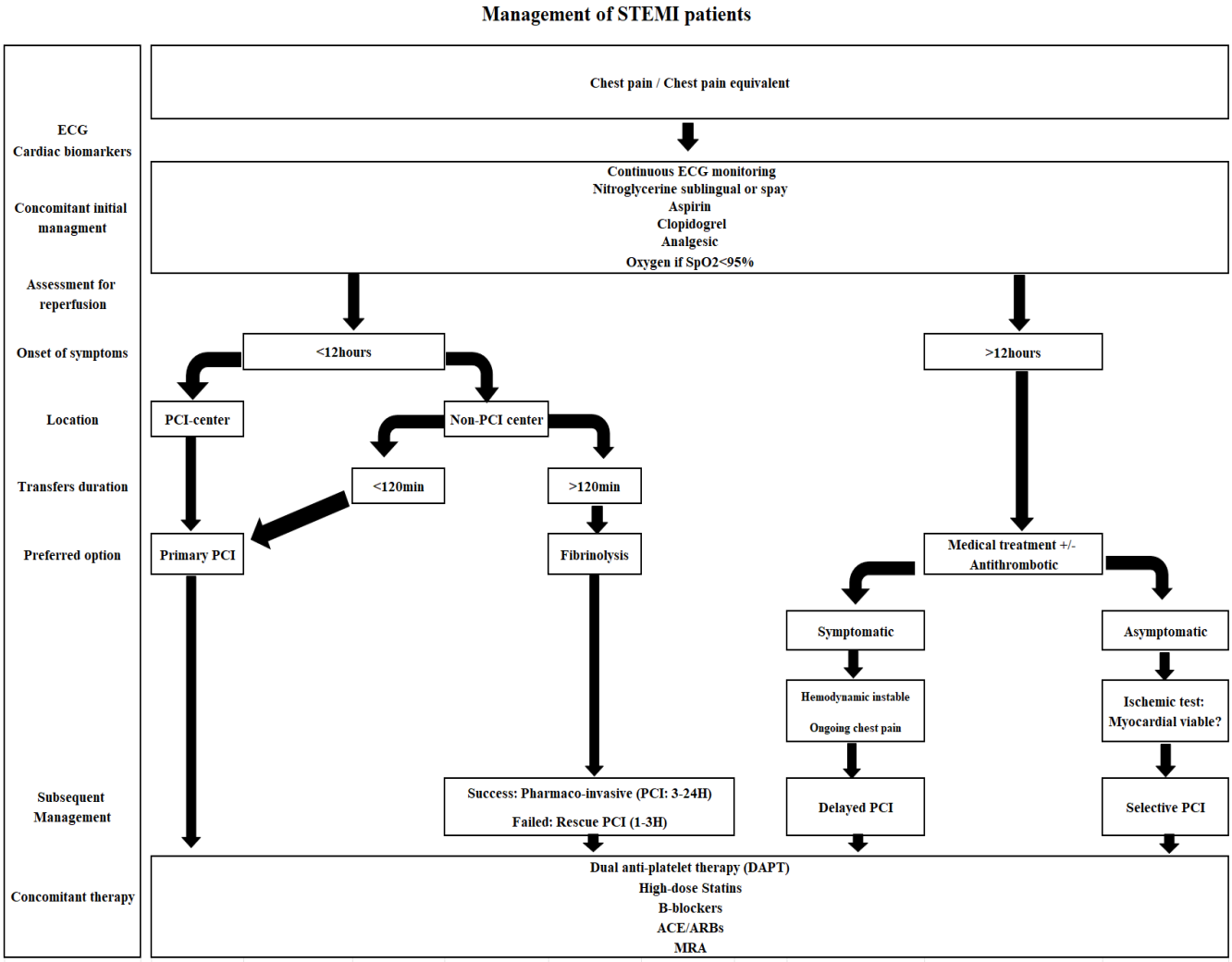
ii. Reperfusion indication:

- Delayed PCI indicated:
    - Ongoing symptoms suggestive of ischemia
    - Hemodynamic instability
    - Life-threatening arrhythmia
- STEMI > 12hours with asymptomatic and stable, PCI (Delayed selective PCI) is indicated depend on age, risk strategy and viable myocardium via non-invasive ischemia test.

6.Treatment adjustment

- Nitroglycerine can't use in case: inferior AMI +/- RV infarction, Low SBP < 90mmHg, severe bradycardia <50bpm, tachycardia >100bpm
- Pulmonary edema: Furosemide
- Malaise: Atropine + vascular filling
- Shock: Norepinephrine, Dobutamine or Dopamine

7.Algorithm



VIII. SPECIAL CASES

- STEMI in elderly: may have atypical symptoms or may present with confusion or altered mental status. Special consideration in managing STEMI in elderly include careful assessment of symptoms, monitoring complication and adjusting treatment plans base on individual patient factors.
- STEMI in Women: may present with atypical symptoms such as fatigue, shortness of breath, or chest discomfort. They may have higher risk of complication and worse outcomes compared to men.
- STEMI in diabetic patients: may have more extensive coronary artery disease and higher risk of complication. Special in managing include aggressive blood sugar control, close monitoring for complications and individualized treatment.
- STEMI with cardiogenic shock: is life-threatening co-condition. Special in managing include immediate revascularization with PCI, aggressive hemodynamic support with medications and mechanical devices and close monitoring in an intensive care unit.
- STEMI with concurrent conditions: STEMI can occur in patients with other conditions such as renal failure, liver disease, or bleeding disorders. Special in managing include careful assessment of risks and benefits of reperfusion therapy, close monitoring for complications, and coordination with specialists in managing the underlying conditions.

IX. EVOLUTION AND PROGNOSIS

- Early reperfusion of STEMI gives good outcome for short and longtime prognosis.
- Without reperfusion treatment, survivors of STEMI face a substantial excess risk of further cardiovascular events, including death, recurrent MI, heart failure, arrhythmia, angina and stroke.

X. COMPLICATIONS

- Arrhythmia: ventricular arrhythmia, Atrial fibrillation, heart block
- Heart failure
- Cardiogenic shock
- Mechanical complications: ventricular septal rupture, papillary muscle rupture, free wall rupture
- Thrombo-embolic events
- Post-infarction angina
- Post-infarction syndrome (pericarditis post infarction)

XI. PREVENTION AND RECOMMENDATION

- All high-risk cardiovascular patient shall be screen for coronary artery disease (CAD) annually.
- Lifestyle modification and managing risk factors can help prevent CAD and reduce risk of STEMI.
- Cardiac rehabilitation after STEMI can help improve cardiovascular health, manage risk factors, and promote lifestyle modification.
- Regular follow-up with a specialist provider is crucial for ongoing management and assessment of cardiovascular health.

XII. REFERECES

1. Robert A Byrne et al.2023 ESC guideline for management of acute coronary syndrome, *European Heart Journal*, Volume 44, Issue 38, Pages3720-3826. https://doi.org/10.1093/eurheartj/ehad191
2. Gulati et al, "2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines," which published ahead of print on October 28, 2021, and appeared in the November 30, 2021, issue of the journal (*Circulation*. 2021;144: doi: 10.1161/CIR.0000000000001029
3. Deqiang Yuan et al. New Concepts on the Pathophysiology of Acute Coronary Syndrome. *Rev. Cardiovasc. Med.* **2023**, 24(4), 112. https://doi.org/10.31083/j.rcm2404112
4. Kimura K et al. Japanese Circulation Society Joint Working Group. JCS 2018 Guideline on Diagnosis and Treatment of Acute Coronary Syndrome. Circ J. 2019 Apr 25;83(5):1085-1196. doi: 10.1253/circj. CJ-19-0133. Epub 2019 Mar 29. PMID: 30930428.
5. 2019 Malaysia Clinical Practice Guideline: Management of Acute ST segment Elevation Myocardial Infarction (STEMI)
6. 2020 Thai Acute Coronary Syndrome Guidelines

ACUTE CORONARY SYNDROME (ACS)
NON-ST ELEVATION MYOCARDIAL INFARCTION (NSTEMI)

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I. DEFINITION

Acute coronary syndromes (ACS) encompass a spectrum of conditions that include patients presenting with recent changes in clinical symptoms or signs, with or without changes on 12-lead electrocardiogram (ECG) and with or without acute elevations in cardiac troponin (cTn) concentrations.

NSTEMI is one type of ACS with characterize by acute chest pain (or chest pain-equivalent signs/symptoms) but without persistent ST-segment elevation (or ST-segment elevation equivalents) on ECG. The majority of patients in this category who subsequently display a typical rise and fall in cardiac troponin levels

II. EPIDEMIOLOGY

Cardiovascular disease (CVD) is the most common cause of mortality and morbidity worldwide, with a substantial portion of this burden borne by low- and middle-income countries. ACS is often the first clinical manifestation of CVD.

In 2019, there were an estimated 5.8 million new cases of ischemic heart disease in the 57 countries. The median age-standardized incidence estimate per 100 000 people was 293.3 (interquartile ratio 195.8–529.5). Ischemic heart disease is the most common cause of CVD death, accounting for 38% of all CVD deaths in females and 44% in males.

III. ETIOLOGY

Acute coronary syndrome (ACS) cause by the rupture or erosion of atherosclerotic plaques in the coronary arteries, leading to the formation of blood clots that block blood flow partially or completely

IV. PATHOPHYSIOLOGY

The underlying pathology of ACS is a mismatch between myocardial oxygen supply and demand. UA, NSTEMI, and STEMI all represent consequences of thrombotic vessel occlusion and varying degrees of this mismatch. Plaque rupture is the most common underlying source of thrombotic occlusion in ACS. Plaque erosion with an intact fibrous cap is the etiology in up to one-third of patients with ACS, typically, women, younger patients, and smokers. Additionally, vasoconstriction at the level of the culprit plaque or of the microcirculation may also cause ACS.

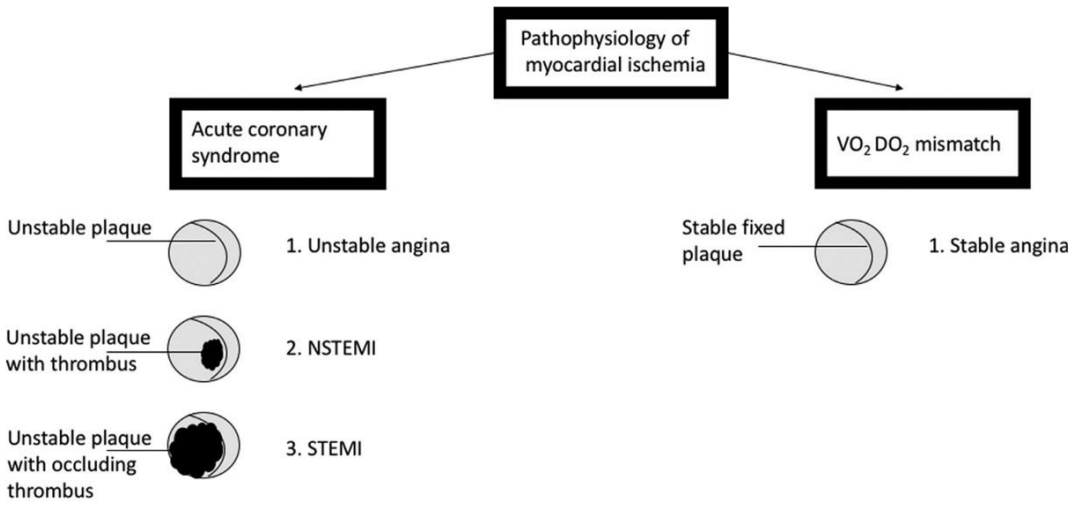


Fig. 1 Mechanism physiopathology of acute coronary syndrome

V. DIAGNOSIS

1. Clinical presentation

- Chest pain Ischemic-type (Angina): retro-sternal, intense, at rest, longer (>30min), irradiate to jaw and neck, trinitro-resistant.

- Acute chest discomfort: Pain, Pressure, tightness, Heaviness or burning. It can radiate from the chest to the neck, jaw, back and sometime both arms. Other symptoms include:

  - Shortness of breath
  - Nausea or vomiting
  - Feeling faint
  - Sweating, weakness and fatigue.

2. Physical examination and history taking

- It is crucial to take a focused medical history and accurately characterize the presenting symptoms in order to manage the patient via the appropriate care pathway as soon as possible.

Vital sign and EKG are recommended at first medical contact (FMC)

- Focused physical examination should include checking for the presence of all major pulses, measurement of blood pressure in both arms, auscultation of the heart and lungs, and assessing for signs of HF or circulatory compromise

3. Investigation and risk stratification

- It is recommended to base the diagnosis and initial short-term risk stratification of ACS on a combination of clinical history, symptoms, vital signs, other physical findings, EKG and hs-cTn.

- 12 lead EKG with in 10mn at FMC:
  - These patients may exhibit other ECG alterations, including transient ST-segment elevation, persistent or transient ST-segment depression, and T wave abnormalities, including hyperacute T waves, T wave inversion, biphasic T waves, flat T waves, and pseudo- normalization of T waves. Alternatively, the ECG may be normal



Normal, Inverted T waves, or ST depression

- High sensitive cardiac troponine (hs-cTn): is recommended in all patients with suspected ACS
  - European Society of Cardiology 0 h/1 h and 0 h/2 h algorithms
- Echocardiography:
  - should not result in relevant delays in transfer to the cardiac catheterization laboratory if there is suspicion of an acute coronary artery occlusion
  - can be useful to identify signs suggestive of ongoing ischaemia or prior MI.
  - can also be useful to suggest alternative etiologies associated with chest pain.
- Coronary CT angiography:
  - Routine, early CCTA in patients with suspected ACS is not recommended.
  - Diagnostic tool of choice for ruling out alternative potentially life-threatening differential diagnoses of ACS, like PE or aortic dissection.

VI. IFFERENTIAL DIAGNOSIS

Cardiac	**Pulmonary**	**Vascular**
Myopericarditis	Pulmonary embolism	Aortic dissection
Tachyarrhythmias	Pneumothorax (Tension)	Symptomatic aortic aneurysm
Acute heart failure	Bronchitis, Pneumonia	Stroke
Hypertensive emergencies	Pleuritis	
Aortic valve stenosis		
Tako-Tsubo cardiomyopathy		
Coronary spasm		
Gastro- intestinal	**Orthopedic**	**Other**
Esophagitis	Musculoskeletal disorder	Anxiety disorder
Peptic ulcer, Gastritis	Chest trauma	Herpes zoster
Pancreatitis	Muscle injury	Anemia
Cholecystitis	Costochondritis	
	Cervical spine pathologies	

VII. ANAGEMENT

1. Objectives
   - The goal of initial management is to restore the coronary flow on time and prevent any complication of NSTEMI-ACS *(TIME IS MUSCLE)*
2. Critical Sign
   - Hemodynamic instability or Cardiogenic Shock.
   - Recurrent or ongoing chest pain refractory to medical treatment.
   - Acute HF presumed secondary to ongoing myocardial ischemia•
   - Life-threatening arrhythmias or cardiac arrest after presentation.
   - Mechanical complications.
   - Recurrent dynamic ECG changes suggestive of ischemia (particularly with intermittent ST-segment elevation).
3. Mortality risk factor
   - **Heart Score** (Predict MACE in 6 weeks)

Heart Score		
History	Highly suspicious	2
	Moderately suspicious	1
	Slightly Suspicious	0
Electrocardiogram	Significant ST depression	2
	Nonspecific repolarization	1
	Normal	0
Age,	> 65	2
	45-65	1
	<45	0
Risk factors	> 3 or history of CAD	2
	1 or 2	1
	None	0
Troponin	> 3x normal limit	2
	1-<3x normal limit	1
	< normal limit	0

Low Risk (0-3)	1.6% chance of cardiac events
Intermediate Risk (4-6)	13% chance of cardiac events
High Risk (7 or higher)	50% chance of cardiac events

- **TIMI Score** (Predict cardiac event in 14 days)

TIMI risk score	
Risk Factor	**Score**
Age >65 y	1
> 3 risk factors for CAD	1
Known CAD (stenosis >50%)	1
Recent (<24H) severe angina	1
Increase cardiac markers	1
ST-deviation > 0.5mm	1

Risk of Cardiac event (%) by 14 days in TIMI		
Risk score	Death or MI	Death, MI or Urgent Revasc
0/1	3	5
2	3	8
3	5	13
4	7	20
5	12	26
6/7	19	41

- **Grace Score:** provides the most accurate stratification of risk both on admission and at discharge (http:// www.gracescore.org/WebSite/default.aspx?ReturnUrl=%2f)

Risk Category	GRACE risk score	In-hospital death(%)
Low	≤ 108	< 1
Intermediate	109-140	1-3
High	>140	> 3
Risk Category	**GRACE risk score**	**Post-discharge to 6 month death (%)**
Low	≤ 88	<3
Intermediate	89-118	3-8
High	> 118	>8

4. Outpatient Management

Clinical Presentation	Unit	Rhythm Monitoring
Unstable Angina	Regular ward or discharge	None
NSTEMI at low Risk (a)	Intermediate care unit or coronary care unit	≤ 24H
NSTEMI at intermediate to high risk (b)	Intensive/Coronary care units or intermediate care unit	> 24H

(a) If none of the following criteria: hemodynamically unstable, major arrhythmias, LVEF < 40%, Failed reperfusion, additional critical coronary stenoses of major vessels or complications related to percutaneous revascularization

(b) If one or more of the above criteria are present

5. First-line treatment
   A. Acute Pharmacotherapy

1. Oxygen:	SpO2 < 90% or Hypoxia sign
2. Strictly bed rest	Monitoring EKG and Vital sign
3. G5% 500ml/24h	
4. Antiplatelet	Table 3 antiplatelet in NSTEM-ACS
5. Anticoagulant	Table 4 anticoagulant in NSTEM-ACS
6. Nitrate:	sublingual NTG (0.3mg to 0.4mg) every 5 minutes for up to 3 doses, after which IV NTG should be administered if needed.

7. Pain relieves	Intravenous opioids (e.g. morphine 5–10 mg) should be considered for the relief of severe chest pain.
8. Betablocker **9.**	Should be considered when no signs of acute HF, a systolic blood pressure (SBP) >120 mmHg, and without other contraindications.
10. ACE or ARB	If no contre-indication
11. Hight dose statin	For all patient if no contre-indication
12. Furosemide	If presence congestive sign
13. Norepinephrine, Dobutamine or Dopamine:	In shock state

B. Reperfusion indication:
- Immediate invasive (<2H): very high-risk patient
- Early invasive (<24H): high risk patient
- Invasive < 72H: intermediate risk patient
- Stress test with coronary CTA (if available) for low-risk patient.

Very High-risk criteria	**Immediate invasive (< 2H)**
o **Hemodynamic instability or cardiogenic shock**.	
o **Recurrent or ongoing chest pain refractory to medical treatment**	
o **Life-threatening arrhythmias or cardiac arrest**	
o **Mechanical complications of myocardial infarction**	
o **Acute Heart failure**	
o **Recurrent dynamic ST-T wave change, particularly with intermittent ST-elevation**	
High-risk criteria	**Early invasive (< 24H)**
• **Rise of fall in cardiac troponin compatible with myocardial infarction**	
• **Dynamic ST – or T-wave change (symptomatic or silent)**	
• **Grace score > 140**	
Intermediate-risk criteria	**Invasive (<72H)**
• **Diabetes mellitus**	
• **Renal insufficiency (eGFR <60ml/mn/1.73m2)**	
• **LVEF < 40% or congestive heart failure**	
• **Early post-infarction angina**	
• **Prior percutaneous coronary intervention**	
• **Prior coronary artery bypass surgery**	
• **Grace score >109 and < 140**	
Low-risk criteria	**Noninvasive test if appropriate**
• **Non all criteria above**	

Table 3
Antiplatelet agents in non–ST-elevation myocardial infarction

Drugs	Dosing and Special Considerations
Aspirin	Loading dose: 162 mg–325 mg Maintenance dose: 81 mg/d, continued indefinitely
Clopidogrel	Loading dose: 300 mg–600 mg Maintenance dose: 75 mg/d for 12 mo
Prasugrel	Loading dose: 60 mg Maintenance dose: 10 mg/d for 12 mo Only in patients triaged to early invasive strategy Loading dose at the time of percutaneous coronary intervention after coronary anatomy known Avoid in patients with prior history of stroke/transient ischemic attack, in patients >75 y, and/or weight <60 kg
Ticagrelor	Loading dose: 180 mg Maintenance dose: 90 mg twice daily Preferred over clopidogrel irrespective of strategy (early invasive or ischemia guided)
GP IIb/IIIa inhibitors Abciximab Tirofiban Eptifibatide	Patients treated with an early invasive strategy and dual-antiplatelet therapy with intermediate/high-risk features Eptifibatide and tirofiban preferred due to their short offset time and reversibility with platelet transfusion

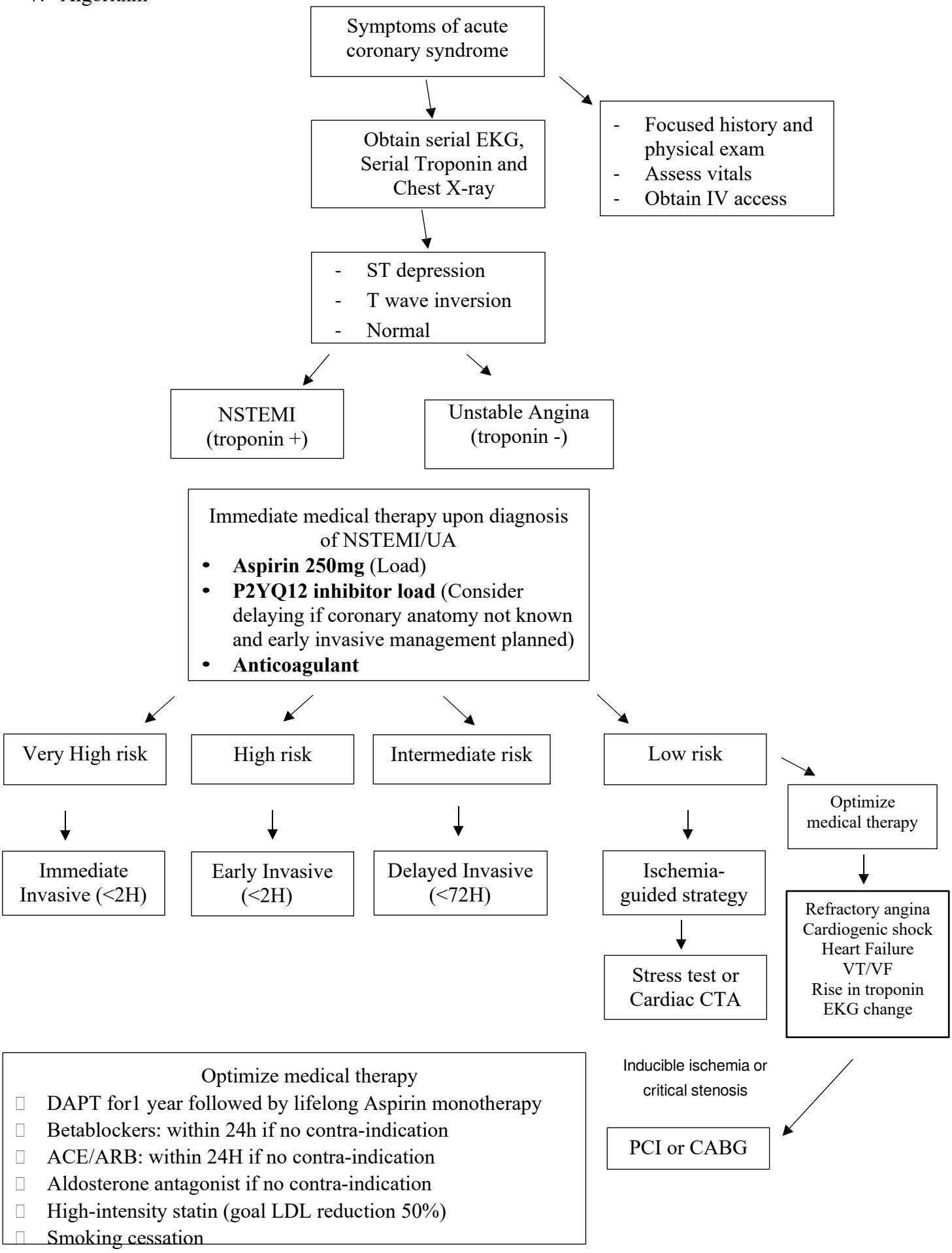
Table 4
Anticoagulants for non–ST-elevation myocardial infarction

Drugs	Dosing and Special Considerations
Enoxaparin	1 mg/kg SC every 12 h for duration of hospitalization or until PCI is performed Reduce dose to 1 mg/kg/d SC in patients with CrCl <30 mL/min (strongly consider unfractionated heparin as an option)
Unfractionated heparin	Initial loading dose 60 IU/kg (maximum 4000 IU) with initial infusion 12 IU/kg/h (maximum 1000 IU/h) for 48 h or until PCI is performed Adjust infusion dose to therapeutic aPTT range
Fondaparinux	2.5 mg SC daily for the duration of hospitalization or until PCI is performed Administer additional anticoagulant if PCI is performed while patient is on fondaparinux. Contraindicated if CrCl is <30 mL/min Does not affect usual anticoagulant parameters, such as aPTT or ACT
Bivalirudin	Loading dose 0.10 mg/kg loading dose followed by 0.25 mg/kg/h Until diagnostic angiography or PCI is performed in patients with early invasive strategy only

Abbreviations: aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; PCI, percutaneous coronary intervention; SC, subcutaneous.

6. Treatment adjustment
   - Cardiac rehabilitation
   - Lifestyle modification: smoking cessation, dietary changes, exercise and weigh management
   - Medical therapy maintenance (ensure adherence)
     - Antithrombotic therapy
     - Lipid-lowering therapy
     - Reach and sustain risk factor treatment targets
       - Systolic BP under 130mmHg
       - LDL < 55mg/dL or < 1.4mmol/L
       - HbA1C: < 7%
   - Regular follow up

7. Algorithm


Symptoms of acute coronary syndrome
Obtain serial EKG, Serial Troponin and Chest X-ray
- Focused history and physical exam
- Assess vitals
- Obtain IV access
- ST depression
- T wave inversion
- Normal
NSTEMI (troponin +)
Unstable Angina (troponin -)
Immediate medical therapy upon diagnosis of NSTEMI/UA
• Aspirin 250mg (Load)
• P2YQ12 inhibitor load (Consider delaying if coronary anatomy not known and early invasive management planned)
• Anticoagulant
Very High risk
High risk
Intermediate risk
Low risk
Optimize medical therapy
Immediate Invasive (<2H)
Early Invasive (<2H)
Delayed Invasive (<72H)
Ischemia-guided strategy
Refractory angina
Cardiogenic shock
Heart Failure
VT/VF
Rise in troponin
EKG change
Stress test or Cardiac CTA
Optimize medical therapy
DAPT for1 year followed by lifelong Aspirin monotherapy
Betablockers: within 24h if no contra-indication
ACE/ARB: within 24H if no contra-indication
Aldosterone antagonist if no contra-indication
High-intensity statin (goal LDL reduction 50%)
Smoking cessation
Inducible ischemia or critical stenosis
PCI or CABG

VIII. SPECIAL CASES

- ACS in elderly: may have atypical symptoms or may present with confusion or altered mental status.
  Special consideration in managing STEMI in elderly include careful assessment of symptoms, monitoring complication and adjusting treatment plans base on individual patient factors.
- CS in Women: may present with atypical symptoms such as fatigue, shortness of breath, or chest discomfort. They may have higher risk of complication and worse outcomes compared to men.
- ACS in diabetic patients: may have more extensive coronary artery disease and higher risk of complication. Special in managing include aggressive blood sugar control, close monitoring for complications and individualized treatment.
- ACS with cardiogenic shock: is life-threatening co-condition. Special in managing include immediate revascularization with PCI, aggressive hemodynamic support with medications and mechanical devices and close monitoring in an intensive care unit.
- ACS with concurrent conditions: STEMI can occur in patients with other conditions such as renal failure, liver disease, or bleeding disorders. Special in managing include careful assessment of risks and benefits of reperfusion therapy, close monitoring for complications, and coordination with specialists in managing the underlying conditions.

IX. VOLUTION AND PROGNOSIS

- Short term prognosis can be vary significantly based on risk factors, age, comorbidities, and the initial clinical response. In general, NSTEMI has a better immediate outcome than STEMI, but It can still result in complications.
- The long-term prognosis can be influenced by various factors, including the severity of coronary artery disease, the presence of left ventricular dysfunction and adherence to medical therapy post-discharge.

X. COMPLICATIONS

- Arrhythmia: ventricular arrhythmia, Atrial fibrillation, heart block
- Heart failure
- Cardiogenic shock
- Mechanical complications: ventricular septal rupture, papillary muscle rupture, free wall rupture
- Thrombo-embolic events
- Post-infarction angina
- Post-infarction syndrome (pericarditis post infarction)

XI. REVENTION AND RECOMMENDATION

- All high-risk cardiovascular patient shall be screen for coronary artery disease (CAD) annually.
- Lifestyle modification and managing risk factors can help prevent CAD and reduce risk of STEMI.
- Cardiac rehabilitation after STEMI can help improve cardiovascular health, manage risk factors, and promote lifestyle modification.
- Regular follow-up with a specialist provider is crucial for ongoing management and assessment of cardiovascular health.

XII. REFERENCES

1. 2023 ESC Guidelines for the management of acute coronary syndromes European Heart Journal (2023) 44, 3720–3826 https://doi.org/10.1093/eurheartj/ehad191
2. Non-ST segment acute coronary syndrome, Cardiol Clin 36 (2018) 37–52 https://doi.org/10.1016/j.ccl.2017.08.003
3. Médecine cardiovasculaire par le Collège national des enseignants de cardiologie. © 2019, Elsevier Masson SAS

CHRONIC CORONARY SYNDROME

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I. DEFINITION ET CLASSIFICATION:

Chronic coronary syndrome categories according to the ESC Guidelines:	
Category	**Description**
1	Patients with suspected CAD and "stable" angina symptoms*
2	Patient with new onset of heart failure or left ventricular dysfunction and suspected CAD
3	Asymptomatic and symptomatic patients <1 year after an ACS or recent revascularisation
4	Patients > 1 year after initial angina diagnosis or revascularisation
5	Patients with angina and suspected vasospastic or microvascular disease
6	Asymptomatic patients in whom CAD is detected at screening
* including dyspnoea as angina equivalent. ACS: acute coronary syndrome, CAD: coronary artery disease, ESC European Society of Cardiology.	

II. EPIDEMIOLOGY:

- CCD is a heterogeneous group of conditions that includes obstructive and nonobstructive CAD with or without previous myocardial infarction (MI) or revascularization, ischemic heart disease diagnosed only by noninvasive testing, and chronic angina syndromes with varying underlying causes.
- Approximately 20.1 million persons (7.2%) in the United States live with CCD, 11.1 million Americans (4.1%) have chronic stable angina pectoris, and approximately one-quarter (n=200 000) of all MIs in the United States occur among the 8.8 million persons with CCD who have had a previous MI.

III. ETIOLOGY:

Chronic coronary syndrome referred to as stable ischemic heart disease (SIHD), based on a classic history of angina pectoris in the presence of either risk factors for or known atherosclerotic cardiovascular disease.

IV. PHYSIOPATHOLOGY:

- Multiple pathophysiologic mechanisms may cause CCS.
- The most common is atherosclerotic epicardial coronary artery obstruction.
- However, as many as one-third of patients may have no significant epicardial disease and often have microvascular disease as the underlying pathophysiology.

V. DIAGNOSIS:

1. Clinic:

- Angina is the main symptom.
- Angina pectoris is characterized by substernal discomfort, heaviness, or a pressure-like feeling, which may radiate to the jaw, shoulder, back, or arm and which typically lasts several minutes.
- Physical examination is often unrevealing in patients with stable angina.

2. Investigation:

*Six steps to diagnosing CAD (adapted from ESC Guideline 2019):

Step 1 Assess symptoms and signs to distinguish between typical and atypical symptoms

Step 2 Assess quality of life and comorbidities. Apply guideline-based risk-factor modification based on commonly applied risk charts e.g. SCORE.

Step 3 Basic testing including troponin assays should be considered. 12 lead ECG and TTE is recommended. CMR may be considered in patients with strong suspicion of CAD where TTE is within normal limits.

Step 4 The clinical likelihood of obstructive CAD is estimated. A new phrase has been coined for the guideline entitled "clinical likelihood of CAD" and is underpinned by the improved PTP score.[3] PTP <15% corresponds to <1% annual risk of cardiovascular death or MI.[4] Therefore, routine testing in these patients can safely be deferred reducing unnecessary procedures and costs. The data on which the PTP in the previous guideline was based has since been updated based on a pooled analysis of 3 cohort studies and has highlighted that the presence of obstructive disease amongst patients with suspected CAD is lower than once thought.

Step 5 Offer diagnostic testing to selected patients screened via steps 1-4 to establish the diagnosis of CAD. This includes the options of invasive and non-invasive imaging depending on the risk. The choice of test also depends on the PTP of CAD with modalities such as CTCA more effective in low clinical probability situations.

Step 6 Once a diagnosis of obstructive CAD has been confirmed, patients undergo risk stratification to guide subsequent therapeutic interventions. The event risk is determined by clinician judgement and depends on the investigation modality used to determine CAD.

VI. DIFFERENTIAL DIAGNOSIS:

The differential diagnosis includes myocardial infarction, valvular disease (especially aortic valve stenosis), aortic dissection, pulmonary embolism, inflammatory myocardial and/or pericardial conditions, chest wall syndrome, psychogenic causes, respiratory tract infections, and esophageal conditions.

VII. MANAGEMENT:

1. Objective:

To reduce angina symptom and exercised-induced ischemia and prevent cardiovascular events**.**

2. Critical Sign:
   Signs related to the complication of CCS (see complications section).
3. Mortality Risk Factors: no consensus data.
4. Outpatient Management:
   Most of CCS patients do not require hospitalization.
5. First-line Treatment: (see algorithm)
6. Treatment Adjustment: (see algorithm)

7. Algorithm:

- Lifestyle Management:

Smoking cessation, healthy diet (fruits and vegetables), Physical activities (30-60min a day), Healthy weight (Keep BMI<25kg/m2), influenza vaccination

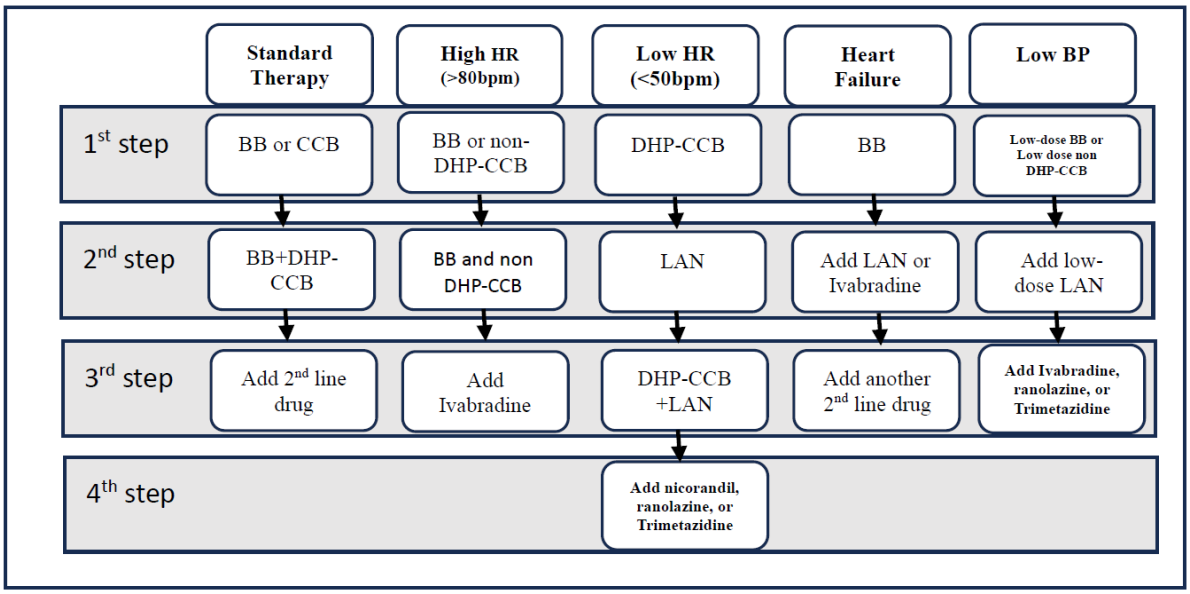
- Pharmacological Management

i. Anti - i sc he mi c dr ugs:

- 1st line drugs**:** Beta-blockers (Bisoprolol, Metoprolol…), Calcium channel blockers.
- 2nd line drugs**:** Ranolazine (Rancard), Trimetazidine (Vastarel), Ivabradine, Nicorandil**.**
- Respond to anti-ischemic therapy should be reassessed after 2-4 weeks of treatment.

ii. P re ve nti on of Car di ovasc ul ar e ve nts:

- Anti-thrombotic therapy (Aspirin, clopidogrel): low dose aspirin 75-100mg 1tab/day.
- Statins and other lipid-lowering drugs (rosuvastatin, atorvastatin, ezetimibe...)
- ACE inhibitor/ARBs**:** if patients have hypertension, heart failure**.**



*BB: beta-blocker, BP: Blood Pressure, CCB: Calcium Channel Blocker, DHP-CCB: Dihydropyridine-Calcium Channel Blocker, HR: Heart Rate, LAN: Long-action Nitrate

- **Revascularization:**

Revascularization with either coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI), as opposed to continuing medical therapy without revascularization, is indicated in two groups of stable patients:

- Patients with specific high-risk anatomy for which revascularization has a proven survival benefit.

- Patients who want revascularization for improved quality of life compared with medical therapy, such as those who are not tolerating medical therapy well or who want to increase their activity level.

VIII. SPECIAL CASES:

- Individuals over the age of 65 years represent a growing proportion of patients with CSS, however, recognition of disease can be more challenging in this population due to a higher prevalence of atypical symptoms, including exertional dyspnea or silent myocardial ischemia.
- The approach to the management of angina in older adults is essentially the same as for younger patients.

IX. EVOLUTION AND PRONOSIS:

According to CLARIFY registry, in patient with CSS, resolution of angina within 1 year with conservative management predicted outcomes similar to lack of angina, whereas persistence or occurrence was associated with worse outcomes.

X. COMPLICATION:

- Acute coronary syndrome (unstable angina or MI),
- Congestive heart failure,
- Cardiac arrhythmias, or sudden death.

XI. PREVENTION AND RECOMMENDATION:

We recommend that all patients with CCS receive education and counseling about issues such as medication compliance, control of risk factors, and regular exercise. In addition, there are several medical therapies which can reduce the risk of cardiovascular events and disease progression.

XII. REFERENCE

1. https://www.uptodate.com/contents/chronic-coronary-syndrome-overview-of-care
2. Ford TJ, Corcoran D, Berry C. Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need. Heart 2018; 104:284.
3. https://www.uptodate.com/contents/chronic-coronary-syndrome-indications-for-revascularization
4. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)
5. JACC 2023 Chronic Coronary Disease Guideline
6. https://www.uptodate.com/contents/new-therapies-for-angina-pectoris?topicRef=1483&source=see_link
7. Maron DJ, Hochman JS, Reynolds HR, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. N Engl J Med 2020; 382:1395.
8. Spertus JA, Jones PG, Maron DJ, et al. Health-Status Outcomes with Invasive or Conservative Care in Coronary Disease. N Engl J Med 2020; 382:1408.

EMERGENCY TACHY-ARRHYTHMIA

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I. INTRODUCTION

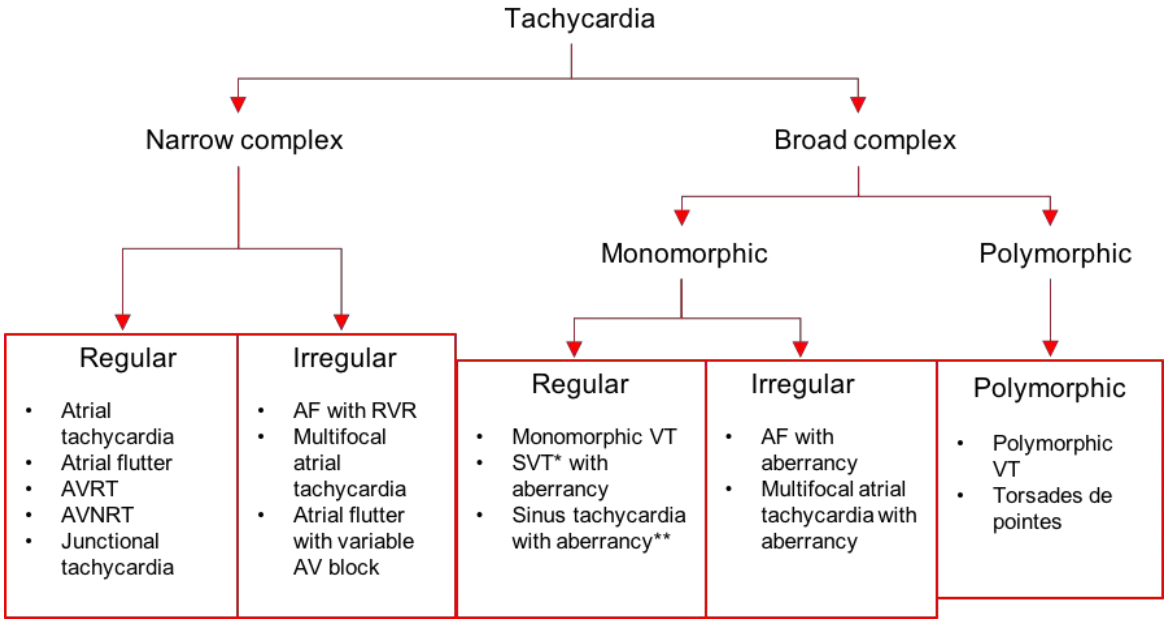
Arrhythmias (cardiac arrhythmias or dysrhythmias) are irregularities in the heartbeat and the electrical impulses may be too fast, too slow or erratic, spans from a relatively benign condition to life-threatening emergencies.

2 types: Tachy-arrhythmia: HR > 100bpm (at resting) and Brady-arrhythmia: HR < 60bpm (at resting)

II. DEFINITION

Tachycardia is when the heart beats too fast, at a rate of more than 100 beats per minute, when at rest. This can depend on age, health status and physical condition.

III. CLASSIFICATION



AF: atrial fibrillation, **AV**: atrioventricular, **AVNRT**: atrioventricular nodal re-entry tachycardia, **AVRT**: atrioventricular re-entry tachycardia, **SVT**: supraventricular tachycardia, **VT**: ventricular tachycardia, **SVT***: any cause of regular tachycardia originating from above the ventricle, **Aberrancy****: any form of abnormal conduction of the electrical impulse (i.e., left bundle branch block)

IV. PIDERMIOLOGY

For SVT: prevalence is 2.25/1000 persons, incidence is 35/100 000 person-years. Women have a risk of developing SVT that is two times greater than that of men, and persons aged >_65 years or have more than five times the risk of developing SVT than younger individuals. [1]

For SCD by ventricular arrhythmia: low incidence during infancy and childhood (1 per 100 000 person years), 25–27 the incidence is approximately 50 per 100 000 person years in middle-aged individuals (in the fifth to sixth decades of life). [2]

IV. TIOLOGIES AND PATHOPHYSIOLOGY

Causes of tachyarrhythmia: [6]

Cardiac	Extra-cardiac	Drug-induced
Coronary artery disease Acute myocardial ischemia Chronic myocardial ischemia Cardiomyopathy (dilative, hypertrophic-obstructive, restrictive) Inflammatory heart disease Myocarditis Pericarditis Congenital heart disease in adult Aquired valvular disease Cardiac neoplasm Hypertrophy (arterial hypertension) Channelopathies	Electrolyte disturbances Toxic (alcohol) Hemochromatosis Renal diseases Hypo- and hyperthyroidism Autoimmune diseases Neoplasm Inflammatory diseases (sarcoidosis, amyoloidosis)	Antiarrhythmic (Ex.: Digitalis) Antidepressives Bronchodilatators Antineoplastic agents Inotropes Stimulants Opoids

3 Mechanisms of tachyarrhythmia: [1,2]

- Abnormal automaticity: When cells outside the normal conduction system generate spontaneous impulse.
- Triggered activity: high levels of intracellular calcium, which can lead to spontaneous calcium release from the sarcoplasmic reticulum.
- Re-entry: A conduction disturbance.

V. DIAGNOSTIC

1- Clinical signs and symptoms

- Palpitations +++
- Chest pain (and if relieved with GTN)
- Shortness of breath/dyspnoea
- Dizziness/syncope/light-headedness

2- Investigations [1,2]

1st line investigations	Further investigation (to consider)
12 leads EKG	24h holter EKG monitor
Full blood screen	Event recorder/Loop recorder
	Echocardiogram
	Exercise testing
	Electrophysiology testing
	Coronary angiography

VI. IFFERENTIAL DIAGNOSIS

Differential diagnosis for tachycardia depends on the type of tachycardia, such as wide QRS complex tachycardia or regular, narrow-QRS tachycardias.

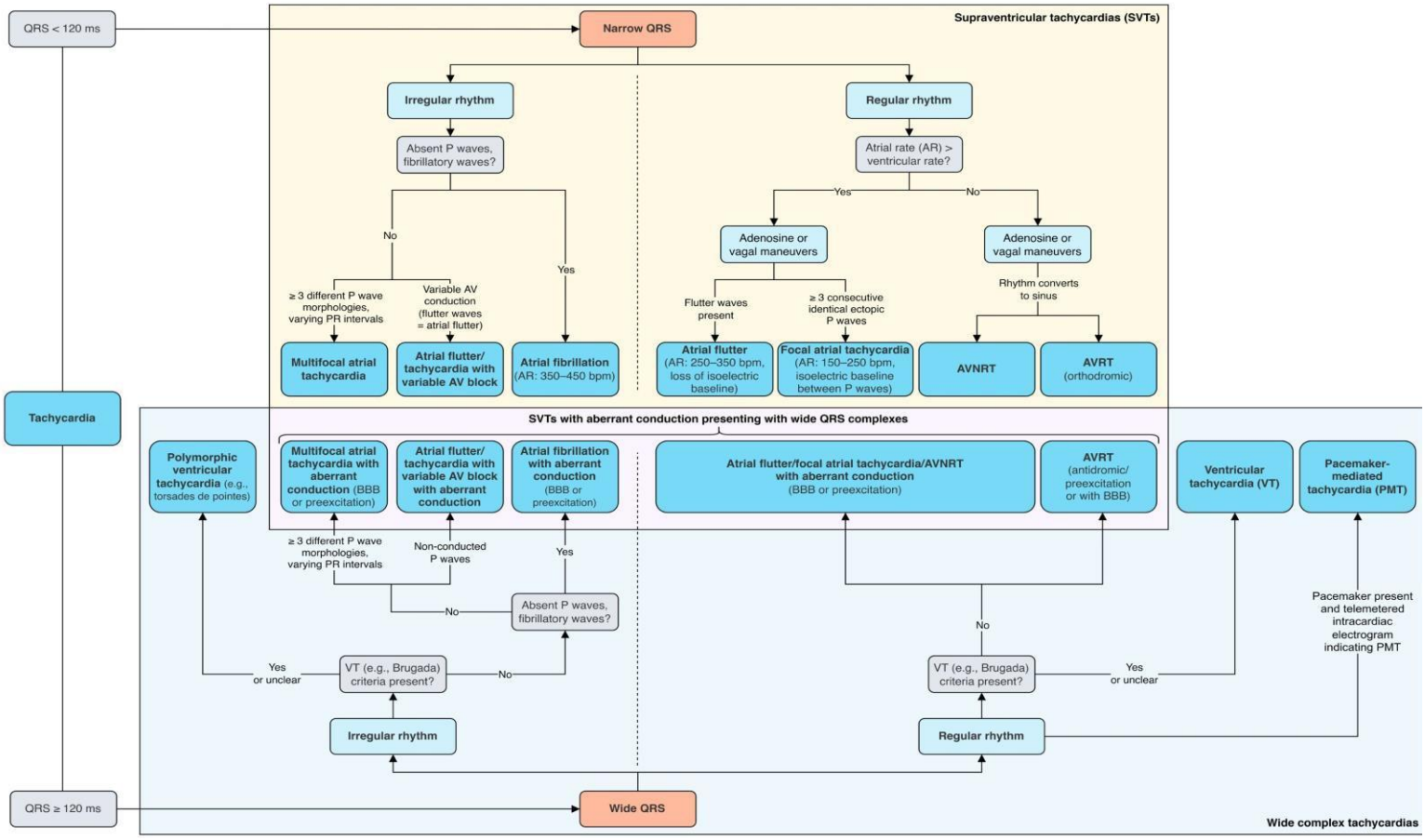


Figure 1. Differential diagnosis for tachycardia

1- **Narrow QRS tachycardia [1]**

A. **Haemodynamically unstable patients**: Synchronized DC cardioversion

B. **Haemodynamically stable patients**:

- **Vagal manoeuvres in the supine position with leg elevation**
- **Medications:**
  - Adenosine (6-18 mg i.v. bolus with normal saline flush) if vagal manoeuvre fail (Except pre-excited Atrial fibrillation)
  - Verapamil (0.075-0.15 mg/kg i.v. (average 5-10 mg) over 2 min) or diltiazem (i.v.) (0.25 mg/kg (average 20 mg) over 2 mi) or Beta-blockers (i.v. esmolol (0.5 mg/kg i.v. bolus or 0.05-0.3 mg/kg/min infusion) or metoprolol (2.5-15 mg given i.v. in 2.5 mg boluses) if vagal maneuvers and adenosine fail
  - Synchronized direct-current cardioversion if drug therapy fails to convert or control the tachycardia)
- **Catheter Ablation**

2- **Wide QRS tachycardia [2,3]**

A. **Treatment of reversible conditions**

- Withdrawal of offending agents is recommended whenever drug-induced arrhythmias
- Investigation for reversible causes (e.g. electrolyte imbalances, ischemia, hypoxemia, fever)

B. **Hemodynamically unstable patients**: Synchronized DC cardioversion
C. **Hemodynamically stable patients**: Medication therapy or Synchronized DC cardioversion if drug therapy fails to convert or control the tachycardia

- **Medications therapy**:
  - Acebutolol PO 200–1200 mg daily or up to 600 mg bid
  - Amiodarone IV: 300 mg bolus for VF/pulseless VT arrest; 150-mg bolus for stable VT; 1 mg/min x 6 h, then 0.5 mg/min x 18 h, PO: 400 mg q8 to 12 h for 1–2 wk, then 300-400 mg daily; reduce dose to 200 mg daily if possible
  - Atenolol PO: 25–100 mg qd or bid,
  - Bisoprolol PO: 2.5–10 mg once daily
  - Carvedilol PO: 3.125–25 mg q 12 h
  - Diltiazem IV: 5-10 mg qd: 15-30 min Extended release: PO: 120–360 mg/day
  - Esmolol IV: 0.5 mg/kg bolus, 0.05mg/kg/min
  - Flecainide PO: 50–200 mg q 12 h
  - Lidocaine IV: 1 mg/kg bolus, 1–3mg/min or 1-1.5 mg/kg. Repeat 0.5–0.75 mg/kg bolus every 5–10 min (max cumulative dose 3 mg/kg). Maintenance infusion is 1–4 mg/min although one could start at 0.5 mg/min
  - Metoprolol IV: 5 mg q 5 min up to 3 doses, PO: 25–100 mg Extended release qd or q 12 h
  - Sotalol IV: 75 mg q 12h, PO: 80–120 mg q 12 h, may increase dose every 3d; max 320 mg/d
  - Procainamide IV: loading dose 10–17mg/kg at 20–50mg/min and Maintenance dose: 1–4mg/min, PO (SR preparation): 500–1250 mg q 6 h
  - **Verapamil is not recommended in wide QRS complex tachycardia of unknown etiology**
- **Administration of potassium and magnesium** has been proposed as helpful adjuncts in the prevention of ventricular arrhythmias
- **Implanted cardioverted defibrillator (ICD)** (for secondary prevention)
- **Catheter ablation**
- **Surgical ablation**
- **Autonomic modulation**: interruption of sympathetic outflow to the heart, pharmacological beta blockade, or through stimulation of the parasympathetic pathway

3- **Algorithm**

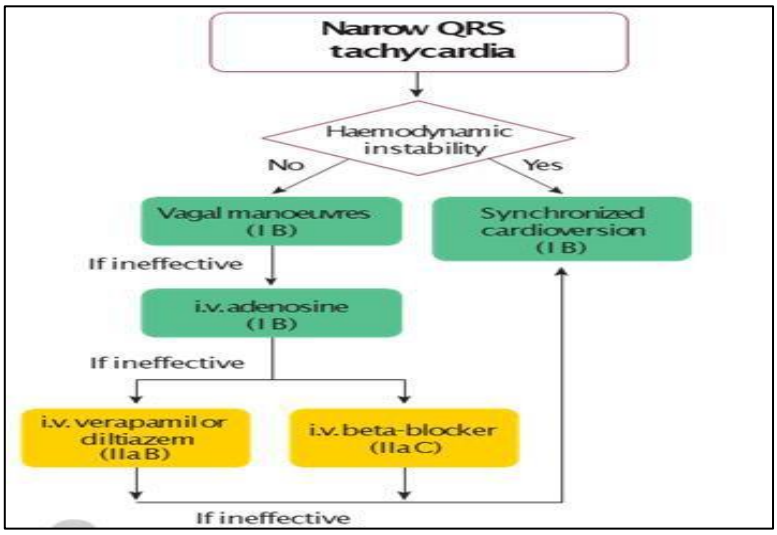


Figure 2. Acute management for narrow QRS complex tachycardia [1]

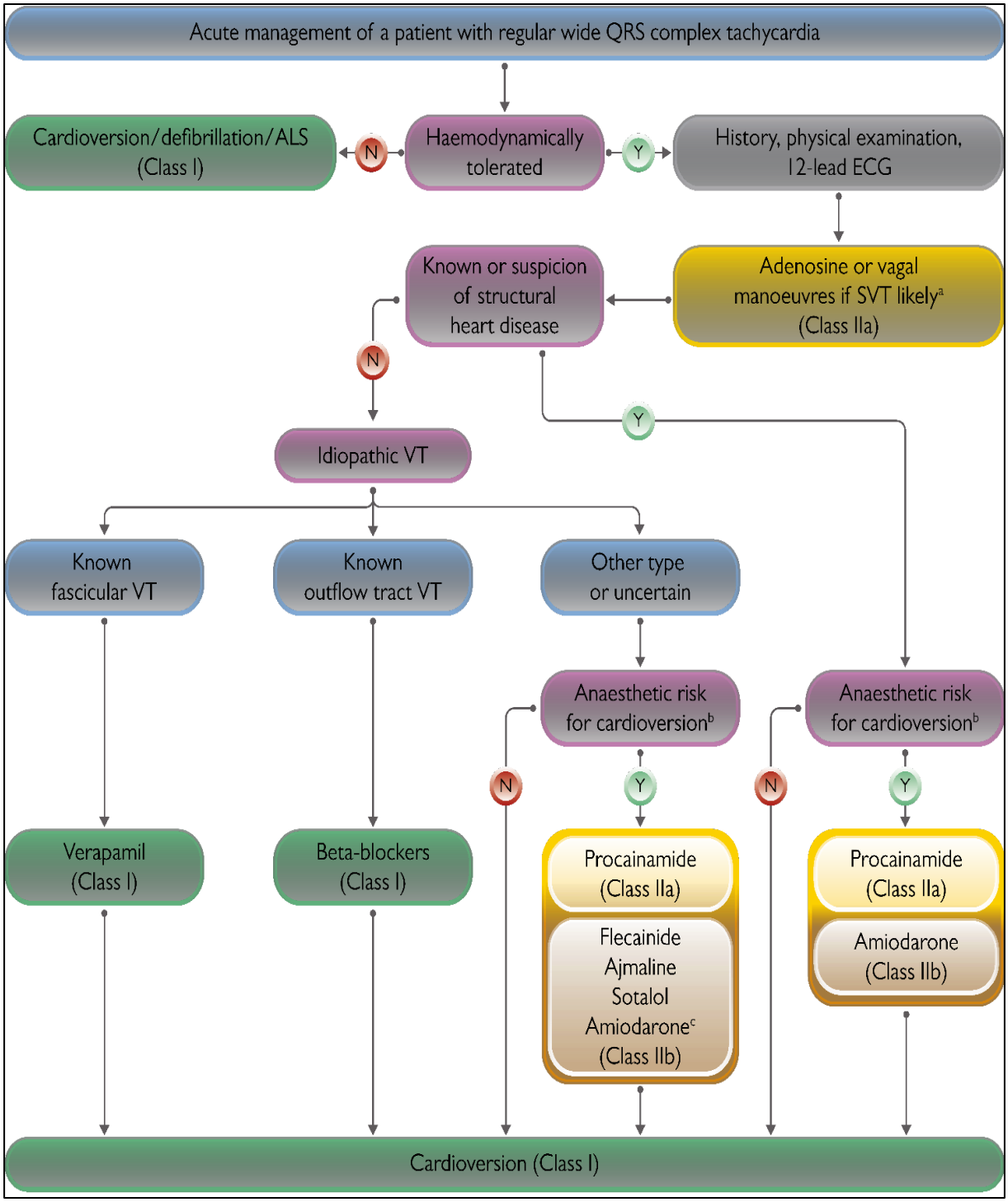


Figure 3. Acute management for regular wide QRS complex tachycardia [1]

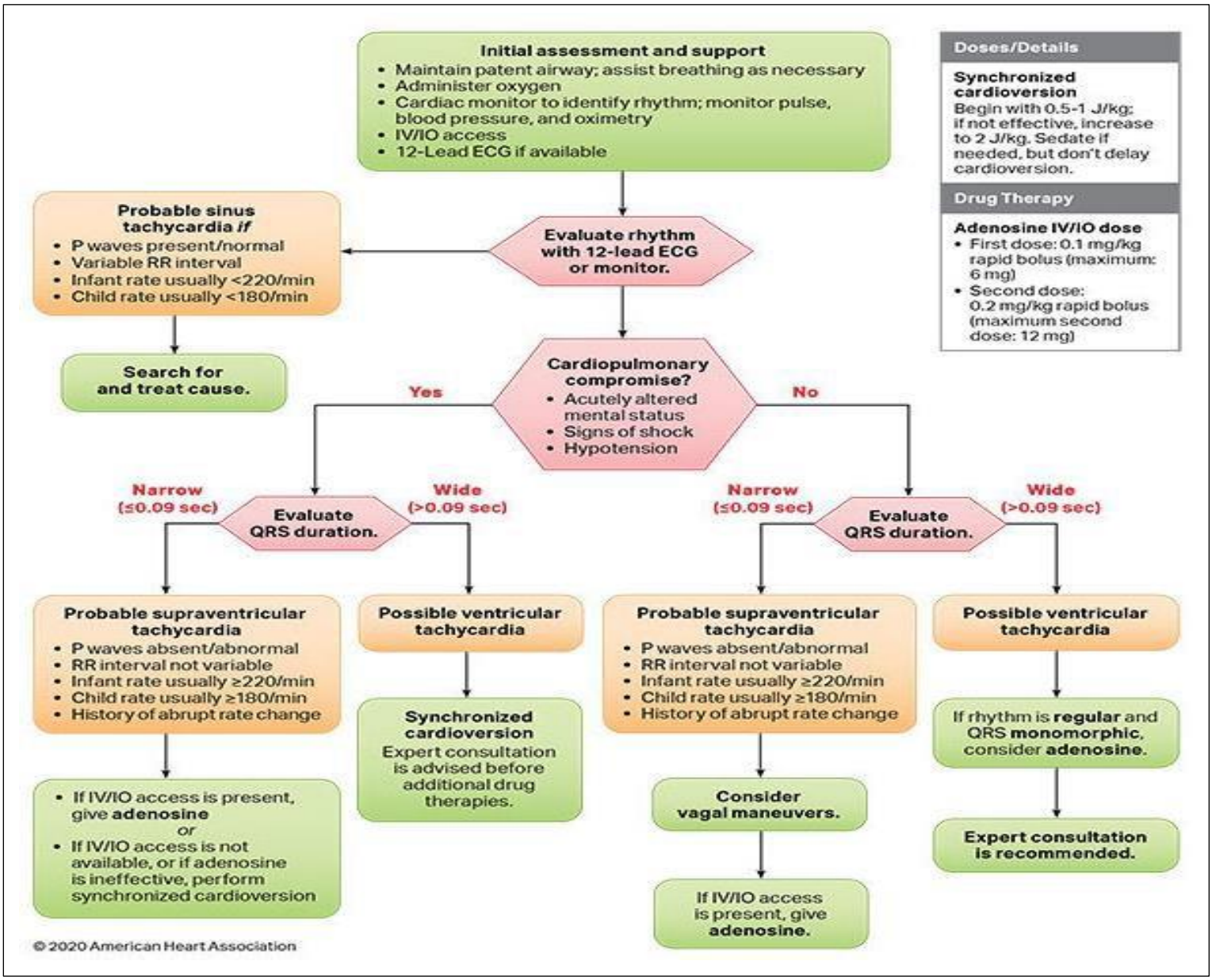


Figure 4. Pediatric Tachycardia with a pulse algorithm [7]

VIII. SPECIAL CASES

Case 1: A 48-year-old woman had a history of palpitations for 5 years. Her episodes started and stopped suddenly, lasted 1 to 2 minutes, and were associated with lightheadedness. She came to a local emergency room with a prolonged episode: ECG showed a narrow QRS tachycardia (by report; no ECG available) that was terminated with adenosine. She was treated with oral diltiazem and metoprolol but continued to have supraventricular tachycardia (SVT) episodes. She had a normal physical exam; non-invasive evaluation showed no structural heart disease. She was referred for catheter ablation of her SVT. [4]

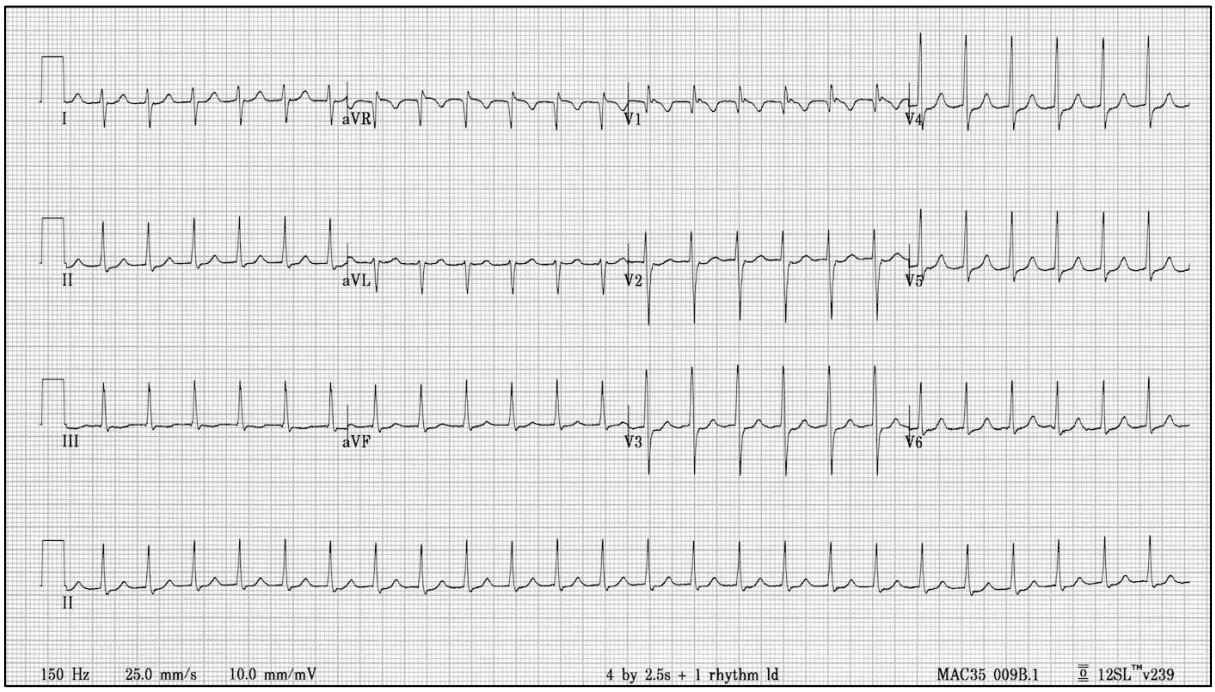


Figure 5. Regular narrow QRS complex tachycardia with short RP'. [5]

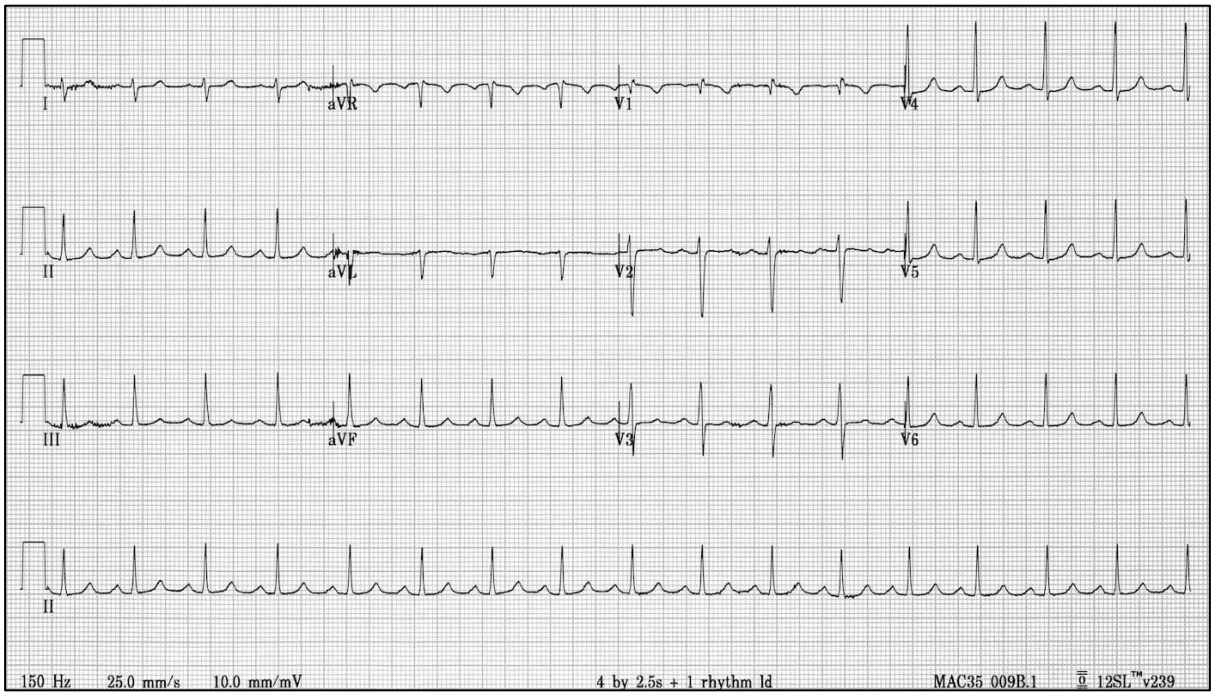


Figure 6. After 6mg of adenosine IV, her ECG is converted to sinus rhythm and the patient was diagnosed with 'Slow-Fast AVNRT' (Atrioventricular Nodal Reentrant Tachycardia) by electrophysiological study and successfully treated by RF catheter ablation. [5]

Case 2: The patient was a 28-year-old woman referred for management of palpitations for the last 2 years. Episodes began after birth of the eighth child and often worsened when she was upset. Ambulatory recorder showed sustained ventricular tachycardia originated from right ventricular outflow tract (having a left bundle branch block (LBBB) and right-inferior axis with a precordial R-wave transition at V3 and smooth R-wave contours in inferior leads). Metoprolol was ineffective at controlling her symptoms

(palpitations and fatigue), which were increasingly bothersome. Physical examination finding was normal aside from skipped beats without signs of shock. Echocardiogram showed mild global hypokinesis (ejection fraction 45%). She was referred for a repeat EP study and ablation. [4]

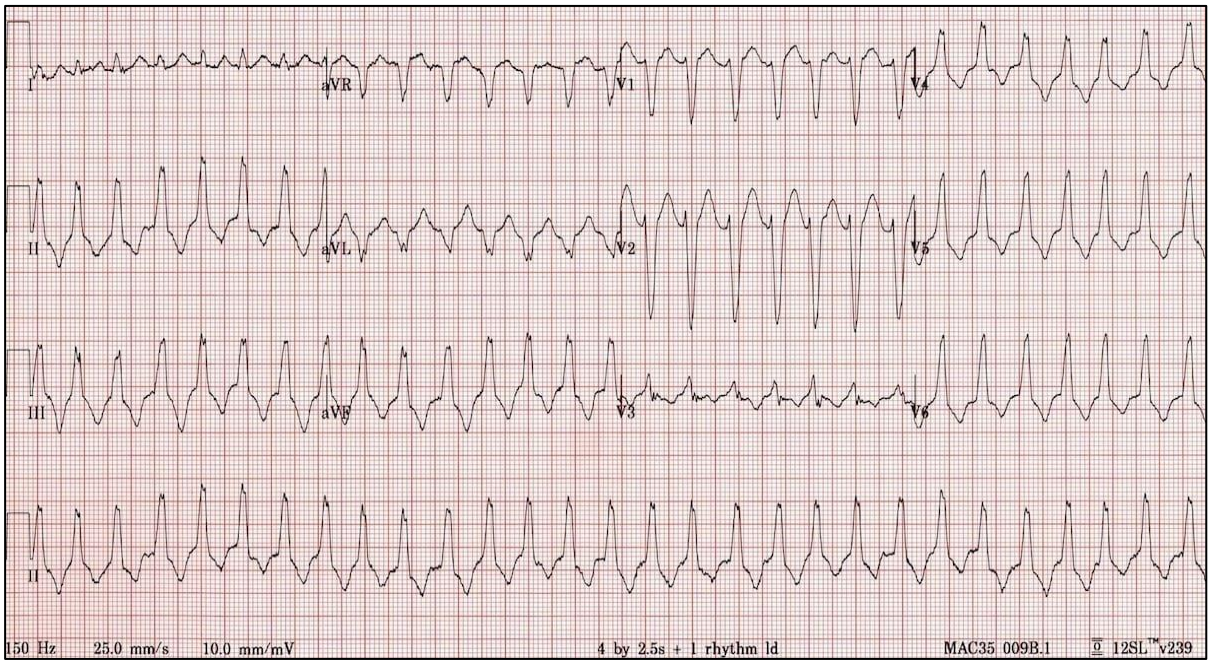


Figure 7. Sustained ventricular tachycardia originated from right ventricular outflow tract [5]



Figure 8. After catheter ablation by radio-frequency, ECG showed sinus rhythm without ventricular tachycardia. [4]

IX. OMPLICATIONS

The common complications include sudden cardiac death, syncope, stroke, heart failure, hypotension and/or shock.

X. REFERENCES

1. Brugada, J., Katritsis, D. G., Arbelo, E., Arribas, F., Bax, J. J., Blomström-Lundqvist, C. Diller, G.-P. (2019). 2019 ESC Guidelines for the management of patients with supraventricular tachycardiaThe Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). European Heart Journal. doi:10.1093/eurheartj/ehz467.

2. Katja Zeppenfeld, et al, ESC Scientific Document Group , 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC), European Heart Journal, Volume 43, Issue 40, 21 October 2022, Pages 3997–4126, https://doi.org/10.1093/eurheartj/ehac262.

3. Al-Khatib, S. M., Stevenson, W. G., Ackerman, M. J., Bryant, W. J., Callans, D. J., Curtis, A. B., Page, R. L. (2018). 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. Journal of the American College of Cardiology. doi:10.1016/j.jacc.2017.10.054.

4. Mark E. Josephson MD, Josephson's Clinical Cardiac Electrophysiology Fifth Edition. https://litfl.com/right-ventricular-outflow-tract-rvot-tachycardia.

5. Trappe, H.-J. (2010). Concept of the five ′A′s for treating emergency arrhythmias. Journal of Emergencies, Trauma, and Shock, 3(2), 129. doi:10.4103/0974-2700.62111 (ETIOLOGY) https://www.resus.org.uk/library/2021-resuscitation-guidelines/adult-advanced-life-support-guidelines.

EMERGENCY BRADYCARDIA

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I. INTRODUCTION

Bradycardia spans from a relatively benign condition to life-threatening emergencies. Bradycardia is a frequent finding in clinical practice and its significance is dependent on *underlying cause* and *clinical presentation*. The goal of initial management is stabilization by increasing the *ventricular rate*.

II. DEFINITION

A normal heart rate is normally between 60 to 100 beats per minute (bpm). An emergency bradycardia is defined as a heart rate < 50 bpm with one of these conditions: **(1)** hemodynamic compromised, **(2)** severe slow heart rate < 35-40 bpm, **(3)** ventricular tachyarrhythmias, **(4)** acute heart failure, **(5)** acutely altered mental status.

III. ETIOLOGIES AND PATHOPHYSIOLOGY

The causes of bradycardia can be separated into *primary* or *secondary* (Table 1). The primary or intrinsic etiologies are relatively rare in the acute setting and occur more often in the elderly patients. Secondary or extrinsic etiologies are more frequently seen in the acute care and are more likely to be reversible with medical therapy.

Primary	Secondary
Idiopathic (ageing) degeneration	Acute myocardial infarction
Ischemic heart disease	Medications: digoxin, betablocker overdose…
Myocarditis, Endocarditis	Hypokalemia, hyperkalemia
Infiltrative disease: sarcoidosis, amyloidosis	Hypothyroidism
Congenital disease	Hypoxia
Surgical trauma: valve replacement	Hypothermia
	Acidosis
	Physical training (athletes, sports)
	Vagal tone

Table 1: The above causes can involve the sinus node and atrio-ventricular node (AV node) or distal His bundle-Purkinje system results in sick sinus syndrome and different degree of AV block at the nodal level or infra-nodal level, respectively.

IV. IAGNOSTIC

1- Clinical signs and symptoms

Bradycardia may present as *fatigue, dizziness, syncope, pre-syncope, shortness of breath, chest pain, palpitations, cardiac arrest*. *Assessment for signs of hypoperfusion or hemodynamic compromised* such as cyanosis, altered mental status, pallor will help guide management.

2- Investigations

A 12-lead standard ECG has the most diagnostic value. ***Prolonged Holter monitoring*** is also helpful for intermittent bradycardia event. Serologic finding such as ***potassium, BUN, Creatinine, thyroid function test*** *(TSH, fT4, fT3)* will reveal common secondary causes of bradycardia. Serum cardiac markers, such as ***troponin, BNP or NT-proBNP*** are requested to assess myocardial ischemia or injury as a cause of bradycardia. ***Chest radiograph*** may reveal

enlarged cardiac silhouette (pericardial effusion or cardiomegaly). ***Cardiac ultrasound*** can identify structural heart disease.

V. DIFFERENTIAL DIAGNOSIS

Premature ventricular complex bigeminy, blocked premature atrial complex.

VI. ANAGEMENT

1- Objectives

The goal of initial management is stabilization by increase the ventricular rate through one of the following: **(1) pharmacological intervention and/or (2) non-pharmacological intervention**.[2, 5] The physicians need to *assess and determine the underlying causes of bradycardia*.

2- Critical sign

(1) hemodynamic compromised, **(2)** severe slow heart rate < 35-40 bpm, **(3)** ventricular tachyarrhythmias, **(4)** acute heart failure, **(5)** acutely altered mental status.

3- Mortality risk factors

Family history of sudden cardiac death, history of syncope, preexistent heart failure, associated cardiovascular and non-cardiovascular comorbidities.

4- Outpatient management

Bradycardia patient with above critical signs are recommended to hospitalization for further investigation and appropriate management.

5- Treatment

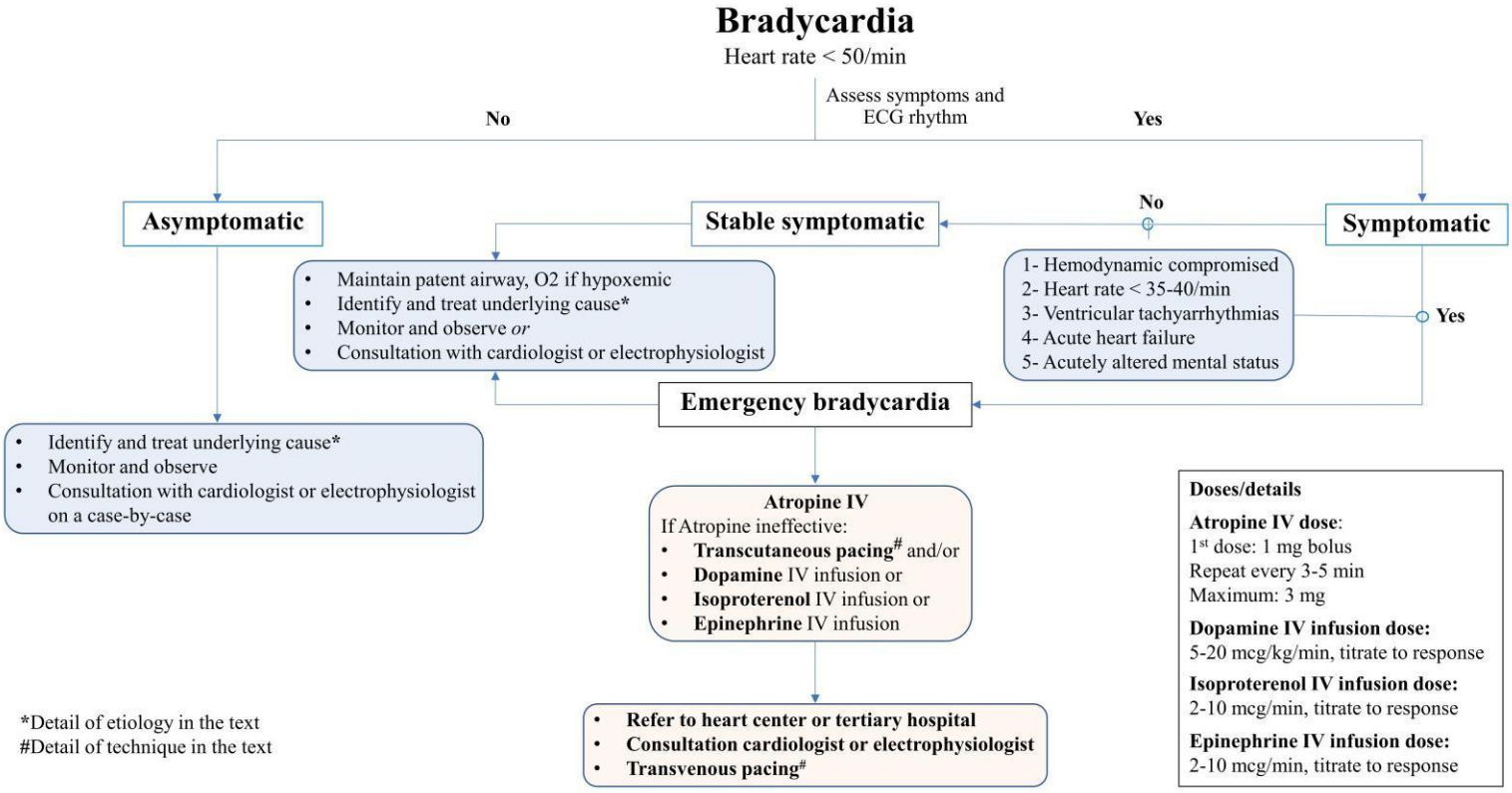
A. Pharmacological intervention

- **Atropine:** first-line drug for unstable and acute symptomatic bradycardia
  - Dosage: 1st dose 1mg IV bolus, repeat every 3 to 5 min and maximal dose is 3 mg, dose lower than 0.5 mg is not recommended
- Alternative drugs: Dopamine, Epinephrine and Isoproterenol
  - Dosage of Dopamine: IV infusion 5 to 20 mcg/kg/min and titrate to patient response
  - Dosage of Epinephrine: IV infusion 2 to 10 mcg/min and titrate to patient response
  - Dosage of Isoproterenol: IV infusion 2 to 10 mcg/min and titrate to patient response
- Pharmacological intervention should not delay implementation of external pacing for patients with poor perfusion

B. Non-pharmacological intervention#

- **Transcutaneous cardiac pacing**
  - Technique: places pads on the patient chest and connects the ECG leads. Turn the pacer on with pacing rate to > 30 bpm above intrinsic rhythm and set 70 mA. Start pacing, once pacing captured, set current at 5-10 mA above the threshold.
  - Complication: severe discomfort and failure to pace and capture.
- **Temporary transvenous cardiac pacing**
  - Technique: equipped with fluoroscopy (usually in Cath-Lab). The site chosen is usually on femoral, subclavian or internal jugular vein. Venous sheath is inserted by Seldinger technique. Temporary pacing lead insertion into the appropriate pacing cardiac chamber (apical RV) and ensuring accurate lead placement.
  - Complication: thrombophlebitis, infection, cardiac perforation.

6- Algorithm



VII. SPECIAL CASES

Case #1: A 74-year-old female with history of hypertension presented multiple episodes of syncope and was admitted at a referral hospital. Her blood pressure was 85/50 mm Hg, heart rate was 36 bpm and SpO2 was 96%. There, physician did a complete clinical examination and lab test which showed no findings of secondary causes. The ECG (Fig. 1) showed complete AV block with ventricular rate 37 bpm. Atropine and Dopamine IV were given based on the algorithm but there was no clinical response. The patient was transferred to a heart center in Phnom Penh where the electrophysiologist performed transvenous pacing and subsequently permanent pacemaker was successfully implanted (Fig. 2).

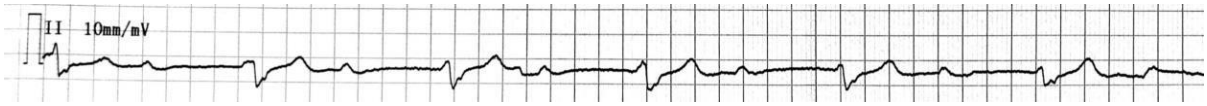


Figure (1). Complete AV dissociation with heart rate 37 bpm suggested complete atrioventricular block.



Figure (2). Restoration of normal heart rate and AV conduction after permanent pacemaker implantation. Pacing spike preceded each QRS complexes following normal P wave.

Case #2: A 53-year-old female with history of diabetes, hypertension and chronic kidney disease presented fatigue, dizziness and vomiting. Blood pressure was 95/62 mm Hg, heart rate was 38 bpm and SpO2 was 92%. The ECG (Fig. 3) showed escape junctional rhythm with heart rate 39 bpm and peaked T wave and shortened QTc. She was found to have severe hyperkalemia (K^+ 7 mmol/L) due to her underlying CKD. Management and correction of hyperkalemia to normal potassium level (K^+ 4.5 mmol/L) resolved the bradycardia (Fig. 4).



Figure (3). Escape junctional rhythm, peaked T wave and shortened QTc consistent with hyperkalemia.



Figure (4). ECG normalized after potassium level correction.

VIII. COMPLICATIONS

The common complications include sudden cardiac death, syncope, trauma secondary to fall after syncope, worsening of heart failure, hypotension and/or shock, ventricular tachycardia/fibrillation, death.

IX. EFERENCES

1. Brignole M, Auricchio A, Baron-Esquivias G et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013 Aug;34(29):2281-329.
2. Panchal AR, Bartos JA, Cabanas JG et al. adult Basic and Advanced Life Support Writing Group. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020 Oct 20;142(16_suppl_2):S366-S468.
3. Kusumoto FM, Schoenfeld MH, Barrett C et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. J Am Coll Cardiol. 2019 Aug 20;74(7):932-987.
4. Gibson M, Ibtisam A. (n.d). Bradycardia natural history, complication and prognosis. https://www.wikidoc.org/ index.php/Bradycardia_natural_history, complications_and_prognosis
5. Tiffany M, Harry S. Evaluation of Bradycardia in the Emergency Department. Emergency Medicine Reports. Practical, Evidence-Based Reviews in Emergency Care. 2017 Sep 15;38(18)

PULMONARY EMBOLISM

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I. DEFINITION

Pulmonary embolism (PE) refers to obstruction of the pulmonary artery or one of its branches by thrombus.

II. EPIDEMIOLOGY

PE incidence varies by region, but it is typically estimated at 39 – 115 cases per 100.000 person-years. Incidence increase with age, particularly in people over 60 years old. PE is slightly more common in women, especially those on hormonal therapies, during pregnancy or in post-partum period.

III. ETIOLOGY

Pulmonary embolism (PE) is typically caused by thrombus formation, most often originating from deep venous thrombosis (DVT) in the legs. The etiology involves three primary factors – **Venous stasis**, **endothelial injury**, and **hypercoagulability** (Virchow's triad). Common triggers include prolong immobility, surgery, trauma, malignancy, hormonal influences (e.g. pregnancy, oral contraceptives), and genetic thrombophilias (e.g Factor V Leiden).

IV. PATHOPHYSIOLOGY

PE occurs when a blood clot, usually from a deep venous thrombosis (DVT) in the legs, travels to the lungs and blocks a pulmonary artery. This obstruction reduces blood flow to the lungs, impairing oxygen exchange, and increase pulmonary artery pressure. Large clots can cause right heart strain, reduce cardiac output, and potentially lead to shock or sudden cardiac death.

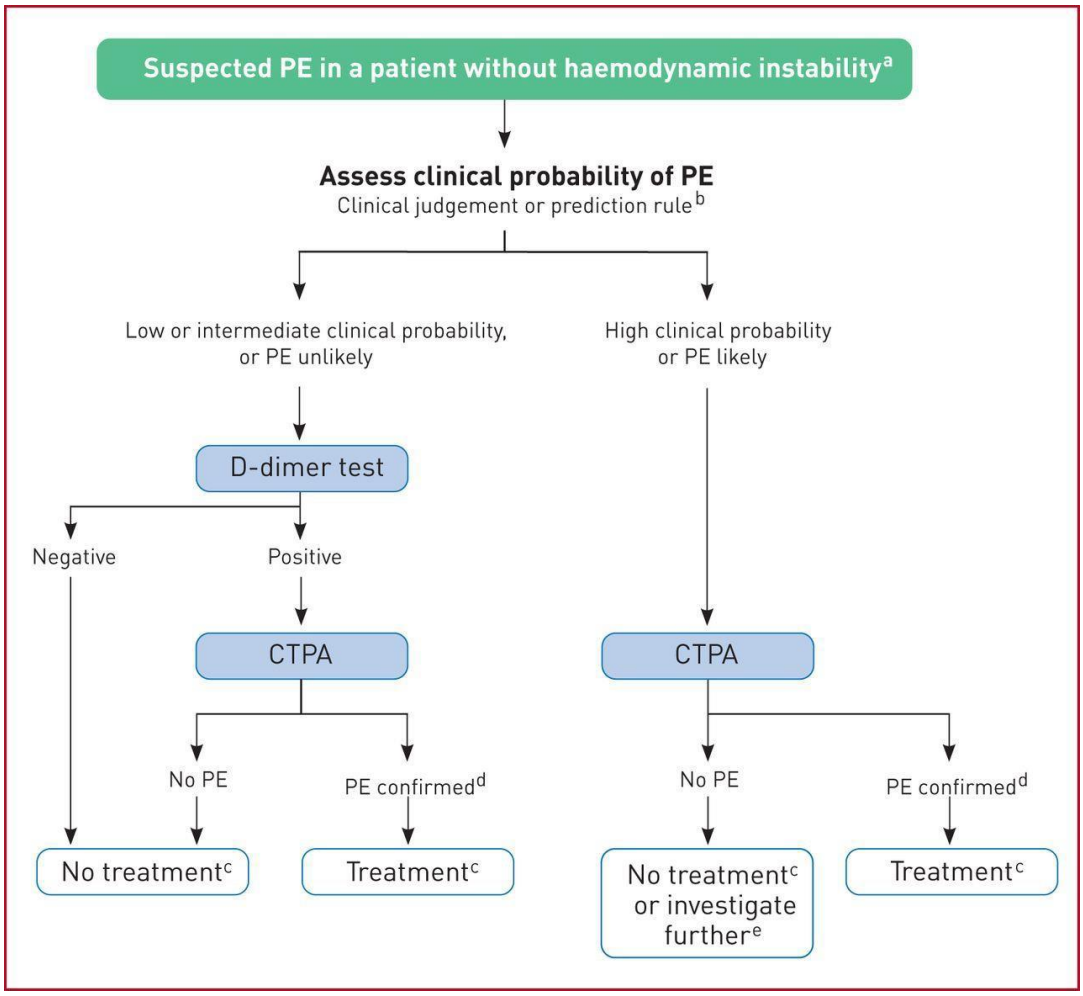
V. DIAGNOSIS

1. Initial assessment:
    - Clinical History and symptoms: assess for dyspnea, chest pain, tachycardia, hemoptysis and risk factors (e.g. recent surgery, immobilization, cancer)
    - Physical examination to assess vital signs, signs of DVT and signs of right heart failure
2. Risk stratification:
    - Use **Modified Wells scoring system** (see Annex 1) or **Revised Geneva scoring system** (see Annex 2) to assess pre-test probability of PE
3. D-dimer testing:
    - If low/intermediate pre-test probability: Perform D-dimer blood test
    - If D-dimer is negative, PE can be ruled out
    - If D-dimer is positive, proceed to Imaging
4. Imaging:
    - CT pulmonary angiography (CTPA): Gold standard imaging technique to visualize and confirm the presence of thrombi.

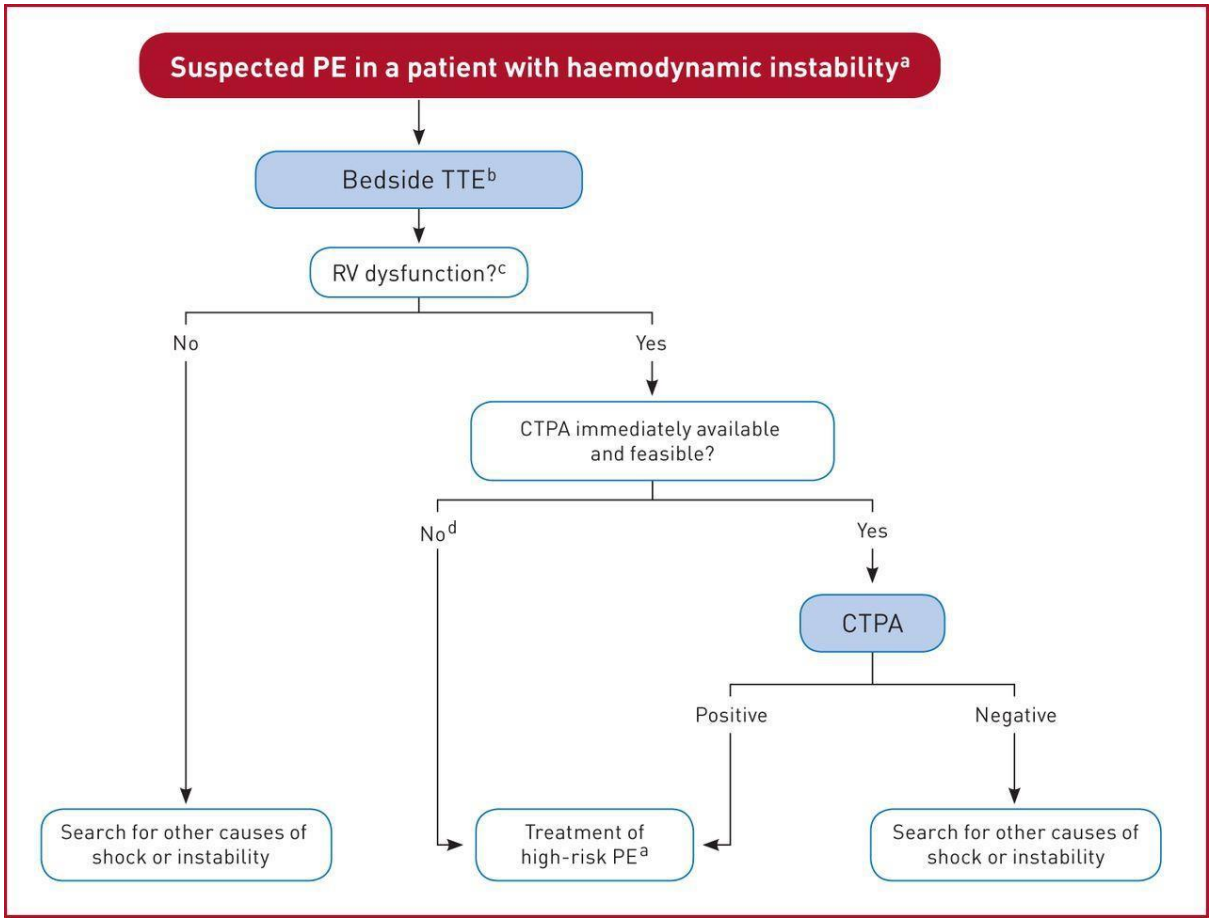
- Ventilation-Perfusion (V/Q) scan: used when CTPA is contraindicated (e.g. renal impairment, contrast allergy)
- Compression ultrasound of the legs: perform if DVT is suspected, especially when symptoms of DVT are present

5. Echocardiography:
    - For **hemodynamically unstable patients**, bedside echocardiography can identify right heart strain suggestive of PE
6. Additional laboratory tests:
    - Arterial blood gas (ABG): show hypoxemia, hypocapnia and respiratory alkalosis.
    - Cardiac markers: Elevated troponins and brain natriuretic peptide (BNP) can indicate RV dysfunction and are associated with worse prognosis.

Diagnostic Algorithm for patient with suspected PE without hemodynamic instability



Diagnostic Algorithm for patient with suspected high-risk PE with hemodynamic instability



VI. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pulmonary embolism (PE) includes conditions with similar symptoms such as **myocardial infarction**, **pneumonia**, **pleuritis**, **pneumothorax**, **congestive heart failure**, and **pericarditis**. Theses can present with chest pain, dyspnea, or tachycardia, mimicking PE. Careful evaluation of clinical history, risk factors and diagnostic imaging is essential to differentiate PE from these conditions.

VII. MANAGEMENT

1. Initial assessment:
    - Stabilization: assess airway, breathing and circulation (ABCs)
    - Vital sign monitoring: monitor HR, BP and oxygen saturation.
2. Risk stratification:
    - Classify PE as **low**, **intermediate** or **high risk** based on clinical presentation and hemodynamic stability
3. Anticoagulation therapy
    - Immediate treatment: **Start anticoagulation as soon as PE is suspected**
        - **Unfractionated Heparin (UFH)**: for high-risk patients

Key points about UFH for PE treatment	
Administration	IV bolus followed by continuous infusion
Dosing protocol	• Initial bolus: 80 units/kg (usually 5000 – 10000 units) • Continuous infusion: 18 units/kg/h, adjusted based on aPTT results (target: 1.5 – 2.5 times normal value)
Monitoring	aPTT measured every 6 hours initially to ensure target level
Reversal (antidote)	Protamine sulfate

- **Low molecular weight heparin (LMWH)**: For stable patients

Key points about LMWH for PE treatment	
Administration	Subcutaneous injection (S/C)
LMWH	Enoxaparin (Lovenox®) 20mg, 40 mg, 60 mg
Dosing protocol	1 mg/kg twice daily
Monitoring	Anti-factor Xa
Duration	LMWH is often used for the initial phase (5 – 10 days). After that, patients are transitioned to oral anticoagulants such as warfarin or direct oral anticoagulant.

- **Direct Oral Anticoagulant (DOACs)**: consider for outpatient management once PE is confirmed, based on guidelines

Key points about DOAC for PE treatment	
DOAC Agents	• Apixaban • Rivaroxaban • Dabigatran • Edoxaban
Dosing protocol	• Apixaban: **initial dose 10 mg twice daily for 7 days**, then 5 mg twice daily • Rivaroxaban: **initial dose 15 mg twice daily for 21 days**, then 20 mg once daily • Dabigatran: initial treatment with parenteral anticoagulation (e.g LMWH) for 5 – 10 days, then switch to 150 mg twice daily • Edoxaban: initial treatment with parenteral anticoagulation (e.g LMWH) for 5 – 10 days, then switch to 60 mg once daily

- **VKA (Vitamin K antagonists): second-line therapy. VKA** are often considered when DOACs are contra-indicated or unsuitable, such as
  - In patients with severe renal impairment (eGFR < 30 ml/min)
  - In patients on certain medications that interact with DOACs, reducing their efficacy or increase bleeding

Key points about VKA for PE treatment	
Overlap with heparin	UFH or LMWH is used for at least 5 days until the INR reaches the therapeutic range (2 – 3) for 2 consecutive days
Agents	• Wafarin (COUMADINE®) • Acenocumarol (SINTROM®)
Monitoring	Frequent INR checks during initiation, then less often (monthly) once stable
Maintenance dose	Adjusted based on INR
Reversal agent	Vitamin K

4. Thrombolytic therapy
    - Indication: for patients with massive PE or those who are hemodynamically unstable (e.g hypotension)

Key points about thrombolytic therapy for PE	
Agent	Alteplase (tPA)
Administration	IV infusion
Dosing protocol	100 mg infusion over 2 hours

5. Mechanical Intervention
    - Inferior Vena Cava (IVC) Filter: consider for patients with contraindication to anticoagulant or recurrent PE despite adequate treatment
6. Monitoring and Supportive Care
    - Monitoring: complications (bleeding, recurrent PE)
    - Supportive Care: administer fluids or vasopressors if necessary for hemodynamic support.
7. Long term management:
    - Anticoagulation duration:
        - Provoked PE: 3 – 6 months of anticoagulation
        - Unprovoked PE: extended anticoagulation based on individual risk factors (e.g cancer, thrombophilia)

VIII. SPECIAL CASES

- **Massive PE:** Hemodynamically unstable, requires immediate thrombolytics or surgical embolectomy
- **Pregnancy-Related PE:** due to physiological changes and venous stasis. Use Low molecular weight heparin (LMWH) for treatment and avoid warfarin in pregnancy
- **Cancer-**Related PE: increased risk in cancer patients, long-term anticoagulation recommended using LMWH or DOACs
- **Pediatric PE:** Less common, often linked to congenital heart disease or surgery, management follow specific pediatric guidelines.

IX. EVOLUTION AND PROGNOSIS

Without treatment, PE can result in severe complications and high mortality rate. Prognosis improve significantly with timely intervention, reducing mortality rates. Long-term outcomes may include chronic issues like pulmonary hypertension, but many patients recover well with appropriate management.

X. COMPLICATIONS

- Right heart failure: due to increased pulmonary pressure
- Hypoxia: from impaired oxygen change
- Pulmonary Hypertension: develop from unresolved clot
- Recurrent PE
- Post-thrombotic syndrome: in case of DVT leading to PE.
- Death: untreated or severe PE can lead to sudden cardiac death

XI. PREVENTION AND RECOMMENDATION

Preventing PE involves assessing risk factors and implementing strategies such as pharmacologic prophylaxis (e.g. LMWH, DOACs) and mechanical measures (e.g. compression stockings). Early mobilization post-surgery and patient education on PE symptoms are crucial.

XII. REFERENCES

1. Phouy Sonaroth, MD, Sok Chour, MD, Nhem Sophoeun, MD. (2013). Clinical Practice Guideline for Medicine. Ministry of Health. Part 1 : Page ; 123-131
2. 2019 ESC Guidelines for the diagnosis and management of Acute Pulmonary Embolism developed in collaboration with the European Respiratory Society (ERS): The task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC).
3. Antithrombotic therapy for VTE Disease: Compendium and Review of CHEST Guidelines 2012 – 2021
4. Mayo Clinic (2022). Pulmonary Embolism – Patient information on symptoms, causes, diagnosis and treatment options. Available from: https://www.mayoclinic.org/diseases-conditions/pulmonary-embolism/diagnosis-treatment/drc-20354653
5. Medscape (2024). Pulmonary embolism clinical scoring systems. Available from: https://emedicine.medscape.com/article/1918940-overview

Annex 1: **Modified Wells Scoring System**

Clinical Characteristic	Score
Previous pulmonary embolism or deep vein thrombosis	+ 1.5
Heart rate >100 beats per minute	+ 1.5
Recent surgery or immobilization (within the last 30 d)	+ 1.5
Clinical signs of deep vein thrombosis	+ 3
Alternative diagnosis less likely than pulmonary embolism	+ 3
Hemoptysis	+ 1
Cancer (treated within the last 6 mo)	+ 1
Clinical Probability of Pulmonary Embolism	**Score**
Low	0 - 1
Intermediate	2 - 6
High	≥ 6

Annex 2: **Revised Geneva Score**

Risk Factors	Points
Age older than 65 y	1
Previous DVT or pulmonary embolism	3
Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month	2
Active malignant condition (solid or hematologic, currently active or considered cured < 1 y)	2
Symptoms	
Unilateral lower limb pain	3
Hemoptysis	2
Clinical Signs	
Heart rate 75-94 beats/min	3
Heart rate ≥95 beats/min	5
Pain on lower limb deep venous palpation and unilateral edema	4
Clinical Probability	**Score**
Low	0 - 3
Intermediate	4 - 10
High	≥ 11

ACUTE PULMONARY EDEMA

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I. DEFINITION

Acute pulmonary edema refers to clinical syndrome of new or worsening symptoms and/or signs of heart failure, leading to an unplanned hospital admission or an emergency department visit.

II. EPIDEMIOLOGY

- Prevalence of heart failure in the population is 2% in Europe and 4% in Southeast Asia.
- Incidence of new cases per 100,000 per year: 219 in USA, 130 in UK, 70 in china
- Main challenges of heart failure hospitalization:
    - 1-4% of total hospital admission
    - > 9/10 patients hospitalized due to worsening chronic heart failure
    - Average length of hospital stay: 5-10 days
    - ¼ or 24% patients are re-hospitalized within 30-days post discharge period, **20% die within 6 months**
- In-hospital mortality (+++):**4.8% in Asia pacific**

III. ETIOLOGY

Table. 1 Etiology of acute heart failure

Cardiovascular	Non-Cardiovascular	Patient-related or iatrogenic
- Acute coronary syndromes - Tachycardia (i.e., Afib) - Bradycardia (i.e. 3rd degree AVB) - Uncontrolled hypertension or hypertensive crisis - Myocarditis - Acute pulmonary embolism - Acute valvular regurgitation (i.e. endocarditis, MI) - Aortic dissection - Cardiac tamponade	- Infections and febrile states - COPD exacerbation or asthma - Renal dysfunction - Anemia - Hyperthyroidism - Hypothyroidism - Strenuous exercise - Emotional stress - Pregnancy (peripartum cardiomyopathy	- Poor compliance with medication - Increased salt or fluid intake - Surgery - Drugs (i.e. NSAID, Thiazolidinediones) - Alcohol abuse

IV. PATHOPHYSIOLOGY

There are two main types of congestion:

1. Peripheral congestion: progressive increase in body weight, peripheral edema, jugular distension, hepatomegaly, ascites and renal venous stasis.
2. Pulmonary congestion: worsening dyspnea, pulmonary rales and B-line at lung ultrasound.

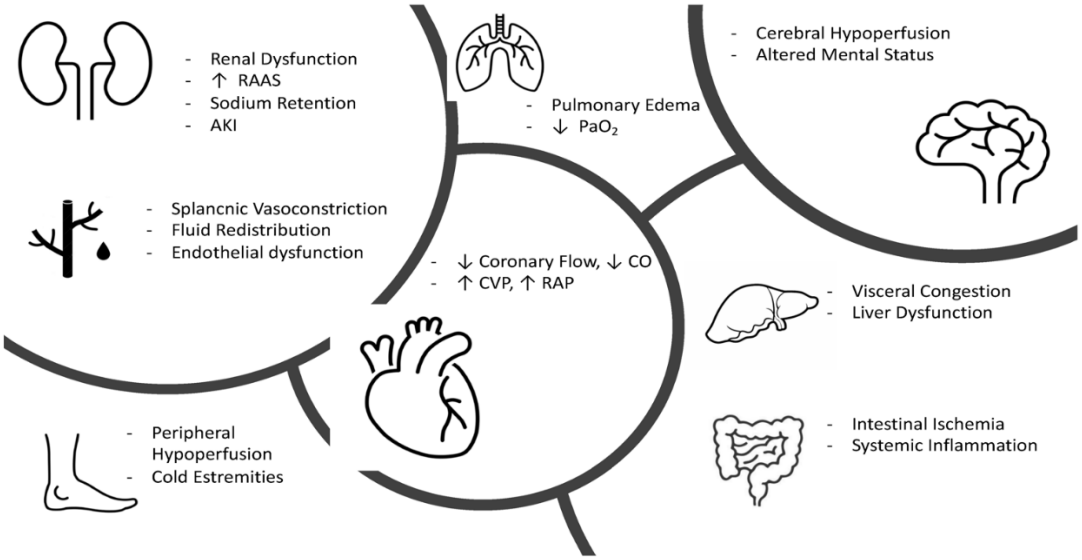


Fig. 1 Pathophysiology of acute heart failure.

RASS, renin angiotensin aldosterone system; AKI, acute kidney injury; CO, cardiac output; CVP, central venous pressure; RAP, right atrial pressure

V. DIAGNOSIS

1.Clinical

- Symptom:
  - Dyspnea: paroxysmal nocturnal dyspnea, reduced exercise tolerance, orthopnea ! Evaluation dyspnea severity classification.
  - Congestion: lower extremity swelling, ankle swelling, abdominal fullness, hepatic congestion
- Physical finding:
  - Vital sings: BP, HR, SpO2, Temperature, RR
  - Heart sounds: Third heart sound (LV dysfunction), Murmur, Jugular venous distension
  - Lung: rales (heart failure)

Table. 2 NYHA Classification

New York Heart Association Dyspnea Classification	
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity
II	Mild symptoms and slight limitation during ordinary activity
III	Significant limitation in activity due to symptoms, comfortable only at rest
IV	Severe limitations. Symptoms event while at rest

2. Investigation: ***Treatment should not be delayed while waiting for the results!***

- Laboratory: complete blood count, chemistries, TSH, ABG, BNP if available, D-dimer if suspicion PE
- Imaging: ECG, chest X-ray, Echocardiography& lung ultrasound-if available

3. Four major Clinical hemodynamics profiles of acute decompensated heart failure (ADHF):

- Acute decompensated heart failure
- Acute pulmonary edema
- Cardiogenic shock
- Isolated right ventricular failure

VI. DIFFERENCIAL DIAGNOSIS

Table. 3 Differential diagnosis of acute heart failure.

Pulmonary Disease	Other
Pneumonia	Severe sepsis
Exacerbated COPD	Anemia
Pleural disease (effusion, pneumothorax...)	Metabolic acidosis
Pulmonary embolism	Neurologic disease
	Anxiety disorder

Table. 4 Differentiation of noncardiogenic from cardiogenic pulmonary edema based on clinical data

Noncardiogenic	Cardiogenic
History	
- Underlying disease (e.g., pancreatitis, sepsis)	- Acute cardiac event (e.g., myocardial infarction)
Physical examination	
- Warm periphery	- Cool, mottled periphery
- Bounding pulses	- Small-volume pulse
- Normal-sized heart	- Cardiomegaly
- Normal JVP	- Elevated JVP
- S3 absent	- S3 present
- No murmur	- Systolic and diastolic murmurs
ECG	
- Normal	- Sings of myocardial infarction/ischemia
Chest X-ray	
- Peripheral infiltrates	- Perihilar infiltrates

VII. MANAGEMENT

1. Objectives
   - Improve symptoms, congestion and low-output symptoms
   - Restore normal oxygenation
   - Optimize volume status
   - Identifying etiology and precipitating factors
   - Initiating and optimizing oral therapy, minimizing side effects
   - Educating patients and considering a disease management program
2. Critical sign
   - Respiratory distress: RR >35/min, SpO2 < 90%, PaO2 < 75mmHg, PaCO2 > 45mmHg
   - Hemodynamic instable: low/high BP (<85/>140mmHg), Severe arrhythmias, HR <60/min or > 130/min
3. Mortality risk factor
   - Patient intubated or likely to require respiratory support/intubation, includes
     - SpO2<90% despite supplement oxygen
     - Using accessory muscles and respiratory rate >25 breaths/min
   - Signs and symptoms of hypoperfusion and/or SBP < 90mmHg

– Heart rate < 40 or > 130bpm

4. Outpatient Management:

All acute pulmonary edema patients are recommended to hospitalization.

5. First-line treatment

i. Basic Assessment

- Positioning: head of bed elevated
- O2 10 L/min → SpO2 ≥95%
- Furosemide: 40-60mg i.v. (equal or 2 times to oral dose)
- Morphine: 2mg i.v. if severe anxiety or distress
- Digoxine: 0.25-0.5mg i.v. if rapid Afib (HR>110/min)

ii. Adequate perfusion

- ***Wet Cold*** (SBP <90mmHg):
  - Inotrope drug: Dobutamine= 3-5µg/kg/min
  - Vasopressor: Norepinephrine= 0.2-0.5µg/kg/min
  - Add Diuretic when perfusion corrected
- ***Wet Warm*** (SBP: elevated or normal): Vasodilatators:
  - Nitroglycerine spray 400µg sublingual, repeat 5-10 min
  - Nitroglycerine i.v. continuously 1mg/ml(10mg in 20ml)
    - Start 1mg/h, check BP after 5 and 10min
    - Increase 0.5mg/h if need (SBP >100mmHg), check BP 5 and 10min after each increase in dosing
    - Check BP every 20min once drip rate is reach (max 2.5mg/h, or drop SBP ≥40mmHg from initial BP)

iii. Reassessed~15-30min after:

- Sufficient respiratory + Ventilation
- Release dyspnea + Symptoms
- Normalization: BP, HR, urinary output
  - **Goals:**
- SpO2 : 94-98%
- pCO2 < 45mmHg, paO2 > 70mmHg
- SBP: 100-120/60,
- HR: 60-100/min + regular
- Urinary output >0.5ml/kg/h

6.Treatment adjustment

- SBP <85mmHg: Increase dose Inotropes and Add Vasopressor
- Respiratory distress *(SpO2 <90% with O2, RR>25/min): CPAP or intubation*
- Urine output < 20ml/h:
  - Bladder catheter
  - Double dose diuretic= 80-120mg i.v bolus or 100mg/6H continuously
  - Combined diuretic= Bumetanide (Burinex), 2mg i.v, repeat every 20min (max 30mg/day)
  - Low-dose dopamine= 3µg/kg/min
  - Dialysis/ultrafiltration

7.Algorithm

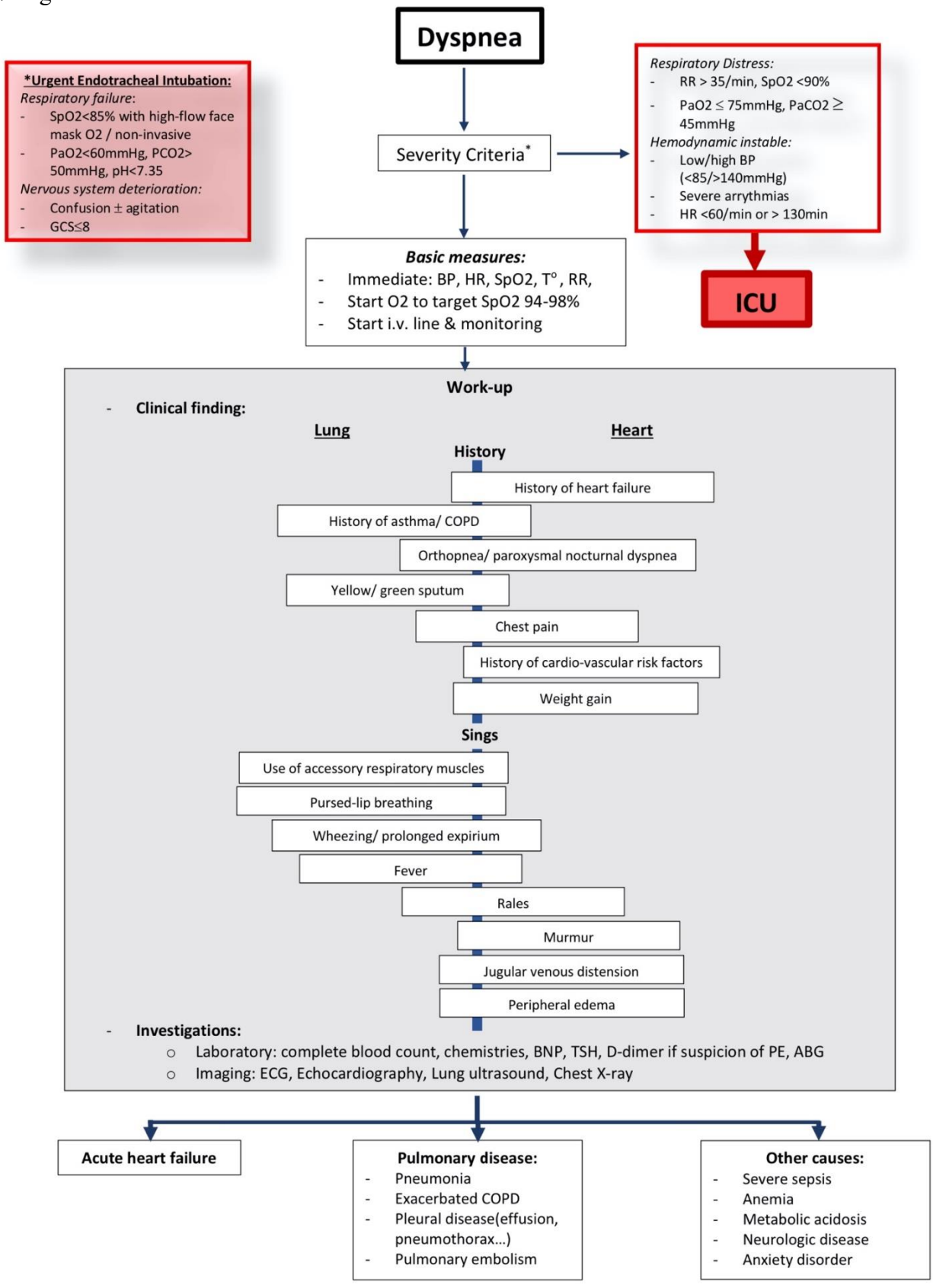

Dyspnea
*Urgent Endotracheal Intubation:
Respiratory failure:
- SpO2<85% with high-flow face mask O2 / non-invasive
- PaO2<60mmHg, PCO2> 50mmHg, pH<7.35
Nervous system deterioration:
- Confusion ± agitation
- GCS≤8
Severity Criteria*
Respiratory Distress:
- RR > 35/min, SpO2 <90%
- PaO2 ≤ 75mmHg, PaCO2 ≥ 45mmHg
Hemodynamic instable:
- Low/high BP (<85/>140mmHg)
- Severe arrythmias
- HR <60/min or > 130min
ICU
Basic measures:
- Immediate: BP, HR, SpO2, T°, RR,
- Start O2 to target SpO2 94-98%
- Start i.v. line & monitoring
Work-up
- Clinical finding:
Lung
Heart
History
History of heart failure
History of asthma/ COPD
Orthopnea/ paroxysmal nocturnal dyspnea
Yellow/ green sputum
Chest pain
History of cardio-vascular risk factors
Weight gain
Sings
Use of accessory respiratory muscles
Pursed-lip breathing
Wheezing/ prolonged expirium
Fever
Rales
Murmur
Jugular venous distension
Peripheral edema
- Investigations:
Laboratory: complete blood count, chemistries, BNP, TSH, D-dimer if suspicion of PE, ABG
Imaging: ECG, Echocardiography, Lung ultrasound, Chest X-ray
Acute heart failure
Pulmonary disease:
- Pneumonia
- Exacerbated COPD
- Pleural disease(effusion, pneumothorax...)
- Pulmonary embolism
Other causes:
- Severe sepsis
- Anemia
- Metabolic acidosis
- Neurologic disease
- Anxiety disorder

Fig. 2 Dyspnea work-out algorithms

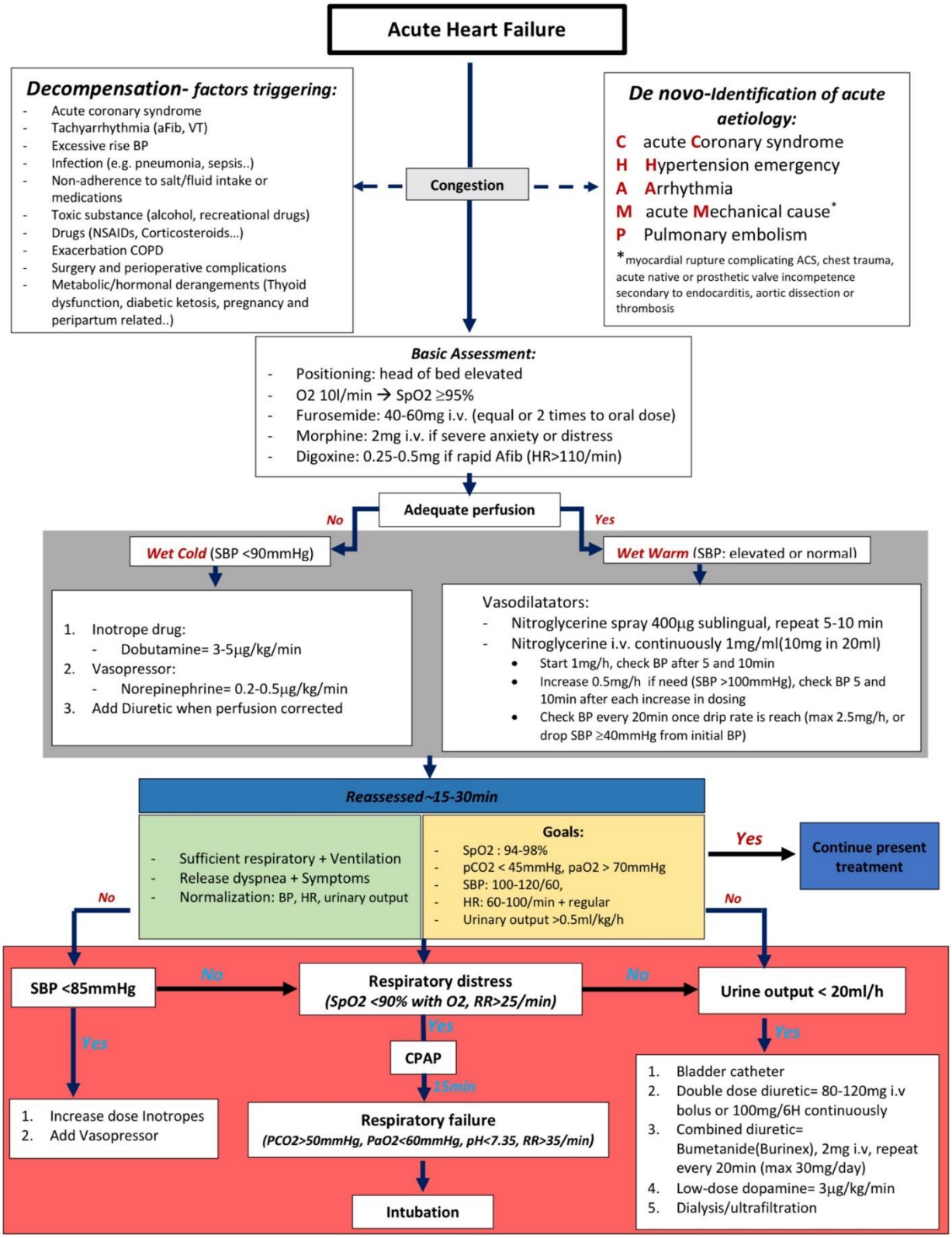


Fig. 3 Acute Pulmonary Edema Management Algorithms

VIII. SPECIAL CASES

- Acute right heart failure: secondary to pulmonary embolism, right ventricular infarction or pulmonary hypertension. Management challenges; focus on optimizing preload, reducing afterload and addressing the underlying cause (e.g., anticoagulant for PE)
- Flash Pulmonary Edema: sudden onset of severe pulmonary congestion. Management: requires rapid afterload reduction; IV nitroglycerine, diuretics and oxygenation support.
- Acute heart failure with acute coronary syndrome: acute MI triggers heart failure. Management requires balancing treatment for both ACS and AHF, revascularization and careful fluid management.
- Heart failure with pregnancy: peripartum cardiomyopathy is a notable cause, management focuses on balancing maternal and fetal health.

IX. EVOLUTION AND PROGNOSIS

- Key predictors of poor prognosis: advanced age, low SBP, High heart rate, sings of hypoperfusion with high comorbidities (diabetes, CKD, COPD or malignancy).
- Prognosis for Acute pulmonary edema remains worse with significant mortality and morbidity risks:
    - In-hospital mortality: 4-12%, higher in cardiogenic shock, sepsis or severe comorbidities
    - 30-days readmission rates: 20-25%
    - 1-year mortality: 20-40%

X. COMPLICATIONS

- Hemodynamic: cardiogenic shock, arrhythmia
- Respiratory: Acute respiratory failure
- Renal: Acute kidney injury (AKI), worsening renal function (Cardiorenal Syndrome)
- Neurological: stroke, delirium
- Metabolic and electrolyte: Hyponatremia, hyperkalemia or hypokalemia, metabolic acidosis

XI. PREVENTION AND RECOMMENDATION

- Primary prevention: manage risk factor of heart disease; blood pressure, lipid levels, treat diabetes, lifestyle changed & screening for asymptomatic HF.
- Secondary prevention: optimized guideline-directed medical therapy (GDMT), prevent decompensation, regular follow-up and patient education.

XII. REFERECES

1. Theresa McDonagh, et al. 2021 ESC guideline for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021-doi:10.1093/eurheartj/ehab368
2. Theresa McDonagh, et al. 2023 focused update of the 2021 ESC guideline for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 44;37;2023:3627-3639
3. Heidenreich PA et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Am Coll Cardiol. 2022
4. Theo E meyer et al. Approach to diagnosis and evaluation of acute decompensated heart failure in adult. UpToDate 2024
5. Wilson S Colucci et al. Treatment of acute decompensated heart failure. UpToDate 2024.
6. Luigi Falco et al. Pathophysiologie-based Mangement of acute heart failure. Clin Pract. 2023 Jan 31;13(1):206-218
7. Jaiyu Feng et al. Epidermiology and burden of heart failure in Asia. JACC:Asia. 2024 Apr, 4(4) 249-264

HYPERTENSION

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I. DEFINITION

High blood pressure is actually a leading risk factor for heart disease and early death. It's sometimes called the <silent killer>.

High blood pressure is also called hypertension, when the systolic blood pressure is ≥140 mmHg and/or the diastolic blood pressure is ≥90 mmHg.

Thresholds for diagnosing HTN based on clinic and out-of-clinic BP	**Asia**
Clinic	140/90
Home	135/85
ABPM (ambulatory BP measurements) Daytime Nighttime 24h average	 135/85 120/70 130/80

Classification	**SBP (mmHg)**		**DBP (mmHg)**
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Hypertension Grade 1 (Mild)	140-159	and/or	90-99
Hypertension Grade 2 (Moderate)	160-179	and/or	100-109
Hypertension Grade 3 (Severe)	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

II. EPIDEMIOLOGY

Recent estimates have suggested the number of patients with hypertension in Cambodia could increase to 26% among 30-79 years in both sexes (WHO 2019).

III. AETIOLOGY

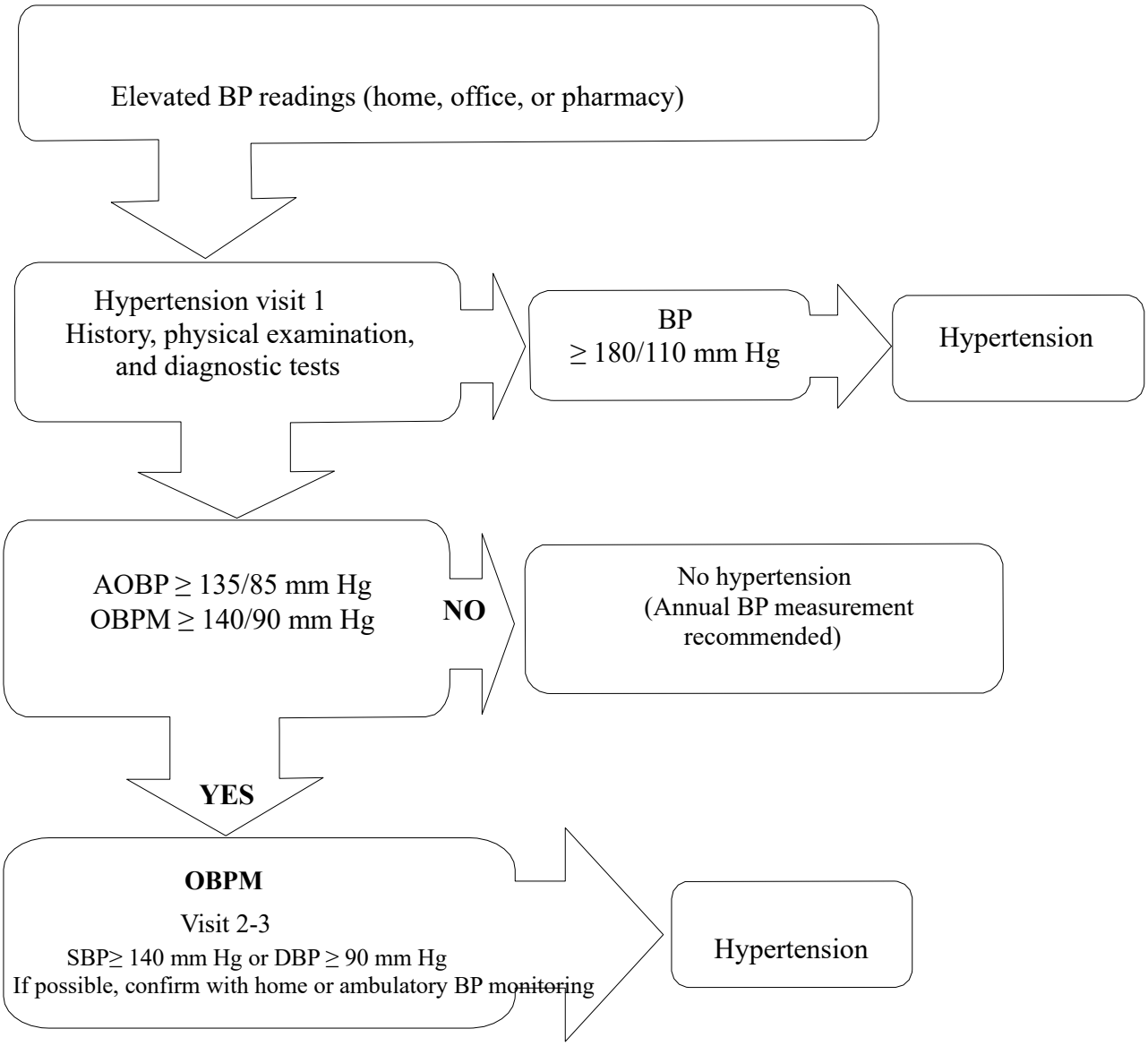
Over 90% of all cases of hypertension are of unknown aetiology (essential hypertension). One of the described risk factors for the development of essential hypertension is:

- Age
- Family history
- Being overweight or obese
- Sedentary lifestyle (lack of exercise)
- Using tobacco of any kind
- Too much salt (sodium) in the diet
- Excessive alcohol intake

IV. PATHOPHYSIOLOGY

There are various mechanisms described for the development of hypertension, which include increased salt absorption resulting in volume expansion, an impaired response of the renin-angiotensin-aldosterone system (RAAS), and increased activation of the sympathetic nervous system. These changes lead to the development of increased total peripheral resistance and increased afterload, which in turn leads to the development of hypertension.

V. DIAGNOSIS



BP Measuring Technique

- Don't smoke, exercise, drink caffeinated beverages or alcohol within 30mn of measurement
- Take at least 2 readings at 1 min interval
- Rest in a chair for at least 5mn with your left arm resting comfortably on a flat surface at heart level
- Sit calmly and don't talk
- Place the bottom of the cuff above the bend of the elbow

Sign and symptom

What are the signs and symptoms of high blood pressure? Usually none. That's why many people don't realize they have high blood pressure.

In some cases, people with more severe high blood pressure may have:

- Severe headaches
- Vision changes
- Nausea/vomiting
- Nosebleeds
- Confusion

Investigations

- Laboratory tests: FBC, electrolytes, renal function, fasting glucose, HbA1c, lipid profile, uric acid, urines test
- ECG
- Heart ultrasound if available

VI. DIFFERENTIAL DIAGNOSIS

Secondary hypertension should always be sought for as the differential, especially if the patient is at extremes of age (young or older).

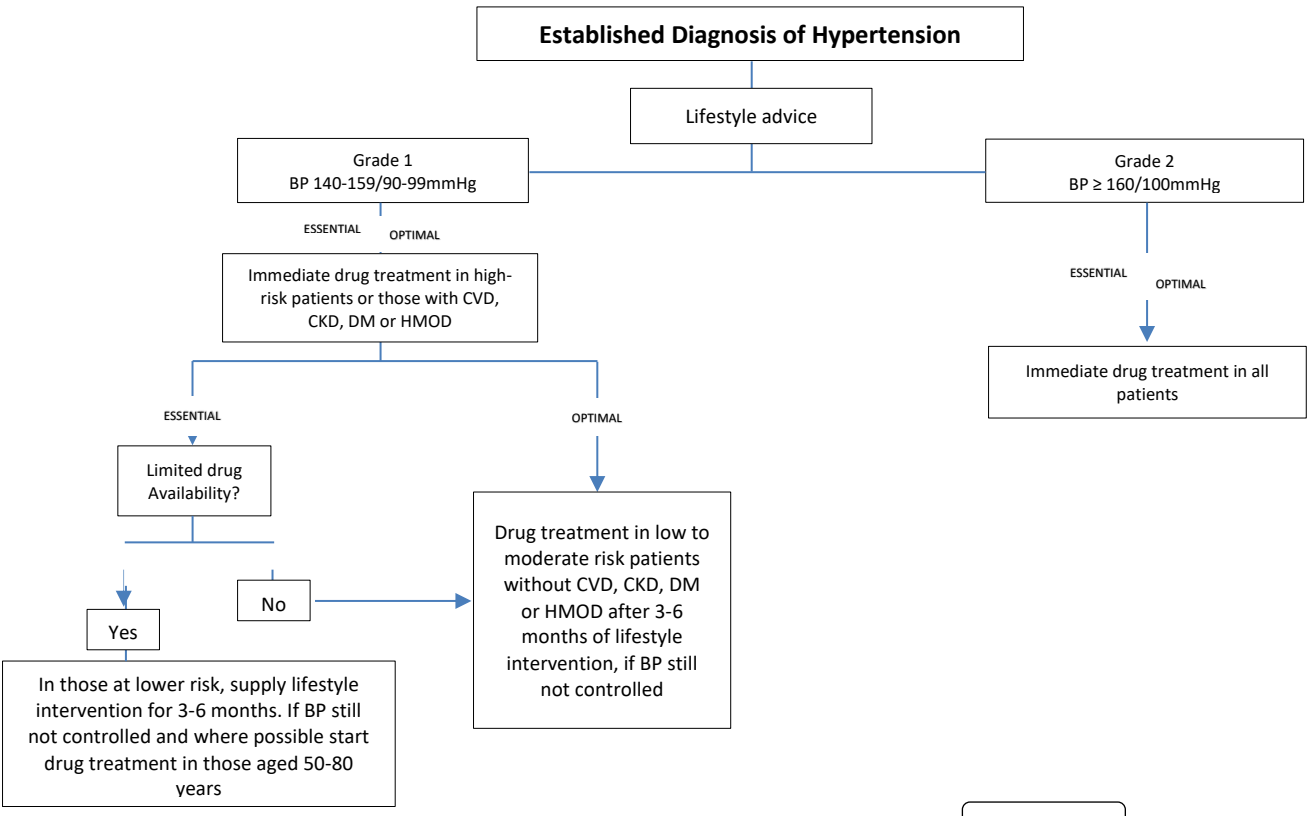
Adrenal tumor, coarctation of the aorta, renal artery stenosis and kidney disease should always be kept in the differential.

VII. MANAGEMENT

Risk stratification

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

Pharmacological treatment



ESSENTIAL

- Use whatever drugs are available with as many of the ideal characteristics as possible.
- Use free combinations if SPCs are not available or unaffordable
- Use thiazide diuretics if thiazide-like diuretics are not available
- Use alternative to DHP CCBs if these are not available or not tolerated (i.e. non-DHP-CCBs: diltiazem or verapamil).

OPTIMAL

Ideally Single Pill Combination Therapy (SPC)

Step 1 Dual low-dose# Combination	$A + C^{a,b,c}$
Step 2 Dual full-dose Combination	$A + C^{a,b}$
Step 3 Triple combination	A + C + D
Step 4 (Resistant Hypertension) Triple Combination +Spironolactone or other drug*	A +C + D Add Spironolactone $(12.5 - 50\ mg\ o.d.)^{d}$

ESSENTIAL **OPTIMAL**

a) Consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 yrs) or frailer patients.
b) Consider A+D in post-stroke very elderly, incipient HF or CCB intolerance.
c) Consider A+C or C+D in black patients.
d) Caution with spironolactone or other potassium sparing diuretics when estimated GFR<45 ml/min/1.73m^2 or K^+>4.5mmol/L.

A= ACE-inhibitor or ARB (Angiotensin Receptor Blocker)
C= DHP-CCB (Dihydropyridine-Calcium Channel Blocker)
D= Thiazide-like diuretic
*Alternatives include: Amiloride, doxazosin, eplerenone or beta-blocker.
low-dose generally refers to halt of the maximum recommended dose

Antihypertensive recommendations based on patient co-morbidities and characteristics

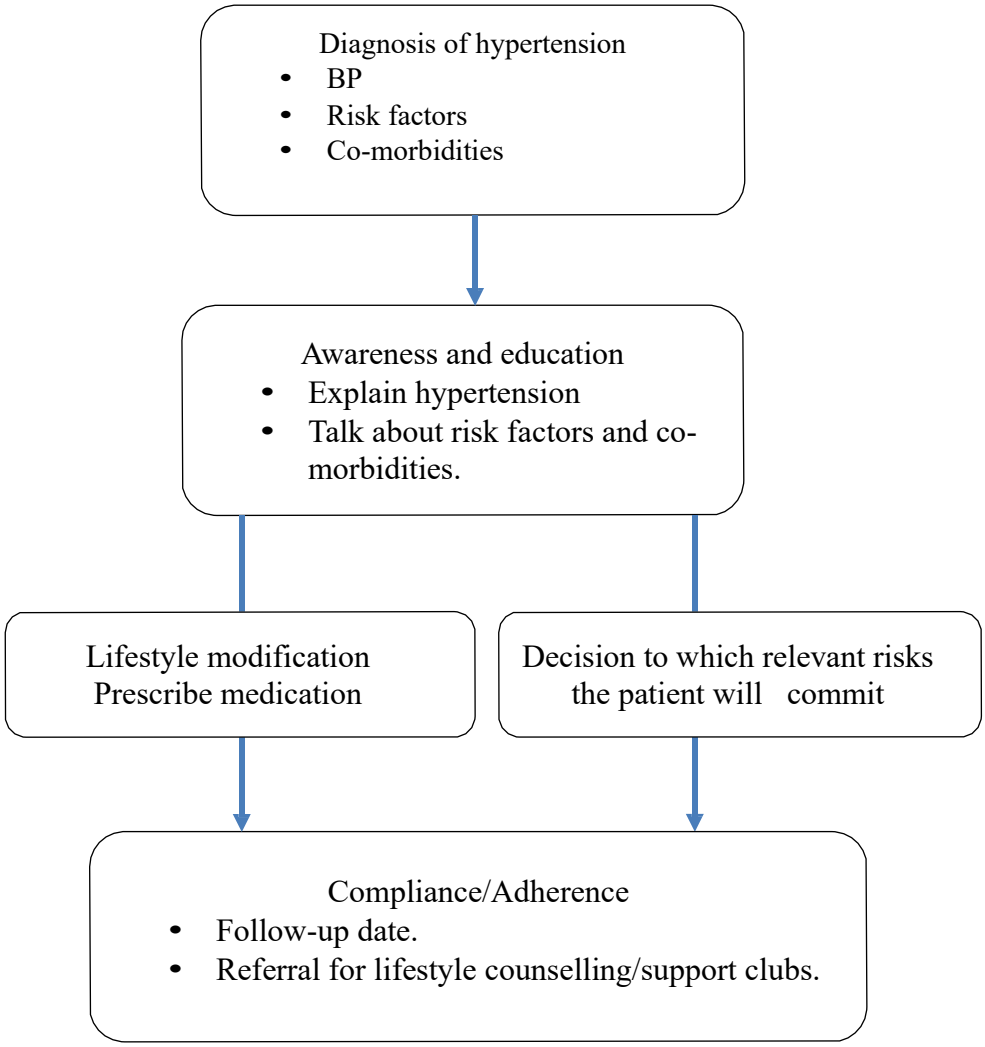
Co-morbidity or characteristic	Potentially Beneficial	Avoid
Chronic kidney disease	• ACE inhibitors or ARBs • Calcium channel blockers • Loop diuretics (if eGFR<30ml/min/1.73m^2)	• High salt intake • Theazides in patients with more than mild renal impairment
Diabetes	• Type 1 -ACE inhibitors or ARBs then thiazide (or thiazide-like) diuretic or calcium channel blocker • Type 2 -ACE inhibitors	• Beta-blockers • High dose thiazide diuretics (low doses are acceptable)
Heart failure or asymptomatic left ventricular dysfunction	• Beta-blockers (dose adjustments may be required for patients with renal dysfunction)	• Non-dihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) • Beta-blockers in uncontrolled heart failure
Acute myocardial infarction	• Beta-blockers without intrinsic sympathomimetic activity, e.g. carvedilol • ACE inhibitors or ARBs	• No specific cautions
Atrial fibrillation	• Beta-blockers • Rate limiting calcium channel blocker, e.g. diltiazem • ACE inhibitors or ARBs	• No specific cautions
Angina	• Beta-blockers • Calcium channel blockers • ACE inhibitors or ARBs	• No specific caution
Cerebrovascular disease, i.e. stroke	• ACE inhibitors or ARBs • Calcium channel blockers • Low-dose thiazide diuretics	• Beta-blockers • Thiazide diuretics in very elderly patients or those with poor daily fluid intake as they could contribute to hypoperfusion
Asthma/COPD	• No specific recommendations	• Beta-blockers, however, low-dose bisoprolol (or metoprolol) can be used if required in patients with asthma/COPD and heart failure
Gout	• Losartan (has a uricosuric effect)	• Thiazide diuretics
Pregnancy	• Labetalol • Nifedipine • Methyldopa	• ACE inhibitors and ARBs

Treatment targets:
For most patients, blood pressure is considered controlled when SBP <140 mmHg and DBP <90 mmHg.
However, for patients with diabetes or a high risk of CVD, recommend lower targets: SBP <130 mmHg and DBP <80 mmHg

Classes of antihypertensive agents

Classes		Dose mg/24h
Diuretic thiazide	indapamide hydrochlorothiazide	1.25–2.5 (od) 12.5–50 (od)
B-blocker	atenolol bisoprolol metoprolol propranolol acebutolol carvedilol	25–100 (od) 2.5–10 (od) 50–100 (bd) 40–160 (bd) 200–800 (bd) 12.5–50 (bd)
Calcium channel blocker (dihydropyridines)	amlodipine felodipine nicardipine SR nifedipine LA	2.5–10 (od) 2.5–20 (od) 60–120 (bd) 30–60 (od)
Calcium channel blocker (non dihydropyridines)	diltiazem verapamil	120–540 (bd) 120–360 (bd or tds)
ACEi	captopril enalapril lisinopril perindopril ramipril	25–100 (bd or tds) 2.5–40 (od or bd) 10–40 (od) 5–10 (od or bd) 2.5–20 (od)
ARB	candesartan irbesartan losartan olmesartan telmisartan valsartan	8–32 (od 150–300 (od) 25–100 (od or bd) 20–40 (od) 20–80 (od) 80–320 (od)

From diagnosis to management

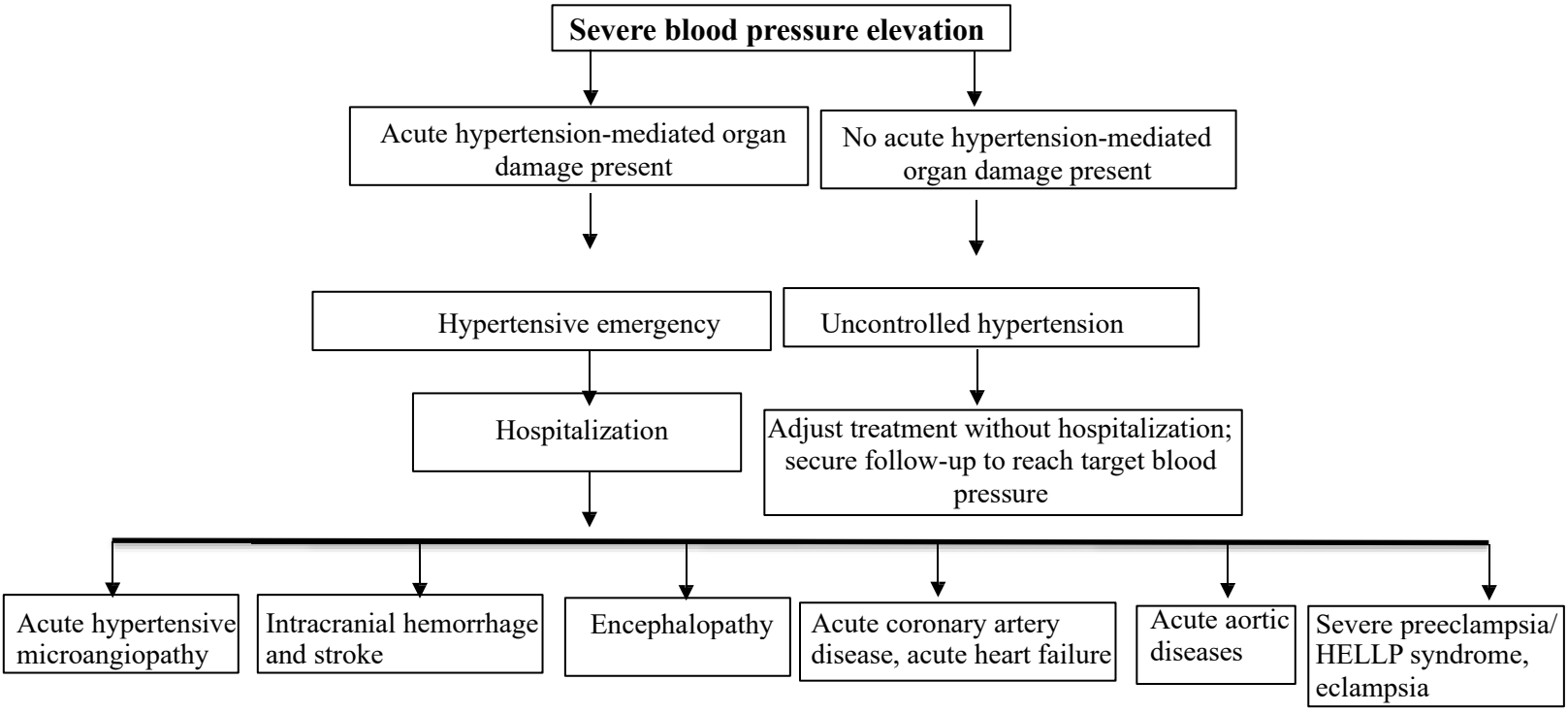


VIII. SPECIAL CASES

Hypertensive emergencies are a heterogeneous group of acute hypertensive disorders which require rapid recognition and treatment with the appropriate therapy to avoid progressive organ dysfunction.

A hypertensive emergency is defined by a blood pressure value above 200/120 mmHg with or without target organ damage.

Management of hypertensive emergencies



Clinical presentation	Timing	Target blood pressure
Acute aortic diseases	Immediate	Systolic BP <120 mmHg and heart rate <60 beats per min
Acute cardiogenic pulmonary oedema	Immediate	Systolic BP <140 mmHg
Acute coronary artery disease	Immediate	Systolic BP <140 mmHg
Severe preeclampsia/HELLP syndrome, eclampsia	Immediate	Systolic BP <160 mmHg and diastolic BP<105 mmHg
Hypertensive encephalopathy	Immediate	Mean arterial pressure -20-25%
Acute intracranial haemorrhage and a systolic BP >180 mmHg	Immediate	Systolic BP 130-180 mmHg
Acute ischaemic stroke with indication for thrombolytic therapy and a BP >185/110 mmHg	1h	Mean arterial pressure -15%
Acute ischaemic stroke and a BP >220/120 mmHg	1h	Mean arterial pressure -15%
Malignant hypertension with or without TMA and/or acute kidney injury	Several hours	Mean arterial pressure-20-25%

Drug for parenteral treatment of hypertensive emergencies

Drug	Onset of actio	Duration of action	Dosing (by IV route)	Mechanism of action	Contraindications	Adverse effects
Esmolol	1-2 min	10-30 min	0.5-1 mg/kg as bolus; 50-300 mg/kg/min as continuous infusion	Beta1 adrenergic block,	2nd-or 3rd-degree AV systolic heart failure, asthma, bradycardia	Bradycardia
Metoprolol	1-2 min	5-8 h	15 mg usually given as 5 mg and repeated at 2-5 min intervals as needed	Beta1 adrenergic blocker	2nd- or 3rd-degree AV block, systolic heart failure, asthma, bradycardia	Bradycardia
Labetalol	5-10 min	3-6 h	0.25-0.5 mg/kg; 2-4 mg/min until target BP is reached, thereafter 5-20 mg/h	Alpha1 and non-selective beta adrenergic blocker	2nd- or 3rd-degree AV block, systolic heart failure, asthma, bradycardia	Bronchocons triction, bradycardia
Phentolamine	1-2 min	10-30 min	0.5-1 mg/kg bolus injections; 50-300 mcg/kg/min as continuous infusion	Non-selective alpha adrenergic blocker		Tachyarrh ythmias, chest pain
Fenoldopam	5-15 min	30-60 min	0.1 mcg/kg/min, increase every 15 min until target BP is reached	Dopamine D1 receptor blocker, weak alpha adrenergic blocker	Caution in glaucoma	

Clonidine	30 min	4-6 h	150-300 mcg over 5-10 min	Centrally acting imidazoline I2 receptor blocker and alpha adrenergic agonist		Sedation, rebound hypertension
Clevidipine	2-3 min	5-15 min	2 mg/h, increase with 2 mg/h every 2 min until target BP is reached	Dihydropyridine calcium channel blocker		Headache, reflex tachycardia
Nicardipine	5-15 min	30-40 min	5-15 mg/h as continuous infusion, starting with 5 mg/h, 2.5 mg increase every 15-30 min until target BP is reached, thereafter decrease to 3 mg/h	Dihydropyridine calcium channel blocker	Hepatic failure	Headache, reflex tachycardia
Glyceryl trinitrate	1-5 min	3-5 min	5-200 mg/min, 5 mg/min increase every 5 min until target BP is reached	Peripheral direct acting vasodilator		Headache, reflex tachycardia
Sodium nitroprusside	Immed iate	1-2 min	0.3-10 mg/kg/min, increase by 0.5 mg/kg/min every 5 min until target BP is reached	Peripheral direct acting vasodilator	Hepatic and renal failure (relative contraindi cation)	Cyanide intoxication
Enalaprilat	5-15 min	4-6 h	0.625-1.25 mg as bolus up to 5 mg x 4	Angiotensin converting enzyme inhibitor	History of angio-oedema	Renal failure

IX. EVOLUTION AND PROGNOSIS

Untreated high blood pressure increases a person's risk of developing heart disease, stroke or kidney failure at an early stage.

X. COMPLICATION

Complications of hypertension account for 9.4 million deaths caused by CVD worldwide every year:

- At least 45% of deaths due to heart disease
- 51% of deaths due to stroke
- It contributes to about **1000 deaths** a day

- Heart: LV hypertrophy, heart failure, coronary artery disease
- Brain: ischemic or haemorrhage stroke
- Retina: haemorrhages or exudates, papilledema
- Kidney: microalbuminuria, chronic kidney disease
- Peripheral vasculature: aortic aneurysm, peripheral artery disease

XI. PREVENTION

The best approach to the primary prevention of HTN is a combination of lifestyle changes:

- Don't smoke
- Weight reduction
- Restriction sodium intake
- Physical activity
- Alcohol consumption with moderation
- Eat a healthy diet

XII. REFERENCE

1. J Clin Hypertens. 2021; 23:422–434
2. 2020 ISG Global HTN Practice Guidelines
3. 2010 Royal College of Physicians of London
4. Training of Trainer Curriculum for HTN and Diabetes Management in PHC-2022, MoH, Cambodia
5. Canadian Journal of Cardiology 36 (2020) 596-624
6. Lancet. 2012; 380 (9859): 2224-60
7. Robert Lowes, September 5, 2012, theheart.org
8. https://www.ncbi.nlm.nih.gov/books/NBK539859/#:~:text=Differential%20Diagnosis&text=Hyperaldosteronism%2%20coarctation%20of%20the%20aorta,be%20kept%20in%20the%20differential
9. https://academic.oup.com/esc/book/35489/chapter/312429354

Abbreviation:

ABPM: ambulatory BP measurement
ACEi: angiotensin converting enzyme inhibitors AOBP: automated office BP
ARB: angiotensin receptor blockers BP: blood pressure

CCB: calcium channel blocker CKD: chronic kidney disease
COPD: chronic obstructive pulmonary disease CVD: cardiovascular disease
DBP: diastolic BP DM: diabetes mellitus
ECG: electrocardiogram FBC: full blood count
HBPM: home BP measurement
HMOD: hypertension-mediated organ damage
HTN: hypertension
LV: left ventricle
OBPM: office BP measurement SPB: systolic BP

CHRONIC HEART FAILURE

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I. DEFINITIONS

1. Heart failure occurs *"The situation when the heart is incapable of maintaining a cardiac output adequate to accommodate metabolic requirements and the venous return."*
2. *HF is a clinical syndrome in which patients have the following features:*
   + ***Symptom typical of HF:*** Breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling.
   + ***Signs typical of HF***: Tachycardia, tachypnea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly.
   + ***Objectif evidence of a structural or functional abnormality of the heart at rest:*** Cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic (BNP or NT-pro-BNP) concentration.
3. ***Classification of HF by ESC****: LVEF may be:*
   + *Reduced LV ejection fraction (LVEF ≤ 40%) - Heart failure with reduced ejection function (HFrEF).*
   + *Preserved LV ejection fraction (LVEF ≥ 50%) - Heart failure with preserved ejection fraction (HFpEF).*
   + *Mid-range LV ejection fraction (LVEF 41%-49%) - Heart Failure with the LVEF being in the mid-range (HFmrEF).*

II. EPIDEMIOLOGY

- The prevalence of HF is around 1-2% of adult in the developing countries:
  + The prevalence increased with age, CVRF, Post MI:
    - Around 1% for those age younger than 55 years,
    - To >10% in those age older than 70 years old.
- The prevalence of HF in Cambodia is around 3-4% in general population.

III. ETIOLOGIES

A. The common underlying causes of HF in adults are:

- *Ischemic Heart Diseases (IHD)*
- *Hypertension*
- *Dilated cardiomyopathy-idiopathic, familial*
- *Valvular heart disease*
- *Diabetic cardiomyopathy*

B. Other causes of HF include:

- *Congenital heart disease*
- *Cor pulmonale*
- *Pericardial disease: constrictive pericarditis, cardiac tamponade*
- *Hypertrophic cardiomyopathy*
- *Viral myocarditis*
- *Acute rheumatic fever*
- *Toxic: Alcohol, cardiotoxic chemotherapy e.g. doxorubicin, trastuzumab (Herceptin), cyclophosphamide.*

- *Endocrine and metabolic disorders: thyroid disease, acromegaly, phaeochromocytoma.*
- *Collagen vascular disease: systemic lupus erythematosis, polymyositis, polyarteritis nodosa.*
- *Tachycardia induced cardiomyopathy eg uncontrolled atrial fibrillation.*
- *Infiltrative cardiac disease e.g. amyloid, hyper-eosinophilic syndrome.*
- *High output HF e.g. severe anaemia, large A-V shunts/malformations.*
- *Peripartum cardiomyopathy.*
- *Stress (Takotsubo) cardiomyopathy.*

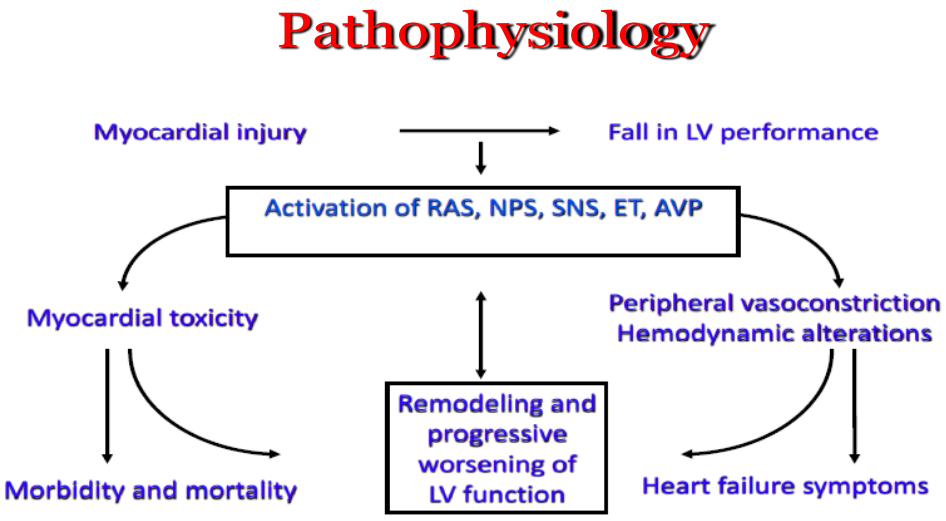
IV. PATHOPHYSIOLOGY

A. ***Pathophysiology***:

a. ***Cardiac Output (CO)***: Stroke Volume (SV) x Heart Rate (HR): depend on:

- SV depend on Pre-load, After-load, Myocardial contractility,
- Neuro-hormonal activations:

+ Sympathetic nervous system (SNS): Beta-1, Beta-2, Alpha-1,
+ System renin angio-tension aldosterone system (RAAS),



b. ***<u>Cardiovascular r isk factors</u>*** :

- HTN,
- Prediabetes/DM,
- Dyslipidemia
- Smoking
- Diet, Alcohol, obesity, physical inactivity,
- Age, gender, ASCVD

V. DIAGNOSIS

A. ***Clinical***

a. ***Past medical history*** of CVDs? CVRF?

b. ***Symptoms***:

- Breathlessness,
- Orthopnea,

- Paroxysmal nocturnal dyspnea,
- Cough+/-wheezing
- Reduce exercise tolerance,
- Fatigue,
- Tiredness,
- Increased time to recover after exercise,
- Leg/Ankle/foot swelling,

c. ***Signs***

- Tachycardia or irregular heart pulse,
- Elevated jugular venous pressure,
- Hepatojugular reflux,
- Third heart sound (gallop rhythm)
- Laterally displaced apical impulse,
- Cardiac murmur,
- Abdominal swelling,
- Rapid weight gain,

d. ***York Heart Association (NYHA) classification***

This system groups heart failure into four categories by number. You may see Roman numerals used for these category names.

- NYHA-I: There are no heart failure symptoms.
- NYHA-II: Everyday activities can be done without difficulty. But exertion causes shortness of breath or fatigue.
- NYHA-III: It's difficult to complete everyday activities.
- NYHA-IV: Shortness of breath occurs even at rest. This category includes the most severe heart failure.

e. American College of Cardiology

- Stage A. risk factors for heart failure but no signs or symptoms.
- Stage B**.** There is heart disease but no signs or symptoms of heart failure.
- Stage C**.** There is heart disease and signs or symptoms of heart failure.
- Stage D**.** Advanced heart failure requires specialized treatments.

f. ***Left-sided heart failure symptoms include***:

- Paroxysmal nocturnal shortness of breath.
- Shortness of breath during exercise or when lying flat.
- Chronic coughing or wheezing.
- Difficulty concentrating.
- Fatigue.
- Fluid retention causing swelling, or edema, in the ankles, legs and/or feet.
- Lack of appetite and nausea.

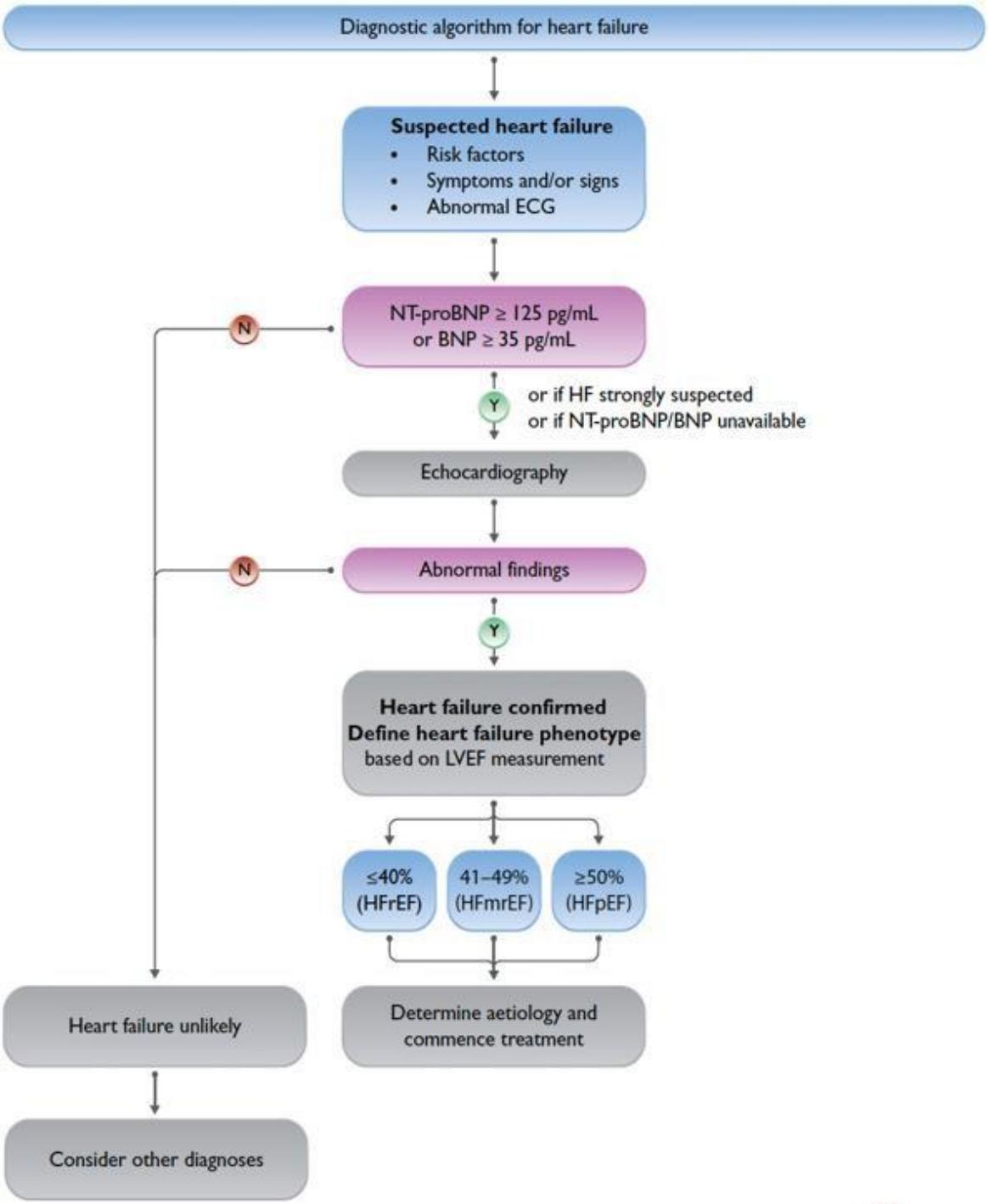
g. ***Right sided heart failure symptoms include***:

- General or inferior limbs oedema,
- Hepatomegalia, hepatalgia
- Turgescence jugular,
- Weight gain and increase abdominal girth.

h. ***Factors triggered acute HF***:

Patients with Chronic HF may occasionally develop acute decompensation. The more important causes that need to be recognised and treated appropriately are:

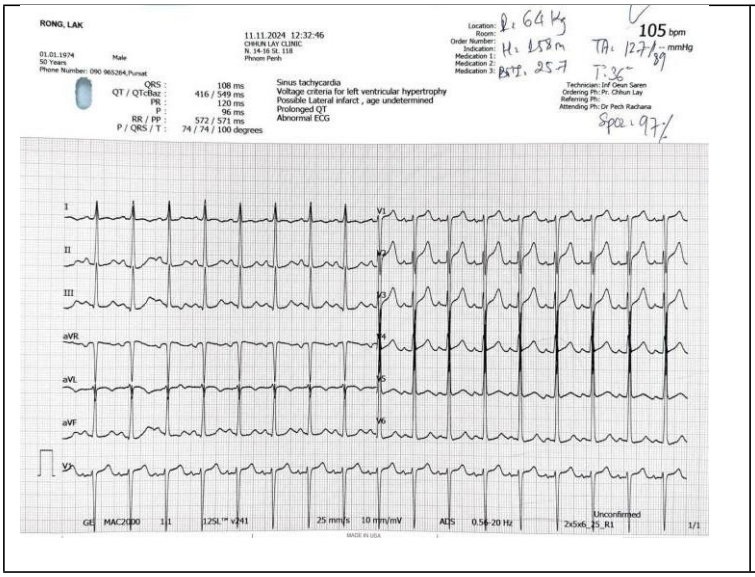
- Acute myocardial infarction/myocardial ischaemia.
- Arrhythmias (e.g. atrial fibrillation).
- Hypertensive emergencies.
- Infections (e.g. pneumonia).
- Non-compliance to medications.
- Excessive fluid and salt intake.
- Anaemia.
- Development of renal impairment.
- Adverse effects of drug therapy (e.g. non-steroidal anti-inflammatory drugs).

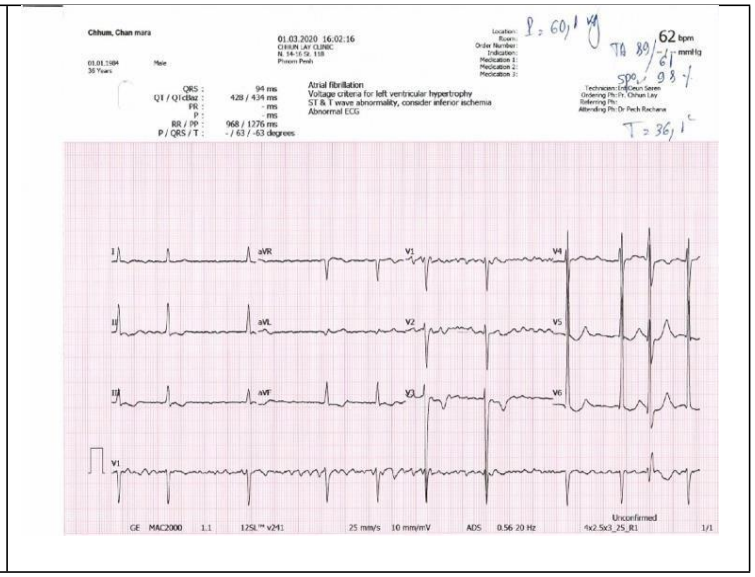


B. *<u>In vastigations :</u>*

a. *ECG*:

- To assess heart rat, rhythm, QRS morphologie, QRS duration, QRS voltage, evidence of ischemia, LV hypertrophic and arrhythmia.





c. ***Chest X-ray***:

- To look for pulmonary congestion, Cardiomegaly and presence of underlying lung pathology, patient with HFpEF may have a cardiac normal size.

d. Blood tests:

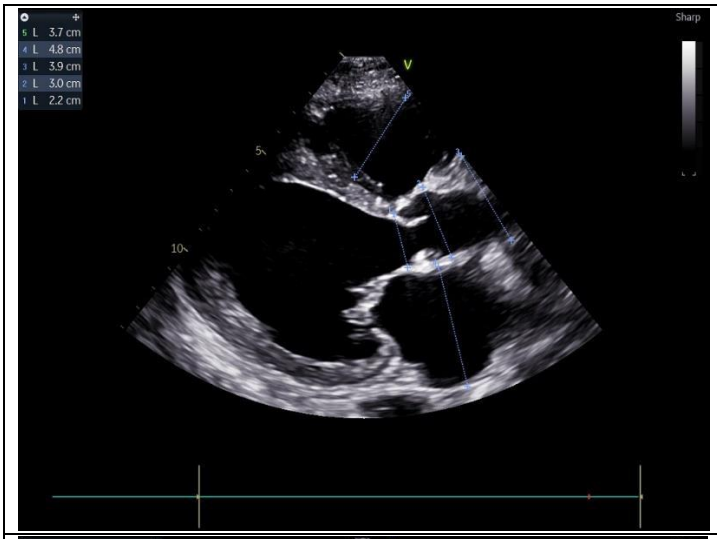
- FBC, renal function, liver function, serum glucose, lipid profile,
- Urinalysis, to look for proteinuria, glucosuria,
- Natriuretic Peptides (NP): (. Brain natriuretic petide (BNP) or . N-terminal pro BNP (NTproBNP)): BNP and NTproBNP are a family of hormones secreted by the ventricules in response to wall stress,

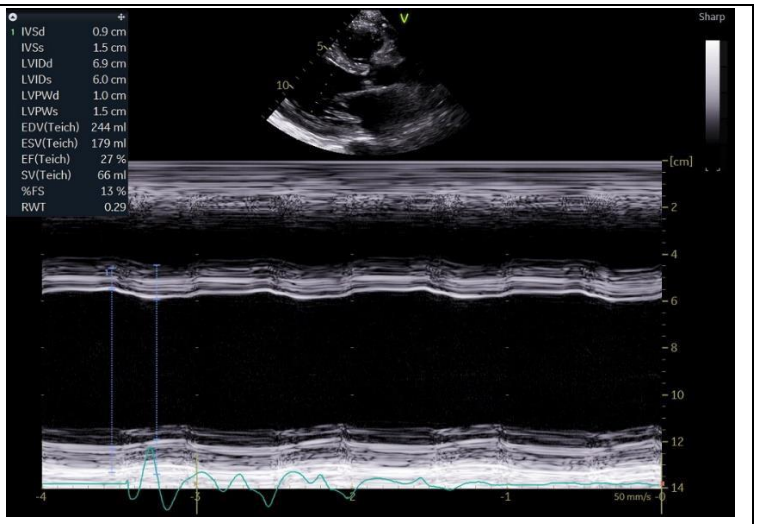
  They are useful in the following situations:

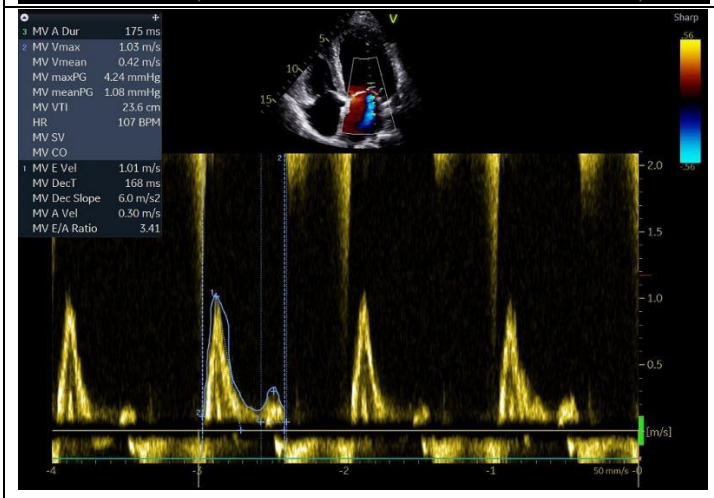
  + In the emergency setting:
    - ➢ NB are useful as a ‘’ rule out” test for patients presenting with acute dyspnea. A level of < 100pg/ml for BNP and < 300mg/ml for NTproBNT makes the diagnosis of acute HF unlikely. These levels are affected by renal function and gender.
    - ➢ A high level supports the diagnosis of acute HF and very high levels correlate with the severity of HF and adverse outcome.

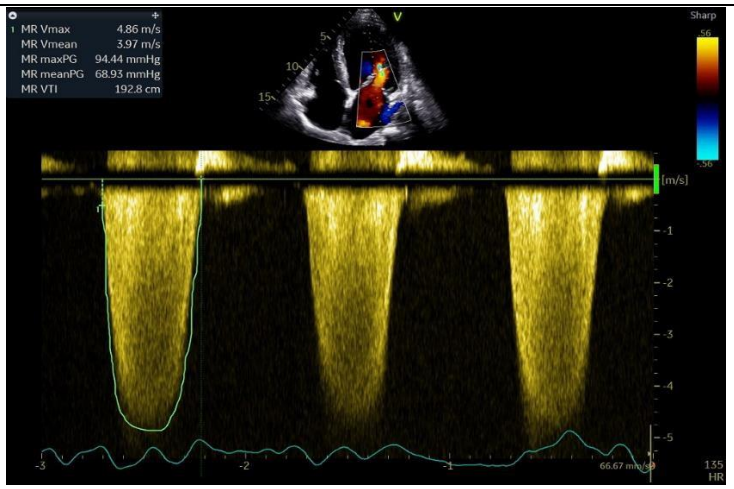
e. ***Heart Ultrasound (Echocardiography)***: this will allow access of:

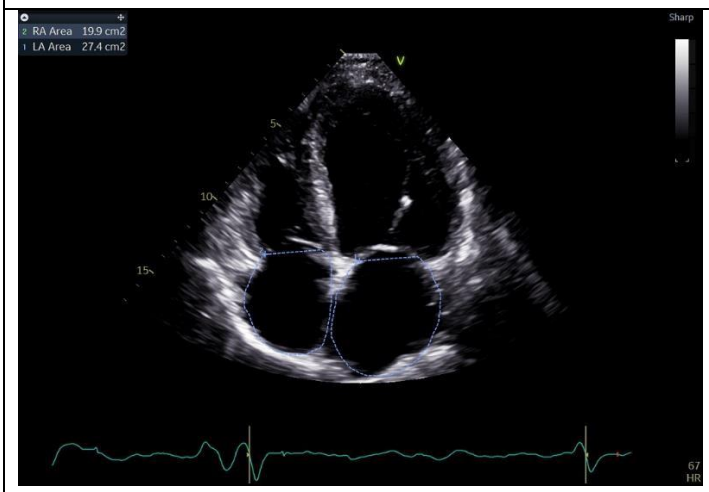
- LV chamber size, volume and systolic function.
- LV wall thickness, evidence of scarring and wall motion abnormalities,
- Diastolic function of the heart,
- Valvular structure and function,
- Congenital cardiac abnormalities,
- LV mechanical dyssynchrony
- Pulmonary hypertension,

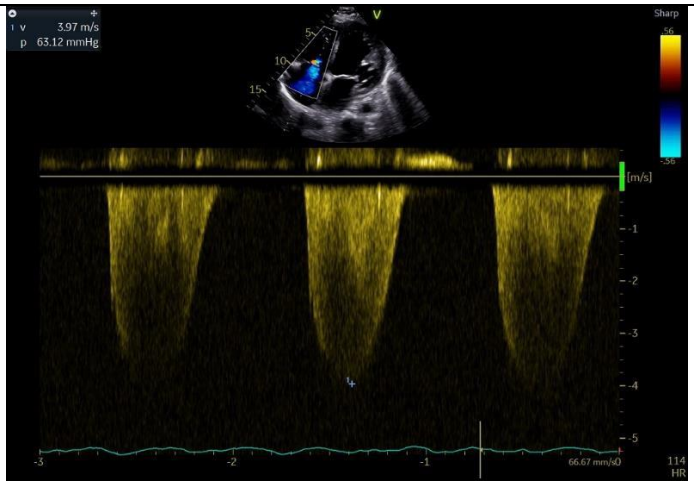












VI. IFFERENTIAL DIAGNOSIS

- Chronic pulmonary disease (COPD), Asthma, Pulmonary fibrosis, Pulmonary hypertension,
- Pneumonia, Pleural effusion, Pneumothorax, Aspiration foreign body

VII. ANAGEMENT OF HF

A. Objectives

- Prevention of recurrents: Etiologies treatement and triggered factors
- Management of asymptoms LV dysfunction.
- Improve quality of life,
- Prolongation of life expectancy.

B. Critical signs

- Orthopnea, APO
- Persistent chest pains or chest discomfort,
- Palpitations with optimal treatment.
- Cardiac arrest. Persistence of symptom after three months of optimal treatment.

C. Mortality risk factors

- Ventricular arrhythmia, Afib with height heart rates,
- Multi-lesion coronary artery disease
- CKD, HTA, T2D
- Anemia,
- Hyponatremia and hypokalemia.

D. Out patient management

- Patient educations, lifestyle management, call 119 in case emergency.
- Regular follow up

E. Medical treatment

- To reduce volume overload: Lube diuretic +/- MRA
- First line medicine to reduce morbid mortalities: ACE-I/ARB/ARNI, BB, MRA, SGLT2i

Chronic Heart Failures treatment

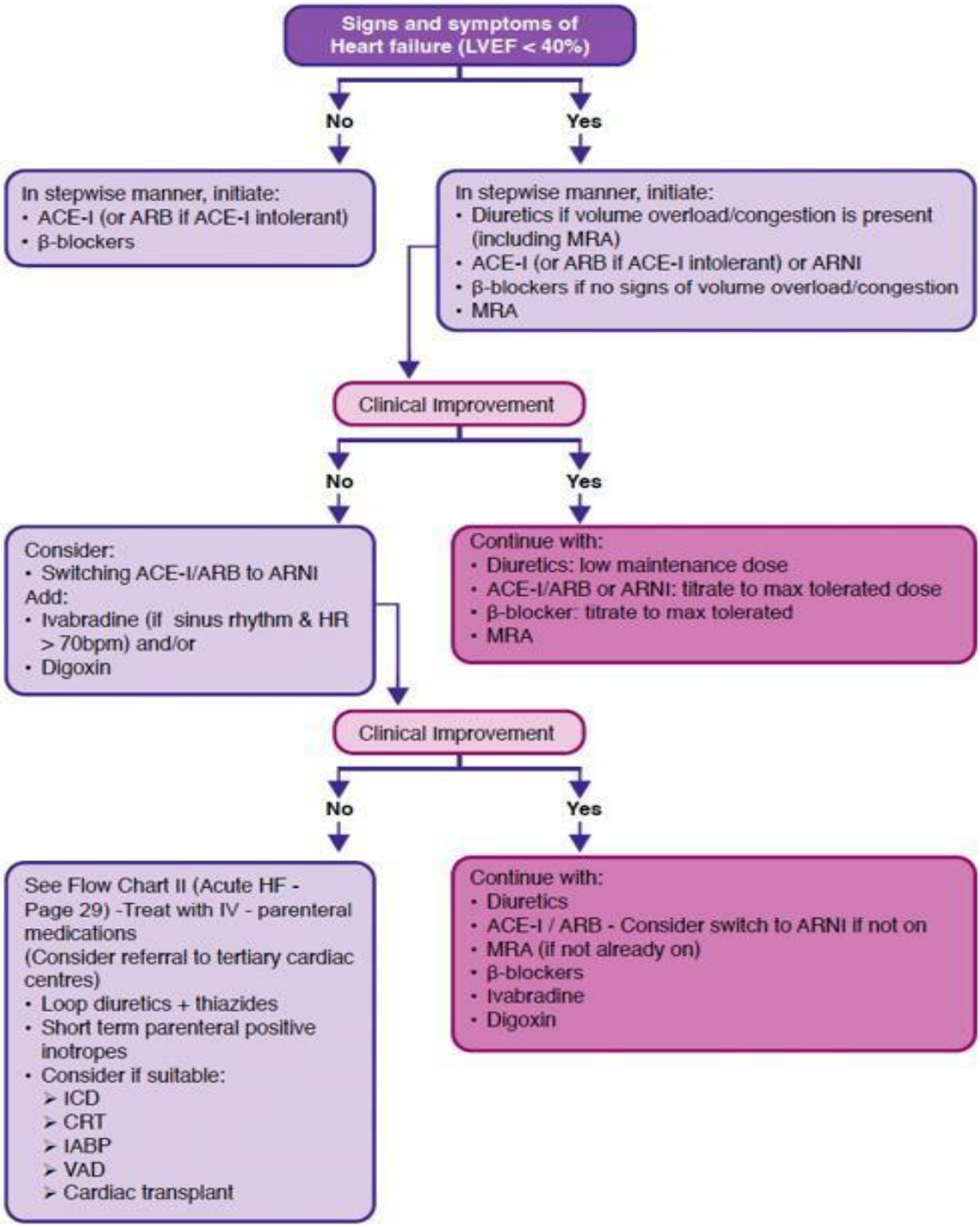
- ***Classic***: Digoxin + Diuretics,
- ***Modern***: Base on the randomized studies: ACE-I/ARB/ARNI + Beta-blocker +/- Diuretics +/- Digoxin.

NB: HF treatment: Treatment of activation neuro-hormones.

+ ***New Guideline HF treatment with LV dysfunction:***

- Stage 1: ACEI /ARB/ARNI +/- Lube diuretics +/- MRA +/- SGLT2i
- Stage 2: ACEI/ARB/ARNI +/- Lube diuretics +/- MRA, Beta-blocker +/- SGLT2i,
- Stage 3: ACEI/ARB/ARNI +/- Lube diuretics +/- MRA +/- Beta-blocker +/- SGLT-2 Inhibitors +/- Digoxin
- Stage 4: ACEI/ARB/ARNI +/- Lube diuretics +/- MRA +/- Beta-blocker +/- SGLT-2 Inhibitors +/- Digoxin

Optimising Drug Therapy In Chronic HF*r*EF



Pharmacological treatments indicated in patients with (NYHA class II-IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class	Level
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA= New York Heart Association.

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www.escardio.org/guidelines

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

	Starting dose	Target dose
ACE-I		
Captopril[a]	6.25 mg *t.i.d.*	50 mg *t.i.d.*
Enalapril	2.5 mg *b.i.d.*	10—20 mg *b.i.d.*
Lisinopril[b]	2.5—5 mg *o.d.*	20—35 mg *o.d.*
Ramipril	2.5 mg *b.i.d.*	5 mg *b.i.d.*
Trandolapril[a]	0.5 mg *o.d.*	4 mg *o.d.*
ARNI		
Sacubitril/valsartan	49/51 mg *b.i.d.*[c]	97/103 mg *b.i.d.*
Beta-blockers		
Bisoprolol	1.25 mg *o.d.*	10 mg *o.d.*
Carvedilol	3.125 mg *b.i.d.*	25 mg *b.i.d.*[e]
Metoprolol succinate (CR/XL)	12.5—25 mg *o.d.*	200 mg *o.d.*
Nebivolol[d]	1.25 mg *o.d.*	10 mg *o.d.*

MRA		
Eplerenone	25 mg *o.d.*	50 mg *o.d.*
Spironolactone	25 mg *o.d.*[f]	50 mg *o.d.*
SGLT2 inhibitor		
Dapagliflozin	10 mg *o.d.*	10 mg *o.d.*
Empagliflozin	10 mg *o.d.*	10 mg *o.d.*
Other agents		
Candesartan	4 mg *o.d.*	32 mg *o.d.*
Losartan	50 mg *o.d.*	150 mg *o.d.*
Valsartan	40 mg *b.i.d.*	160 mg *b.i.d.*
Ivabradine	5 mg *b.i.d.*	7.5 mg *b.i.d.*
Vericiguat	2.5 mg *o.d.*	10 mg *o.d.*
Digoxin	62.5 µg *o.d.*	250 µg *o.d.*
Hydralazine/ Isosorbide dinitrate	37.5 mg *t.i.d.*/20 mg *t.i.d.*	75 mg *t.i.d.*/40 mg *t.i.d.*

Management of HFrEF

To reduce mortality -for all patients

ACE-I/ARNI | BB | MRA | SGLT2i

To reduce HF hospitalization/mortality - for selected patients

Volume overload

Di

SR with LBBB / 50 ms

CRT-P/D

SR with LBBB 130-149 ms or non *LBBB / 50 ms*

CRT-P/0

lschaemic aetiology

Non-ischaemic aetiology

ICD)

Atrial fibrillation

Anticoa lat

Atrial fibrillation

Digoxin PVI)

Coronary artery disease

CABG

Iron defidency

Ferric ca altose

Aortic stenosis

SAVRITAV ;;

Mitral regurgitation

TEE MV Repair)

Heart rate SR> 70 *bpm*

lvabradine)

Black Race

Hydralazine/ISDN

ACE-1/ARNI intolerance

ARB

For selected advanced H F patients

Heart transplantation

MCS as BTT/BTC

Long-term MCS as DT)

To reduce HF hospitalization and improve QOL -for all patients

Exer.cise r.ehabilitation

Multi-professional d

VIII. SPECIAL CASES

- HF with CHD,
- Diabetes and HF,
- HF in pregnancy,
- HF in adult congenital heart disease (ACHD),
- Arrhythmia-induced HF,
- Cardio-oncology and HF,
- HF and kidney dysfunction,
- HF with desynchronization
- Advanced HF/Refractory Hf/Heart transplant,
- HF with Mechanical circulatory support,
- Palliative and end of life care.

IX. EVOLUTION AND PROGNOSIS

- The prognostic of HF depends on its comorbid-mortality.
- Latest studies have shown that the survival rates of people with chronic HF were:
  - 80% to 90% for one year,
  - 50% to 60% for year five,
  - Most people with end-stage HF have a life expectancy of less than one year.

X. PREVENTION AND RECOMMENDATIONS

- Lifestyle change, patience education,
- Vaccination, flux, pneumonias, typhoïde, etc.,
- Optimal management of LV dysfunction asymptomatic.
- Optimal management of HF base on new guideline.
- Optimized all causes, IHD, VHD, CHD etc.
- Optimized treatment of comorbid-mortality of HF,
- Optimized medical treatment of cardiovascular risk factors.
- Vaccinations,

XI. URGERIES AND DEVICES

- Heart surgeries and Intervention cardiology for heart disease that causes HF.
- Devices
  - Cardiac resynchronization therapy (CRT): biventricular pacing, is used to help improve the heart's rhythm and the symptoms associated with the arrhythmia. In effect, it is "resynchronizing'' the heart.
  - Implantable cardioverter defibrillator (ICD): If an abnormal of heart rhythm is detected, the device will deliver an electric shock to restore a normal heartbeat.
  - Heart transplantation: remains de gold standard for the treatment of advanced HF in the absence of contraindication.

KEYS MESSAGES

- *Patients with HF are classified based on their LVEF. Those with a LVEF between 41% and 49% are defined as 'mildly reduced LVEF (HFmrEF).*
- *Measurement of NPs and echocardiography have key roles in the diagnosis of HF.*
- *ACE-I or ARNI, beta-blockers, MRA, and SGLT2 inhibitors are recommended as cornerstone therapies for patients with HFrEF.*
- *ICDs are recommended in selected patients with HFrEF of an ischaemic aetiology and should be considered in those with a nonischaemic aetiology.*
- *CRT-P/D is recommended in those patients with HFrEF, in sinus rhythm, with a LBBB >_150 ms and should be considered in those with a LBBB >130-149 ms or non-LBBB >_150 ms.*
- *Advanced HF strategies (heart transplantation/MCS) may be appropriate in selected patients.*
- *ACE-I/ARNI, beta-blockers, and MRA may be considered in patients with HFmrEF.*
- *The diagnosis of HFpEF requires objective evidence of cardiac structural, or functional abnormalities as well as elevated plasma NP concentrations consistent with the presence of LV diastolic dysfunction and raised LV filling pressures. A diastolic stress test is recommended when these markers are equivocal.*
- *To date, no treatment has been shown to reduce mortality and morbidity in patients with HFpEF.*
- *Exercise is recommended for all patients who are able, to improve exercise capacity andQOL, and reduce HF hospitalization.*
- *Patients with advanced HF refractory to medical/device therapy and who do not have absolute contraindications should be referred for consideration of heart transplantation. MCS should also be considered as BTT or DT in selected patients.*
- *Patients hospitalized for HF should be carefully evaluated to exclude persistent signs of congestion. Oral treatment should be optimized before discharge.*
- *It is recommended that patients with type II diabetes are treated with SGLT2 inhibitors.*

XII. REFERENCES

1. ESC Heart Failure Guideline 2021
2. ACC Heart Failure Guidelin 2022
3. Adlbrecht C, Huelsmann M, Berger R, Moertl D, Strunk G, Oesterle A et al. Cost analysis and cost-effectiveness of NT-proBNP-guided heart failure specialist care in addition to home-based nurse care. European Journal of Clinical Investigation. 2011; 41(3):315–22
4. Agostoni P, Magini A, Andreini D, Contini M, Apostolo A, Bussotti M et al. Spironolactone improves lung diffusion in chronic heart failure. European Heart Journal. 2005; 26(2):159–164
5. Agvall B, Alehagen U, Dahlstrom U. The benefits of using a heart failure management programme in Swedish primary healthcare. European Journal of Heart Failure. 2013; 15(2):228–36

6. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. Journal of the American College of Cardiology. 2014; 63(12):1123–1133
7. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure Circulation. 2009; 120(16):1577–84
8. Anderson L, Sharp GA, Norton RJ, Dalal H, Dean SG, Jolly K et al. Home-based versus centre-based cardiac rehabilitation. Cochrane Database of Systematic Reviews 2017, Issue Art. No.: CD007130. DOI: 10.1002/14651858.CD007130.pub4.
9. Angermann CE, Stork S, Gelbrich G, Faller H, Jahns R, Frantz S et al. Mode of action and effects of standardized collaborative disease management on mortality and morbidity in patients with systolic heart failure the interdisciplinary network for heart failure (INH) study. Circulation: Heart Failure. 2012; 5(1):25–35
10. Anguita M, Esteban F, Castillo JC, Mazuelos F, Lopez-Granados A, Arizon JM et al. [Usefulness of brain natriuretic peptide levels, as compared with usual clinical control, for the treatment monitoring of patients with heart failure]. Medicina Clínica. 2010; 135(10):435–40
11. Anker SD, Colet JC, Filippatos G, Willenheimer R, Dickstein K, Drexler H et al. Rationale and design of Ferinject assessment in patients with IRon deficiency and chronic Heart Failure (FAIR-HF) study: a randomized, placebo-controlled study of intravenous iron supplementation in patients with and without anaemia. European Journal of Heart Failure. 2009; 11(11):1084–91
12. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. New England Journal of Medicine. 2009; 361(25):2436–48
13. Antonicelli R, Testarmata P, Spazzafumo L, Gagliardi C, Bilo G, Valentini M et al. Impact of telemonitoring at home on the management of elderly patients with congestive heart failure. Journal of Telemedicine and Telecare. 2008; 14(6):300–5
14. Askoxylakis V, Thieke C, Pleger ST, Most P, Tanner J, Lindel K et al. Long-term survival of cancer patients compared to heart failure and stroke: a systematic review. BMC Cancer. 2010; 10:105
15. Athanasakis K, Bilitou A, Lee D, Karampli E, Karavidas A, Parissis J et al. Cost-effectiveness of eplerenone in NYHA class II chronic heart failure patients with reduced LVEF: an analysis for Greece. Clinicoeconomics & Outcomes Research. 2016; 8:583–590
16. Atienza F, Anguita M, Martinez-Alzamora N, Osca J, Ojeda S, Almenar L et al. Multicenter randomized trial of a comprehensive hospital discharge and outpatient heart failure management program. European Journal of Heart Failure. 2004; 6(5):643–652

AORTIC REGURGITATION (AR)

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I. DEFINITION

Failure of the aortic valve to close tightly causes back flow of blood into the left ventricle in diastolic.

II. EPIDEMIOLOGY

The prevalence of rheumatic valvular heart disease in developed countries is declining, with an estimated incidence 41millions in world wide. The prevalence is higher in developing nations than in US. In Cambodia, the prevalence is more than 35 case per 100000.

III. ETIOLOGY

- Rheumatic fever more than 95%,
- Degenerative,
- Infective endocarditis
- Congenitally bicuspid,
- Prolapse from VSD
- Systemic hypertension,
- Marfan or Marfan-like syndrome
- Malignant carcinoid syndrome,
- Silence Syphilis
- Systemic lupus erythematosus, Whipple disease, Fabry disease, and rheumatoide arthristis.

IV. PHYSIOPATHOLOGY

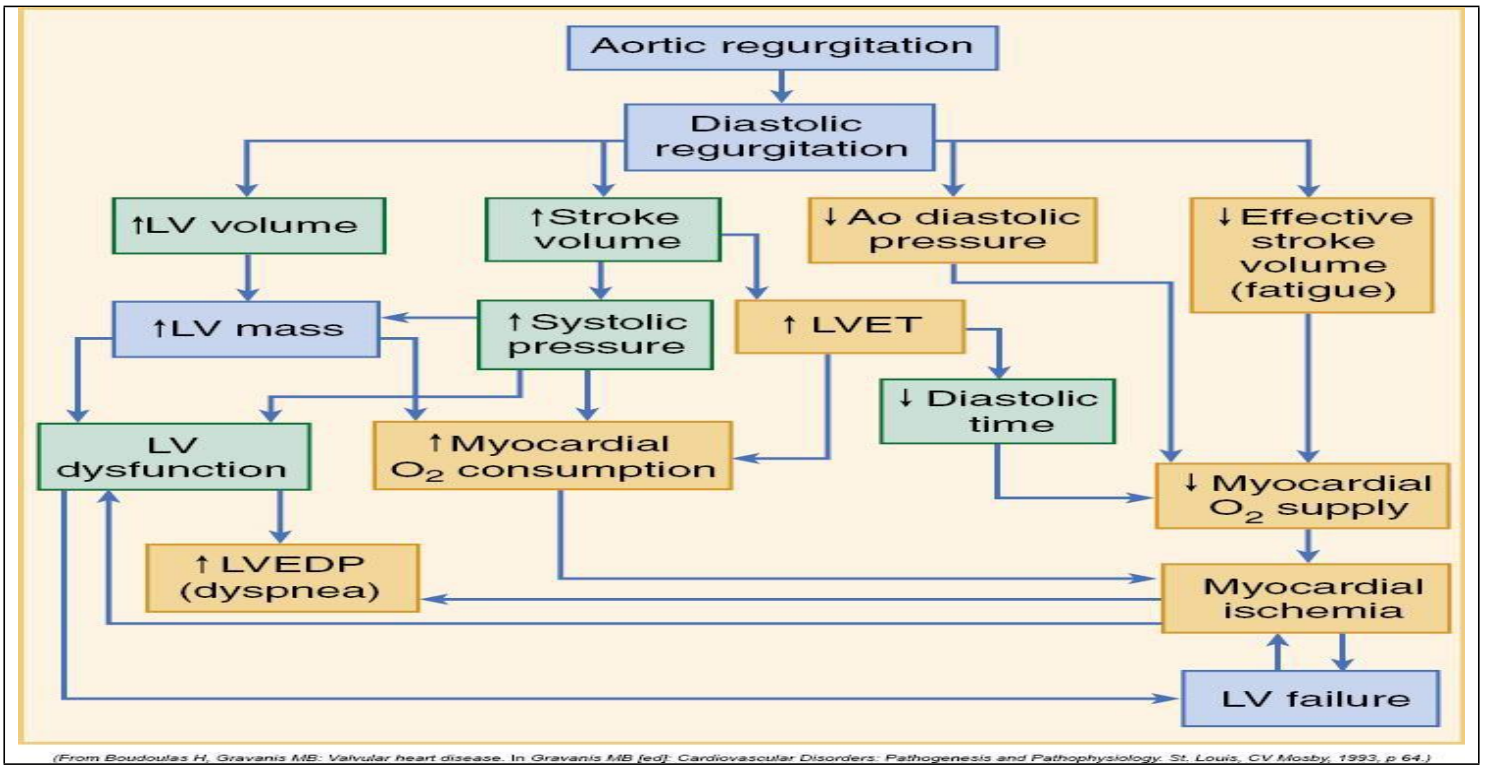
A. Acute Aortic insufficiency:

In acute aortic insufficiency, the retrograde backflow of blood results in a quick rise in the LVEDV. The acute increase in preload and afterload does not allow the time for the LV to adapt to the rapid increase in volume during diastole, and this also results in a sharp rise inf LV diastolic pressure. When the LV diastolic pressure rises above the level of LA pressure, premature mitral valve closure and MR can be seen. Additionally, there will be increases in LA pressure and pulmonary capillary wedge pressure that cause pulmonary edema. Compensatory tachycardia may occur to blunt the decline in anterograde stroke volume, and concentric hypertrophy with increased wall thickness can occur.

B. Chronic Aortic Insufficiency:

In chronic aortic insufficiency, the LV compensates for the diastolic regurgitation of blood from the aorta into the LV by remodeling of the LV via eccentric hypertrophy of the cardiomyocytes and LV dilatation to allow for an increase in LV stroke volume and a lesser increase in wall thickness than that which would be seen in acute aortic insufficiency. However, the left end-diastolic volume and

pressure rise to a high degree such that the sarcomeres can become maximally stretched, LV remodeling and compensation mechanisms fail, and interstitial fibrosis and a drop in LV compliance occur. The composite result of these changes is a decline in the initially compensated and elevated LV stroke volume.



(From Boudoulas H, Gravanis MB: Valvular heart disease. In Gravanis MB [ed]: Cardiovascular Disorders: Pathogenesis and Pathophysiology. St. Louis, CV Mosby, 1993, p 64.)

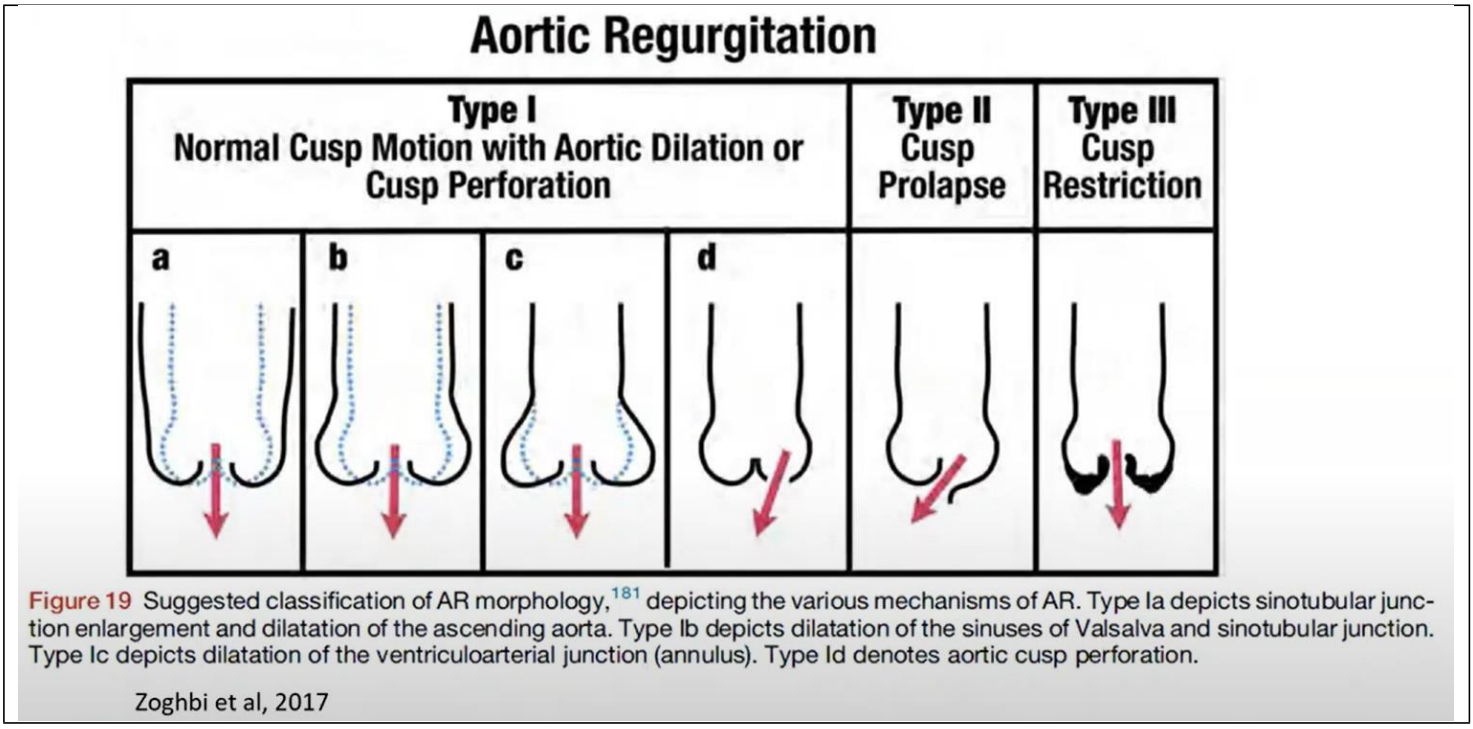


Figure 19 Suggested classification of AR morphology,[181] depicting the various mechanisms of AR. Type Ia depicts sinotubular junction enlargement and dilatation of the ascending aorta. Type Ib depicts dilatation of the sinuses of Valsalva and sinotubular junction. Type Ic depicts dilatation of the ventriculoarterial junction (annulus). Type Id denotes aortic cusp perforation.

Zoghbi et al, 2017

V. DIAGNOSIS

A. Discovered diagnostic: Systemic examination, heart auscultation, ECG, heart ultrasound, chest x-ray.

B. Clinical presentation:

1. Symptoms: Aortic Regurgitation are long time tolerance, 20 to 40 years after an episode of rheumatic fever

- The most common symptoms are shortness of breath, dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea.
- Palpitations, chest discomfort, chest pain.

2. Signs:

- Heart Auscultation: Diastolic murmur

- **Austin Flint murmur**: This is believed to occur due to the regurgitant jet of the aortic regurgitation causing premature closing of the mitral valve. This mimics functional mitral stenosis and is described as a low-pitched and rumbling mid to late diastolic or presystolic mitral murmur best heard at the apex.

- **Pulsus bisferiens**: A biphasic pulse with two systolic peaks seen on pressure tracings.

- **Corrigan sign**: A bounding pulse in large arteries such as the carotids that expands and suddenly collapses and empties between beats.

- **De Musset sign**: Head nodding with every heartbeat.

- **Muller sign**: Systolic pulsation of the uvula.

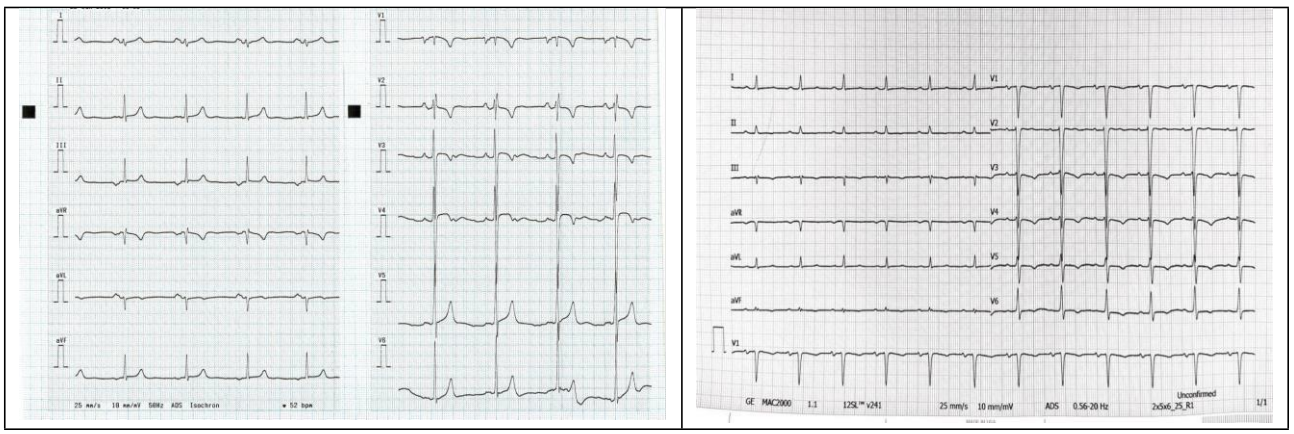
- **Quincke sign**: Repeatedly alternating blushing and blanching of capillaries in the nail folds upon palpation.

- **Traube sign:** Pistol shot sounds heard on the femoral artery upon compression of the artery.

- **Waterhammer Pulse**: Peripheral arterial pulses are rapidly dissipated or "bounding". This finding can be accentuated by raising the extremities.

C. ***Test***:

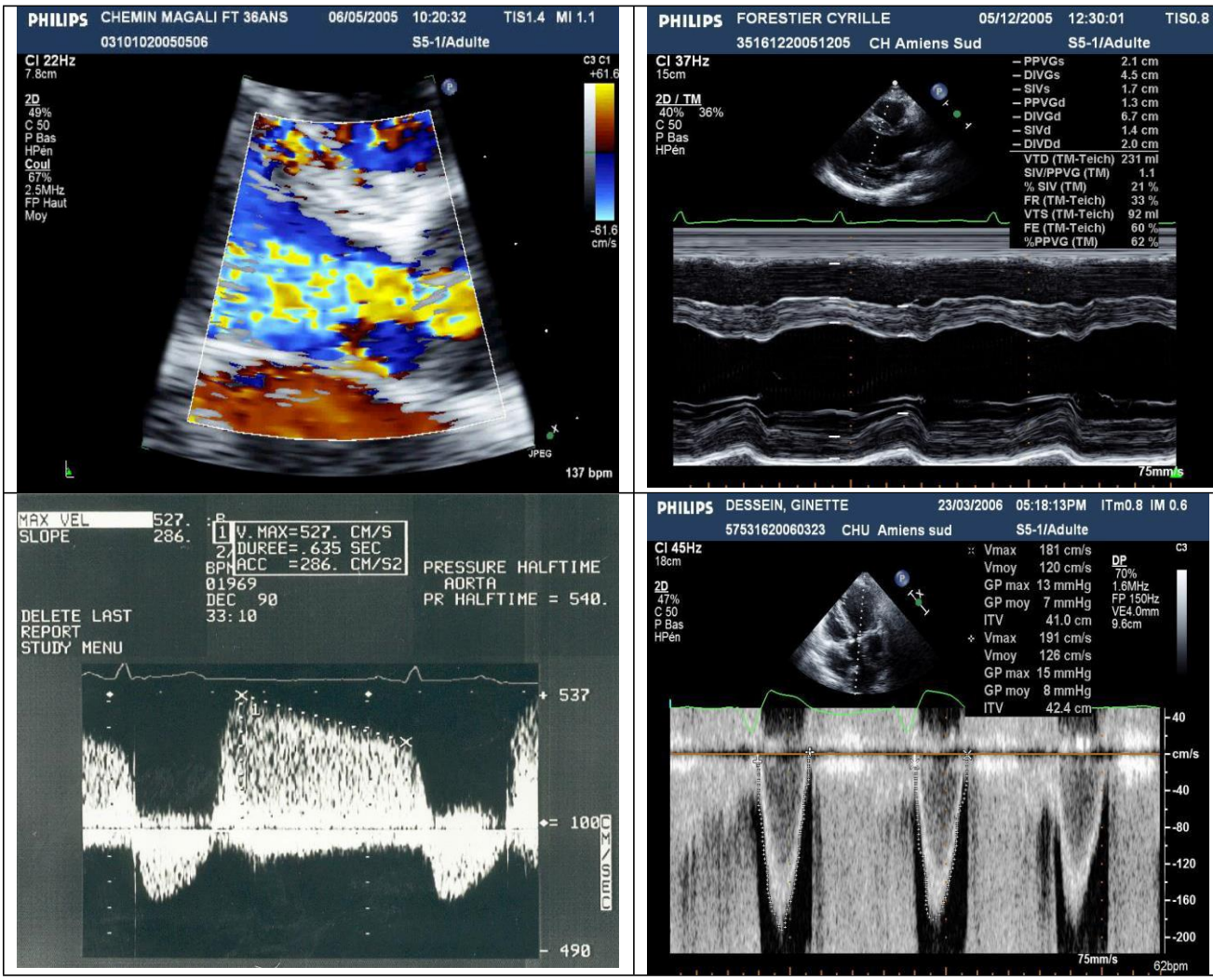
a. ***ECG***: Sinus rhythm or Sinus tachycardia, or Afib,



b. ***Heart ultrasound***: key diagnosis of AR

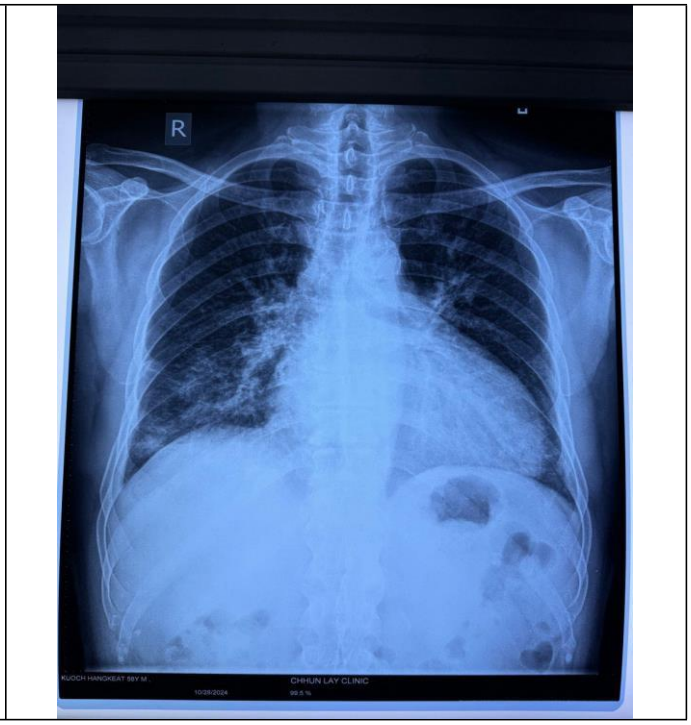
- Positive diagnosis base on ultrasound doppler,
- Diagnosis mechanism and etiology bas on 2D echocardiography,

- Diagnosis of severity base many criteria
  . 2D echocardiography,
  . M-mode to mesure LVED and other mesure
  . Color doppler to mesure Vena Contracta diameter, PISA,
- Selection patient for surgery indications



3. ***Chest X-ray***:
   . A chest X-ray is a picture of the heart and lungs. It can show whether the heart is enlarged, which can be a sign of certain types of heart valve disease.





4. ***Blood test***: CBC, Diabetes screanning (Fasting Glucose, HbA1C), Kidney function (Iono, urea, creat), Uric acide, lipid (TC, HDL, LD, TG), liver functions (Transaminases, GGT, Bilirubines, PAL, Albumine), Thyroid function (TSH, T4), Cortisol, Calcium, Magnesium,

VI. DIFFERENTIAL DIAGNOSIS

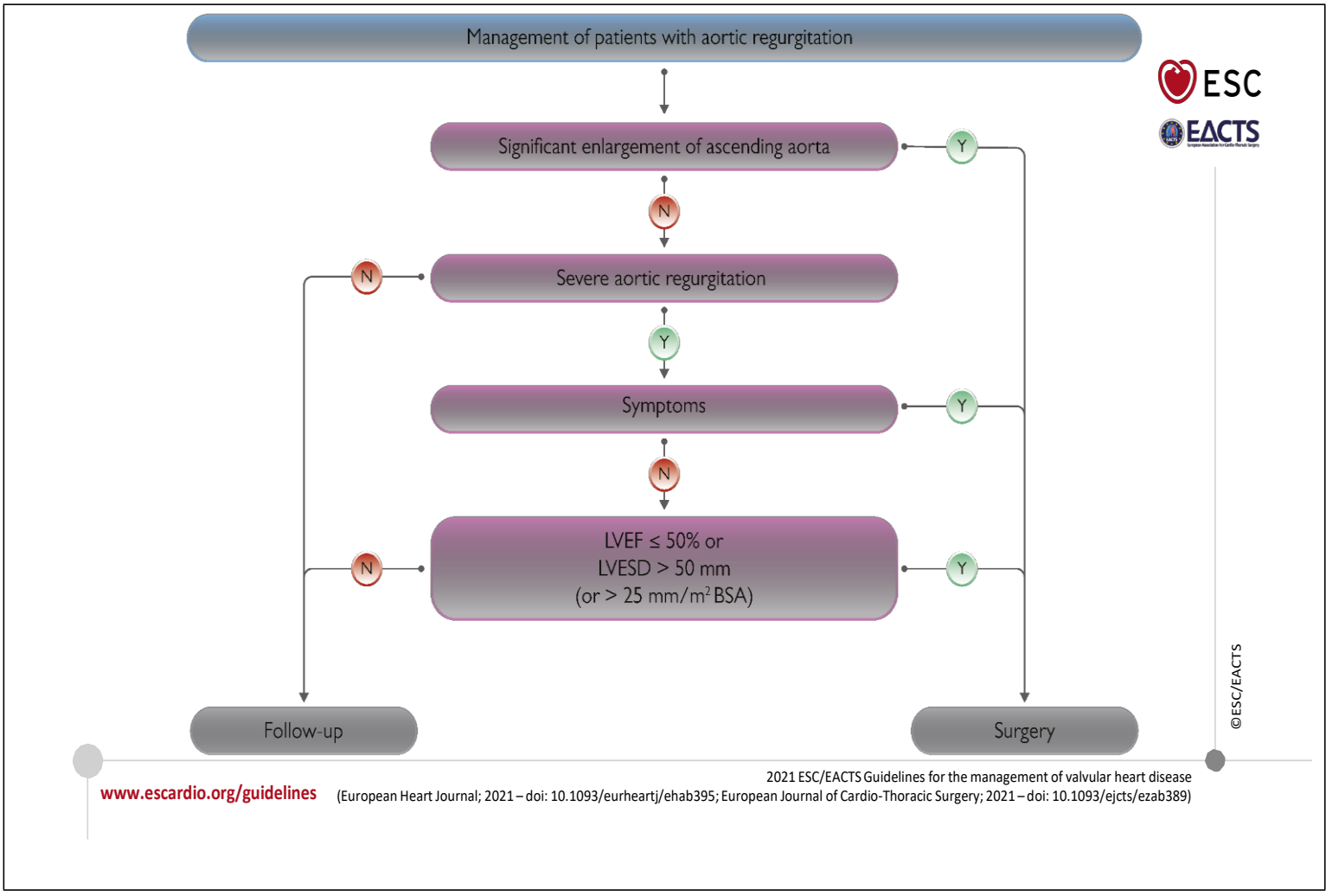
- Pulmonary valve regurgitation,
- Aortic stenosis
- Matral regurgitation,

VII. MANGEMENT

1. The goals of aortic valve regurgitation treatment are ease symptoms and prevent complications.
   - If your symptoms are mild or you don't have symptoms, you may only need regular health checkups. You may need regular echocardiograms to check the health of the aortic valve. Heart-healthy lifestyle changes also are usually recommended.
2. Prevention recurrent of Acute Rheumatic Fever and Endocarditis (See ARF and Endocarditis)
3. Medical treatment:
   - Treat symptoms
   - Reduce the risk of complications
   - Lower blood pressure
     - Volume overload: Loop diuretic with or without MRA, ACEi, ARB (see HF treatment)
     - Prevention LV remodelling: ACEi, ARB, BB, MRA
     - Thrombo-embolic prevention: if sinus rhythm undergone ASP-75-81mg/day, if Afib or Fluter: AVK (INR: 2-3) or NOAC,

- Surgery indications: May be needed especially if the condition and symptoms are severe. Asymptom patient and echocardiography showed sever aortic regurgitations (see algorhythm)
- Mechanical AVR: undergone AVK (INR: 2-3),
- Biological AVR: Sinus rhythm undergone anti-agregant platelats, if Afib undergone anti-coagulation.

4. Algorhythm



VIII. SPECIAL CASES

- AR associated with others VHD: reevaluated may need to operate together.
- AR associate with CAD, CAG help to make diagnosis to do P
- Pregnancy:
  - Mild to moderated AR closely followed up small dose of diuretic if volume overload.
  - Severe symptomatic AR with advanced HF, need to do cesarean or abortion
- Stroke: Stroke treatment and HF management.

IX. COMPLICATIONS

- Heart failures: First left HF and the right HF,
- Ventricular arrhythmia and sudden cardiac death,

- Arrhythmia: Atrial flutter, Afib need undergone systemic thrombo-embolic prevention.
- Strokes
- Infectious endocarditis,

X. EVOLUTION AND PROGNOSIS

Good prognosis if early good management, bad prognosis if presence severe LV dysfunction.

XI. PREVENTION AND RECOMMENDATION:

- Prevention: Acute rheumatism and endocarditis, closely followed up for moderated and severe AR.
- Recommendation: (see Algorhythme)
  - Mild to moderated MS: followed up
  - Severe AR with symptoms or a symptom AR and echocardiography showed important LV dilated or LV dysfunction: AVR.

XII. REFERENCES

1. Enriquez-Sarano M, Tajik AJ. Clinical practice. Aortic regurgitation. N Engl J Med. 2004 Oct 07;351(15):1539-46.
2. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol. 1999 Mar 15;83(6):897-902.
3. Flint N, Wunderlich NC, Shmueli H, Ben-Zekry S, Siegel RJ, Beigel R. Aortic Regurgitation. Curr Cardiol Rep. 2019 Jun 03;21(7):65.
4. Hamirani YS, Dietl CA, Voyles W, Peralta M, Begay D, Raizada V. Acute aortic regurgitation. Circulation. 2012 Aug 28;126(9):1121-6.
5. Dong N, Jiang W, Yin P, Hu X, Wang Y. Predictors of Long-Term Outcome of Isolated Surgical Aortic Valve Replacement in Aortic Regurgitation With Reduced Left Ventricular Ejection Fraction and Extreme Left Ventricular Dilatation. Am J Cardiol. 2020 May 01;125(9):1385-1390.
6. Bonow RO. Chronic mitral regurgitation and aortic regurgitation: have indications for surgery changed? J Am Coll Cardiol. 2013 Feb 19;61(7):693-701.
7. Yang LT, Michelena HI, Maleszewski JJ, Schaff HV, Pellikka PA. Contemporary Etiologies, Mechanisms, and Surgical Approaches in Pure Native Aortic Regurgitation. Mayo Clin Proc. 2019 Jul;94(7):1158-1170.
8. Bisleri G. Aortic valve repair. Curr Opin Cardiol. 2016 Nov;31(6):581-584.
9. Wong CHM, Chan JSK, Sanli D, Rahimli R, Harky A. Aortic valve repair or replacement in patients with aortic regurgitation: A systematic review and meta-analysis. J Card Surg. 2019 Jun;34(6):377-384.
10. Mentias A, Feng K, Alashi A, Rodriguez LL, Gillinov AM, Johnston DR, Sabik JF, Svensson LG, Grimm RA, Griffin BP, Desai MY. Long-Term Outcomes in Patients With Aortic Regurgitation and Preserved Left Ventricular Ejection Fraction. J Am Coll Cardiol. 2016 Nov 15;68(20):2144-2153.

AORTIC STENOSIS (AS)

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I. DEFINITION

Uncompleted opened aortic valves less than 2cm2 during LV telesystolic (normal Aortic Surface Area: 2,5 to 3,5cm^2. Severe AS <0,75cm^2 or <0,50cm^2/m^2. Moderated AS: 0,75 to 1,5cm^2 or 0,5 to 1cm^2/m^2. Mild AS: 1,5 to 2cm^2).

II. EPIDEMIOLOGY

The prevalence of rheumatic disease in developed countries is declining, with an estimated incidence of 41 million worldwide. The prevalence is higher in developing nations than in US. In Cambodia, the prevalence is more than 35 case per 100000.

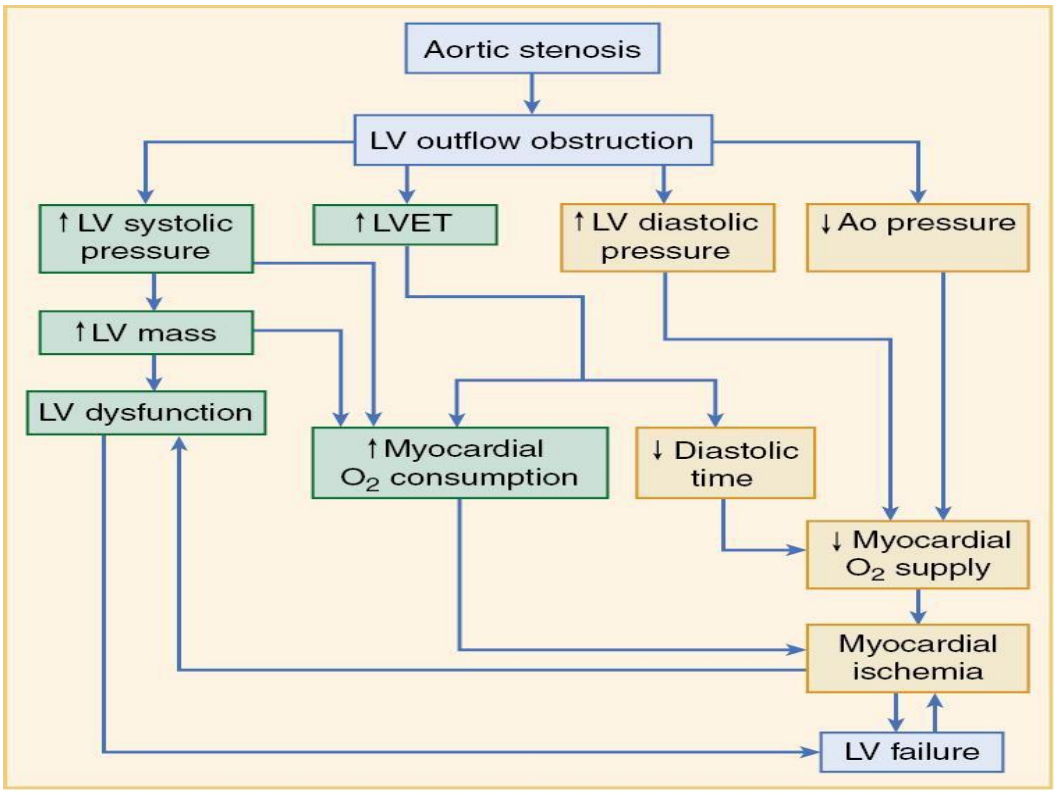
There are large differences in the epidemiology of aortic valve disease between high-income and low-income countries. Rheumatic valvulopathy is most commonly seen in low-income countries. The incidences of aortic stenosis in the developing countries with the population age older than 75 years is high (374 cases per 100,000).

III. ETIOLOGY

- Rheumatic fever more than 90% (in Cambodia)
- Calcification (in developing countries)
- Congenitally bicuspid,
- Monkeberg disease
- Malignant carcinoid syndrome,
- Systemic lupus erythematosus, Whipple disease, Fabry disease, and rheumatoid arthritis.

IV. PHYSIOPATHOLOGY:

Left ventricular (LV) obstruction caused by the stenosis of the valve increases LV systolic pressure. It also results in increased LV ejection time (LVET), decreased aortic pressure, and increased LV end-diastolic pressure. The increased afterload, in addition, to an increase in LV volume overload, leads to an increase in LV mass, ultimately leading to LV dysfunction and failure. Myocardial oxygen consumption increases with increased LV systolic pressure, LV mass, and LVET, while myocardial perfusion time decreases with increased LVET. Hence, LV function further deteriorates with increased myocardial oxygen consumption and decreased myocardial oxygen supply.



(From Boudoulas H, Gravanis MB: Valvular heart disease. In Gravanis MB [ed]: Cardiovascular Disorders: Pathogenesis and Pathophysiology. St. Louis, CV Mosby, 1993, p 64.)

V. DIAGNOSIS

Many people with aortic stenosis, or AS, don't experience noticeable symptoms until the amount of restricted blood flow becomes greatly reduced or Aortic surface less than 1cm2

A. Discovered diagnostic: Systemic examination, heart auscultation, ECG, heart ultrasound, chest x-ray.

B. Clinical presentation:

a. Symptoms:

- Angina, chest discomfort on exertion
- Syncope
- Shortness of breath, dyspnea, Symptom
- Acute pulmonary oedema.
- Palpitations,

In severe aortic stenosis with these symptoms indicated the time to surgery, if patients delay surgery will have mortality approximately 100% in five years in coming.

b. Signs:

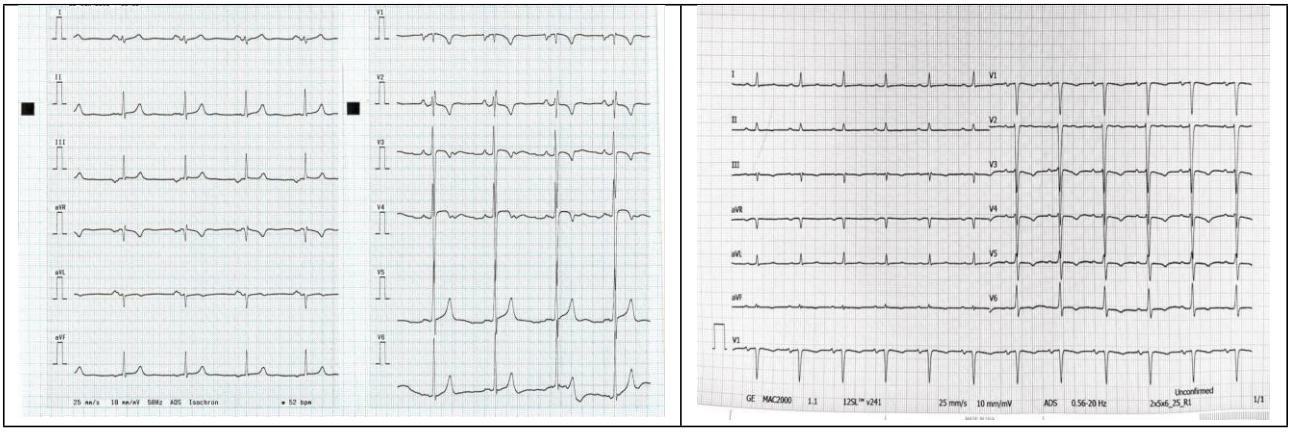
- Heart Auscultation:

. Systolic murmur: Maximal at left sternum, 2nd space of intercostal (ribs), radiation to jaw, apec. The second heart sound may lack a split and can be heard as a single sound during inspiration.

. Palpation: Carotid upstroke can be observed. A slow-rising, late-peaking, and a low-amplitude carotid impulse, *pulsus parvus et tardus,* is an expected finding in severe aortic stenosis and, when present, is specific to aortic stenosis.

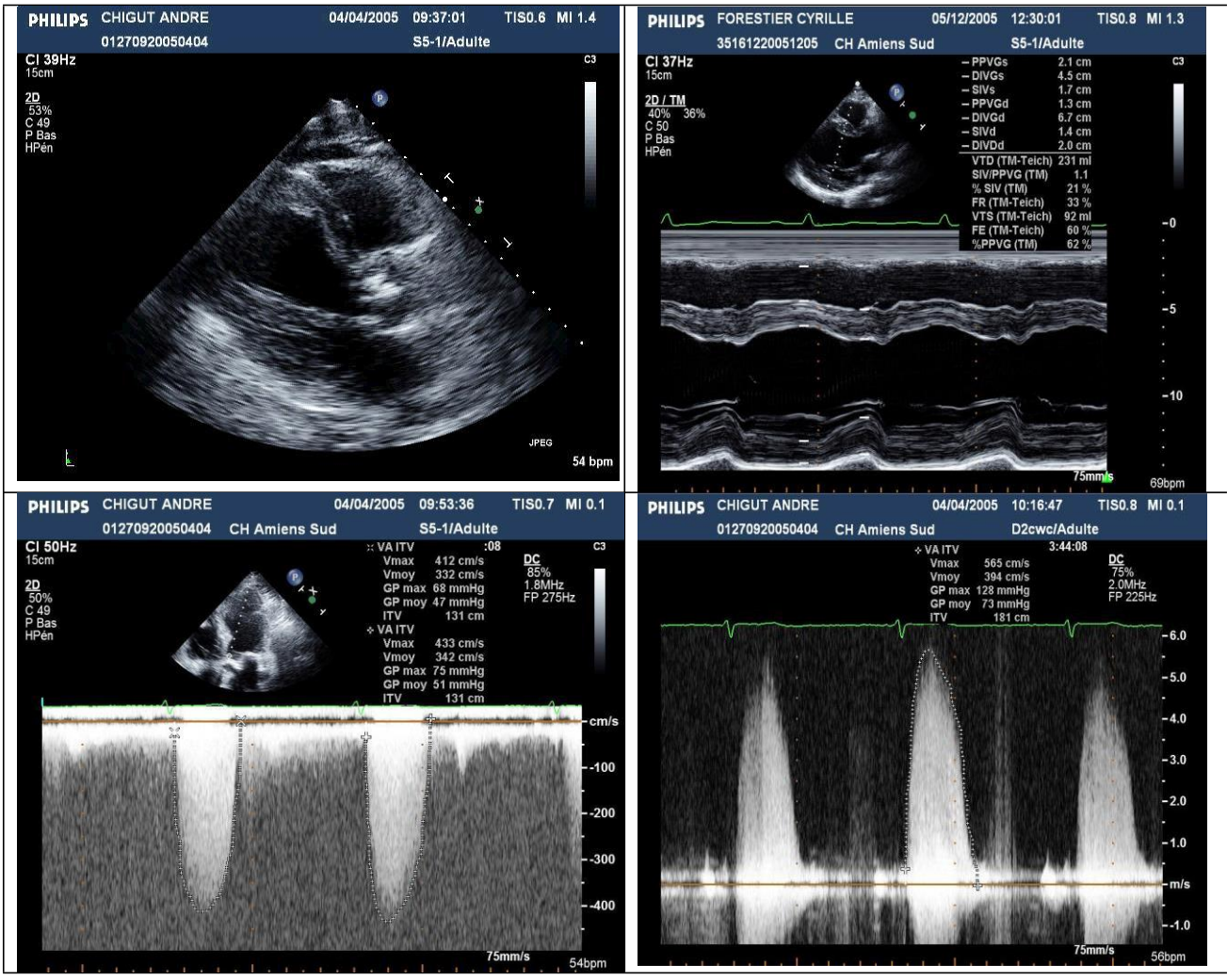
C. ***Test***:

a. ***ECG***: Sinus rhythm or Sinus tachycardia, or Afib,



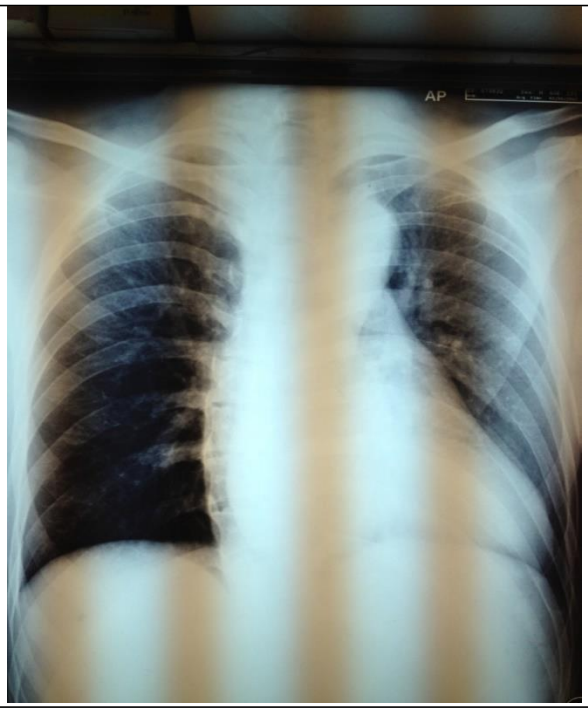
b. ***Heart ultrasound***: key diagnosis of AS

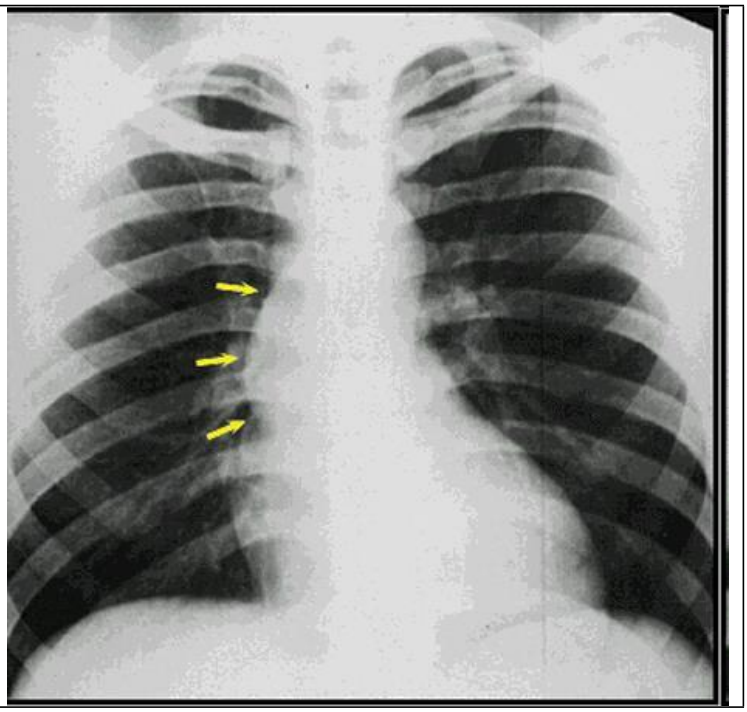
- Positive diagnosis and sererity base on ultrasound doppler. 2D and M-mode,
- Diagnosis mechanism and etiology bas on 2D echocardiography,
- Selection patient for surgery indications



a. ***Chest X-ray***:

. A chest X-ray is a picture of the heart and lungs. It can show whether the heart is enlarged, which can be a sign of certain types of heart valve disease.





b. ***Blood test***: CBC, Diabetes screanning (Fasting Glucose, HbA1C), Kidney function (Iono, urea, creat), Uric acide, lipid (TC, HDL, LD, TG), liver functions (Transaminases, GGT, Bilirubines, PAL, Albumine), Thyroid function (TSH, T4), Cortisol, Calcium, Magnesium,

VI. DIFFERENTIAL DIAGNOSIS

a. Pulmonary stenosis,
b. VSD
c. Mitral regurgitation,

VII. MANAGEMENT

A. The goals of aortic valve stenosis treatment are to prevent sudden cardiac death and prevent complications.
If patients symptoms are mild or asymptoms, they may only need regular health checkups. They may need regular echocardiograms to check the health of the aortic valve. Heart-healthy lifestyle changes also are usually recommended.

B. Prevention recurrent of Acute Rheumatic Fever and Endocarditis (See ARF and Endocarditis)

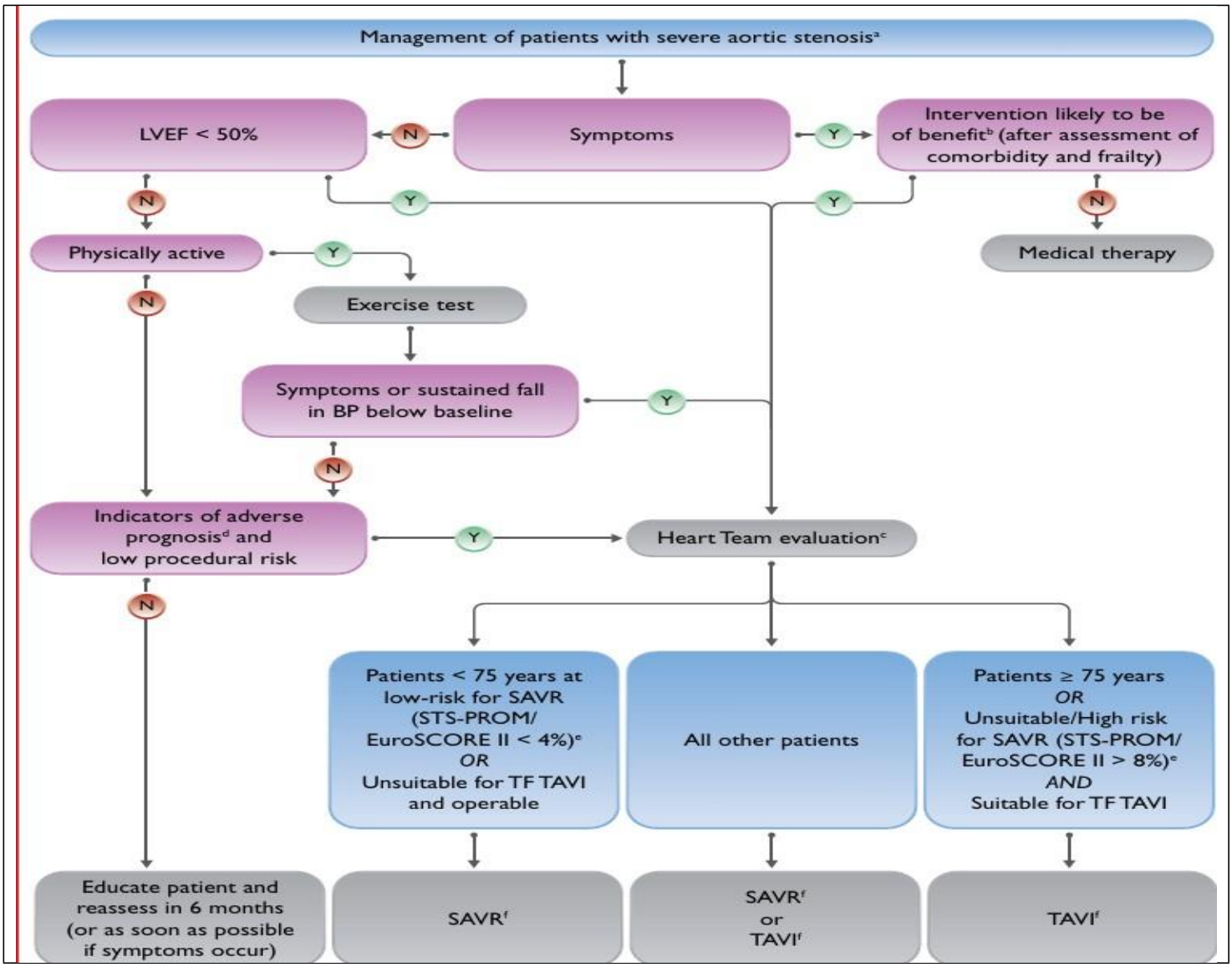
C. ***Medical treatment***:

- Treat symptoms
- Reduce the risk of complications,
  . Volume overload: Loop diuretic with or without MRA. (see HF treatment)
  . Prevention LV remodelling,
  . Thrombo-embolic prevention: if sinus rhythm undergone ASP-75-81mg/day, if Afib or Fluter: AVK (INR: 2-3) or NOAC,

D. ***Surgery indications***: when patients have symptoms (Angina, syncope, shortness of breath or HF, Acute pulmonary oedema.
. Mechanical AVR: undergone AVK (INR: 2-3),

. Biological AVR: Sinus rhythm undergone anti-agregant platelate, if Afib or Flutter undergone anti-coagulation, AVK or NOAC.

E. ***Algorithm***:



VIII. SPECIAL CASES

- ***Pregnancy***:
  - Mild to moderated AS closely followed, no special medical management.
  - Severe symptoms, angina, syncope, HF symptoms, acute pulmonary oedema: Closely followed up, HF treatments, cesarean or obortion if need,
- ***Associated with others VHD***: need surgery same time.
- ***Coronary artery diseases***: need PCI, or CABG with AVR.
- ***Stroke***: Stroke treatment and HF management.

IX. EVOLUTION AND COMPLICATIONS

- Ventricular arrhythmia and sudden cardiac death,
- Heart failures: First left HF and then right HF,

- Arrhythmia: Atrial flutter, Afib need undergone systemic thrombo-embolic prevention.
- Strokes
- Infectious endocarditis,

X. PROGNOSIS

Good prognosis if early management before complications,

XI. PREVENTION AND RECOMMENDATION

a. Prevention: Acute rheumatism and endocarditis, closely followed up for moderated and severe AS
b. Recommendation: (see Algorithm)

- Mild to moderate AS: followed up
- Severe AS with symptoms: need surgery, AVR.

XII. REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006 Sep 16;368(9540):1005-11.
2. Généreux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, Pibarot P, Bax JJ, Bonow RO, Leon MB. Natural History, Diagnostic Approaches, and Therapeutic Strategies for Patients With Asymptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2016 May 17;67(19):2263-2288.
3. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. (2017). AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Jul 11;70(2):252-289.
4. Lafitte S, Perlant M, Reant P, Serri K, Douard H, DeMaria A, Roudaut R. Impact of impaired myocardial deformations on exercise tolerance and prognosis in patients with asymptomatic aortic stenosis. Eur J Echocardiogr. 2009 May;10(3):414-9. [
5. Dahl JS, Videbæk L, Poulsen MK, Rudbæk TR, Pellikka PA, Møller JE. Global strain in severe aortic valve stenosis: relation to clinical outcome after aortic valve replacement. Circ Cardiovasc Imaging. 2012 Sep 01;5(5):613-20.
6. Lancellotti P, Donal E, Magne J, Moonen M, O'Connor K, Daubert JC, Pierard LA. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart. 2010 Sep;96(17):1364-71.
7. Magne J, Lancellotti P, Piérard LA. Exercise testing in asymptomatic severe aortic stenosis. JACC Cardiovasc Imaging. 2014 Feb;7(2):188-99.
8. Otto CM, Prendergast B. Aortic-valve stenosis--from patients at risk to severe valve obstruction. N Engl J Med. 2014 Aug 21;371(8):744-56.
9. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 10;129(23):e521-643.

MANAGEMENT OF AORTIC ANEURYSM

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I. DEFINITION

Aortic dilatation, in clinical practice, aortic root dilatation can be suspected in male adults when aortic diameter is >40 mm and in females at >36 mm or with an indexed diameter/BSA (aortic size index [ASI]) >22 mm/m2.

Arterial aneurysm is defined as a diameter >1.5 times (>50%) larger than the predicted one.

Aneurysm is a pathologic dilation of a blood vessel, affecting all three layers of the vessel wall. An aneurysm is a permanent, localized arterial dilation to more than 50% of the normal diameter. True aneurysms involve all three layers, while **pseudoaneurysms** disrupt intimal and medial layers.

Aneurysms can be classified by appearance, fusiform or saccular aneurysm.

- **Fusiform:** Circumferential widening of the artery
- **Saccular:** Localized, typically asymmetric, outpouchings of the artery wall.

Ectasia is an arterial dilatation <150% of normal arterial diameter.

II. EPIDEMIOLOGY

A. Thoracic Aortic Aneurysms (TAA)

Thoracic Aortic Aneurysms (TAA) have an estimated incidence of at least 5 to 10 per 100,000 person-years. Aortic root or ascending aortic aneurysms are most common (approximately 60%), followed by aneurysms of the descending aorta (approximately 35%) and aortic arch (<10%).

B. Abdominal Aortic Aneurysms (AAA)

AAAs occur in 3% to 9% of men older than 50 years and are the most common form of aortic aneurysms. Most AAAs (>80%) arise in the infrarenal aorta.

- 90% of all abdominal aortic aneurysms >4.0 cm is related to atherosclerotic disease.
- Risk of rupture increases with size: the 5-years risk of aneurysms < 5cm is 1-2%; whereas it is 20-40% for aneurysms > 5 cm in diameter.

III. PATHOGENESIS AND ETIOLOGY

Aortic aneurysms result from conditions that cause degradation or abnormal production of the structural components of the aortic wall: elastin and collagen.

The causes of aortic aneurysms may be broadly categorized as degenerative disorders, genetic or developmental diseases, vasculitis, infections, and trauma.

A. Thoracic Aortic Aneurysms (TAA)

*Aortic root or ascending aorta:

- **Syndromic**: Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome, Turner syndrome.
- **Non-Syndromic**: Bicuspid aortic valve, Sporadic TAA, Familial TAA.

*Descending aorta:

- Atherosclerosis
- Aortitis (non-infectious): vasculitis disorders (eg, giant cell arteritis, Takayasu arteritis, granulomatosis with polyangiitis).
- Aortitis (infectious): Syphilis, Infected (mycotic) TAA cause by systemic or local infections (eg, sepsis, pneumonia), lymphangitic spread (eg, tuberculosis).

B. Abdominal Aortic Aneurysms (AAA)

- Atherosclerosis (majority cause): risk factor: Smoking, age, HTN, Hyperlipidemia, Male sex; Family history of AAA, other cardiovascular disease
- Inflammatory aneurysm
- Infectious aneurysm
- Inherited connective tissue disorders (eg, Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome).

IV. PATHOPHYSIOLOGY

A wide variety of pathological factors are associated with aortic aneurysms. These include degenerative diseases, inherited disorders, infections, inflammatory conditions (i.e., vasculitis), and trauma.

V. DIAGNOSIS

1. Clinic

A. Thoracic Aortic Aneurysm (TAA):

Most TAAs are asymptomatic and are discovered incidentally. Less frequently revealed by clinical symptoms:

- Pain - tearing, radiating to back
- Heart failure - due to AR
- Thromboembolic (stroke, painful/parenthesis of limbs)
- Hoarseness of voice (compression of recurrent laryngeal nerve), dysphagia, plethora and edema from superior vena cava compression
- Aorto-esophageal fistula and hemoptysis can also be seen.
- Can mimic other acute disorders (AMI, renal colic, pancreatitis)

B. Abdominal Aortic Aneurysm (AAA):

- Asymptomatic
- Incidental finding on abdominal imaging examination: as a palpable, pulsatile, expansile, and nontender mass, frank ecchymosis.
- Acute abdominal pain and hypotension occur with rupture of the aneurysm, which requires an emergency operation or endovascular repair.

2. Investigation

A. Thoracic Aortic Aneurysm (TAA):

- Chest x-ray: widening of the mediastinal shadow and displacement or compression of the trachea or left main stem bronchus
- Echocardiogram or transesophageal echocardiography, can be used to assess the proximal ascending aorta and descending thoracic aorta
- Contrast-enhanced CT or MRI are sensitive and specific tests for assessment of aneurysms of the thoracic aorta and involvement of branch.

B. Abdominal Aortic Aneurysm (AAA):

- Abdomen x-ray: demonstrate the calcified outline of the aneurysm; 25% not calcified.
- Ultrasonography: screening and surveillance.
- CT or MRI: **gold standard's** in the pre-operative and post-operative evaluation of AAA.
- Since the presence of mural thrombi may reduce the luminal size, aortography may underestimate the diameter of an aneurysm.

VI. DIFFERENCIAL DIAGNOSIS

- Chest pain
  - Acute myocardial infarction
  - Pulmonary embolism
  - Spontaneous pneumothorax
  - Esophageal rupture
- Abdominal pain
  - Renal/biliary colic
  - Bowel obstruction/perforation
  - Non-dissection-related mesenteric ischemia
- Back pain
  - Renal colic
  - Musculoskeletal pain
  - Intervertebral disc herniation
- Focal neurologic deficit
  - Primary ischemic cerebrovascular accident
  - Cauda equina syndrome

VII. MANAGEMENT

1. Objective

The goal is to slow the growth of the aneurysm and prevent the rupture or dissection.

2. Critical signs

*Risk of dissection:

- Diameter > 60mm of ascending aorta
- Diameter > 70mm of descending aorta.

A. Thoracic Aortic Aneurysms (TAA):

a. Medical therapy:

- Control blood pressure: (target BP< 130/80 mmHg for non-diabetic patient and BP < 140/90mmHg for diabetic; target HR: 60bpm.)
  - Beta blocker (Atenolol; Bisoprolol, Metoprolol…)
    - ACEi or ARB
- Statin for dyslipidemia target LDL cholesterol <70 mg/dL.
- Screening 6 months after initial scan then every 12 months unless symptomatic or increased rate of expansion or if size is **4.5cm - 5.5cm**.
- Smoking Cessation

b. Percutaneous or surgical intervention:

Indication for surgery:

- Instable Hemodynamic
- Symptomatic

- Diameter ≥ 55mm or rate of growth ≥ 1.0cm per year.
- Causing bronchial compression, aortobronchial or aortoesophageal fistulas
- Traumatic, Mycotic

*Thoracic Endovascular Aortic Repair (TEVAR) or Open surgery repair.

B. Abdominal Aortic Aneurysms (AAA):

- AAA diameter **of 25-29 mm**, Ultrasound imaging should be considered 4 years later.
- Patient with small diameter **(30-55mm**), The interval for imaging should be considered:
  - Every **3 years** for AAA of **30-39mm**.
  - Every **2 years** for AAA of **40-44mm** diameter.
  - **Every year** for AAA of **> 45mm** diameter.

a. Medical Therapy:

- Control blood pressure: (target BP< 130/80 mmHg for non-diabetic patient and BP < 140/90mmHg for diabetic or CKD; target HR: 60bpm.). Beta blocker is 1st line in HTA drug with AAA. ACEi, ARB and other Antihypertension is drug of choice.
- Statins: reduce the risk of cardiovascular events related to atherosclerosis
  - cardiovascular disease and rupture.
- Antiplatelet to reduce intraluminal mural thrombus is controversial but usually use in
  - others indication of CVD.
- Smoking Cessation

b. Surgical Therapy Indication:

- Asymptomatic AAA:
  - Diameter >55mm.
  - Aneurysm growth >10mm per year.
- Symptomatic AAA
  - In case of ruptured AAA, emergency repair is indicated.
  - In case of symptomatic but non ruptured AAA, urgent repair is indicated.

AAA repair methods:

- Open aortic aneurysm repair
- Endovascular aortic aneurysm repair (EAVR)

VIII. SPECIAL CASES

Bicuspid aortic valve (BAV) is the most common congenital cardiac abnormality. A thoracic aortic aneurysm (TAA) is present ≈ 50% of BAV patients, who also have an 8-fold higher risk of aortic dissection than the general population.

IX. EVOLUTION AND PROGNOSIS

- Thoracic abdominal aneurysms (TAA) enlarge an average of 3 to 5 mm/year.
- Risk factors for rapid enlargement include larger size of aneurysm, location in the descending aorta, and presence of mural thrombi.
- The risk of rupture appears to rise abruptly as TAAs reach 6 cm in diameter.
- Survival rate of patients with untreated large TAAs is 54% at 5 years.
- TAA rupture has a mortality of 97%.
- Abdominal aortic aneurysms (AAAs) typically enlarge at a rate of 10%/year, but some

-

enlarge exponentially; about 20% remain the same size indefinitely**.**

X. COMPLICATIONS

- Rupture or Dissection
- Thrombus embolism.
- Lower Limb ischemia.
- Infected (mycotic) aneurysms
- Aorto-enteric fistulas, Aorto-caval fistulas

XI. PREVENTION AND RECOMMENDATION

- Stringent control of hypertension
- Lipid profile optimization
- Smoking cessation
- Other atherosclerosis risk reduction measures.
- Avoid isometric exercises

XII. REFERECES

1. 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases.
2. Mark A. Creager, J. L. (2022). Disease of aorta, Harrison's_Internal Medicine 21th Edition (pp. 2101-2104).
3. Schermerhorn, A. C. (2019). Diseases of the Aorta, Braunwald's Heart Disease Edition 11th (pp. 1295-1305).
4. Mark A. Farber, Federico E. Parodi, MD. 2023, Thoracic Aortic Aneurysms, Abdominal Aortic Aneurysms
5. E. Ladich, J. Butany and R. Virmani (2016), Aneurysms of the aorta: ascending, thoracic, and abdominal and their management, Cardiovascular Pathology 4th Edition, (pp. 169-211).

MITRAL REGURGITATION (MR)

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I. DEFINITION

Is the heart valve condition in which the flaps of the mitral valve do not close properly, causing a backward flow of blood back to the left atrium.

II. EPIDEMIOLOGY

MR is the most common valvular abnormality worldwide, affecting over 2 to 3% of the total population and has a prevalence that increases with age.

III. ETIOLOGY

A. ***Primary MR***:

a. ***Infectious/Rheumatic***:

- Rheumatism valvular heart disease is most common cause of VHD, more than 95% of total VHD in the developing country,
- Endocarditis

b. ***Degenerative***:

- Mitral valve prolapses,
- Myxomatous degenerative,
- Maorfanc syndrome

c. ***Congenital***:

- Congenital malformations of the mitral valve,

B. ***Secondary MR***:

a. ***Papillary Muscle Rupture:***

- Papillary muscle rupture is a very rare condition seen in 1% to 2% of patients after myocardial infarction (MI)
- or infective endocarditis. It leads to severe mitral regurgitation due to dysfunction of the papillary muscles,

b. ***Ischemic MR (IMR):***

- IMR results from prior MI associated with normal mitral valve leaflets and chordae. Ischemia of the segments underlying the papillary muscles results in remodeling. This phenomenon causes papillary muscle displacement, which results in a more apical position of the leaflets known as a “seagull sign”.

c. ***Congestive heart failure (CHF) Associated****:*

- *Cause by annulus dilation*
- *Remodeling of left LV*

d. ***Chronic Atrial Fibrillation,***

e. ***Hypertrophic Cardiomyopathy***

f. Other rare causes of MR such as prolonged use of certain medications can cause MR,

IV. PHYSIOPATHOLOGY

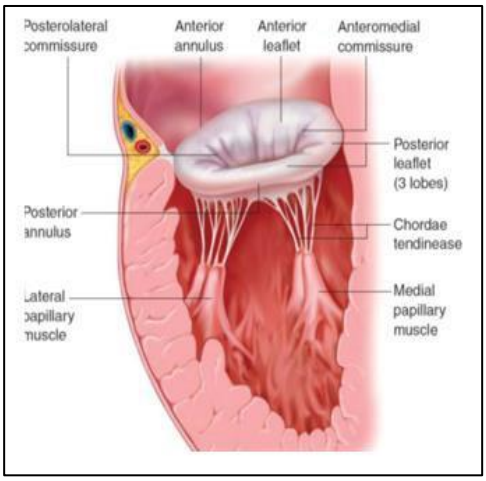
A. ***Pathophysiology mechanism***:

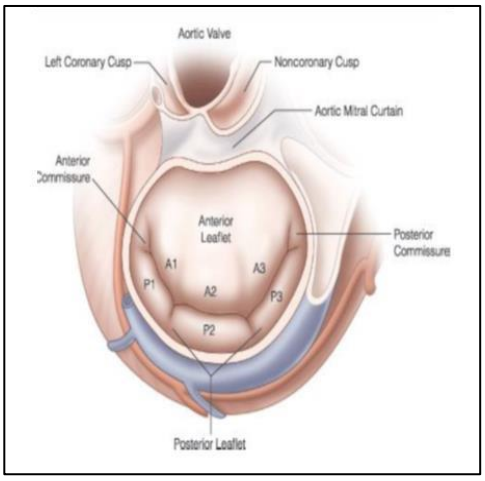
- The definition of mitral regurgitation is a retrograde flow from the left ventricle into the left atrium.
- Mitral regurgitation leads to left ventricular volume overload due to increased stroke volume, caused by an increase in blood volume within the left atrium and hence an increased preload delivered to the left ventricle during diastole.
- In chronic progressive MR, ventricular remodeling occurs, allowing maintenance of cardiac output, and an initial increase in ejection fraction (EF) is usually observed. - --
- However, depending on the regurgitant fraction, the effective EF can be considerably lower. Over time, there is a positive feedback loop by which volume overload from MR causes ventricular dilatation, widening of the mitral annulus, and diminished coaptation of leaflets, leading to further worsening of MR.
- Eventually, volume overload becomes so severe that excitation-contraction coupling becomes impaired and wall stress-related afterload on the left ventricle leading to dilatation and decreased contractility, resulting in a reduction of EF.

B. ***Anatomy pathology: Any disease affection these anatomies can cause MR,***

- Mitral leaflets (anterior and posterior)

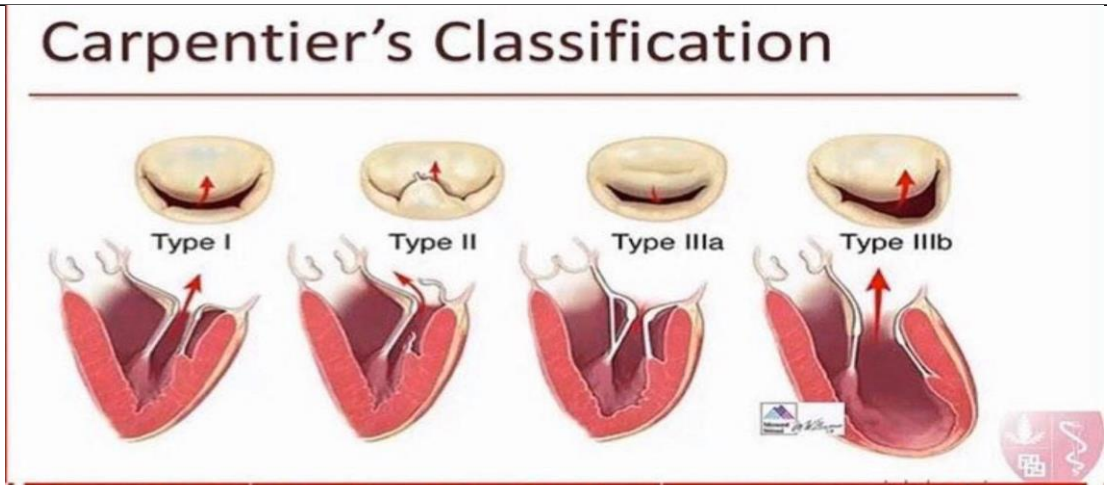
- Mitral valve annulus,
- Chordae teninease
- Papillary muscle
- LV remodeling,





C. ***Carpentier classification***:

- Type I: Normal leaflet motion
  + annular dilation, leaflet perforation
  + regurgitation jet directed centrally
- Type II: Excessive leaflet motion
  + papillary muscle rupture, chordal rupture, redundant chordae,
  + eccentric jet, directed away from involved leaflet.
- Type III: restricted leaflet motion,
  + IIIa: leaflet motion restricted in both systole and diastole,
    . rheumatic heart disease,
    . jet may be centrally or eccentrically directed,
  + IIIb: leaflet motion restricted in diastole
    . papillary muscle dysfunction, LV dilation,
    . jet may be centrally or eccentrically directed.



Carpentier's	Functional Classification	Example(s)
Type I	Normal leaflet motion	Annular dilation (secondary MR) or leaflet perforation
Type II	Excessive leaflet motion	Mitral prolapse or flail
Type III	Restricted leaflet motion	LV dilatation
IIIa	Restricted opening (during systole & diastole)	Rheumatic disease
IIIb	Restricted closure (during systole)	Ischemic MR, functional MR

V. DIAGNOSIS

A. ***Clinical presentation***: normally patients asymptom for long decade for mild or moderated chronic MR (inferior than grad III)

B. ***Symptoms***:

1. Acute severe MR:

- Palpitation, chest discomfort,
- Dyspnea NYHA III, IV,
- Orthopnea, Acute pulmonary embolism,

2. ***Chronic Rheumatic severe MR***:

- Long term compensated
- For severe chronic Rheumatic MR superior than grade III,

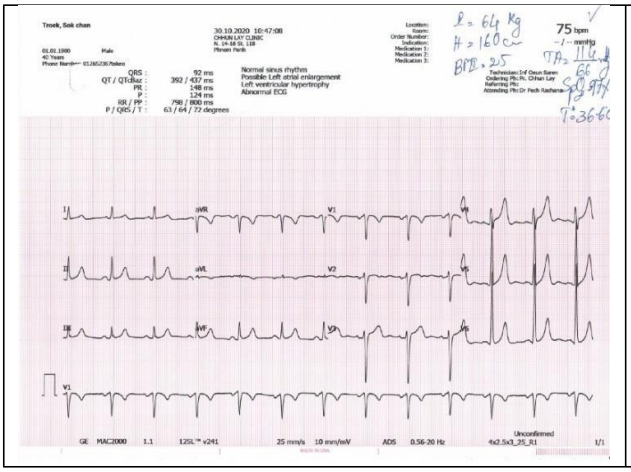
+ Fatigue,
+ Shortness of breaths (dyspnea) on exertion, grade by NYHA
+ Orthopnea, Acute pulmonary embolism.
+ Palpitations,
+ Chest discomforts,

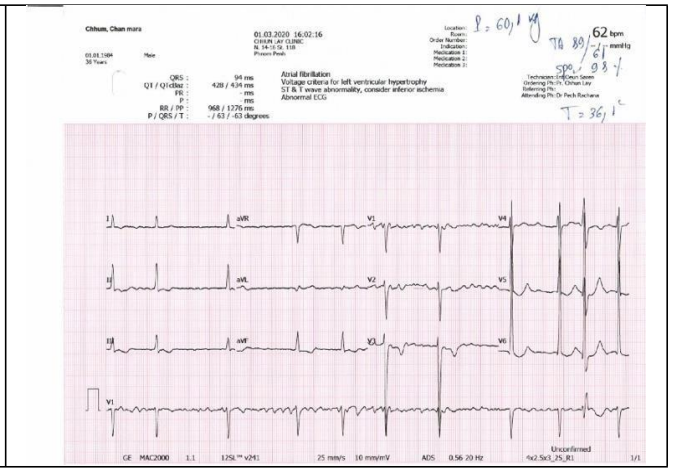
C. ***Signes***:

+ Heart Auscultation: Holosystolic murmur, maximum apex, radiated to axillary,
+ Galop of S3 or Galops,
+ Tachycardia: regular (sinus rhythm) or irregular (Atrial Fibrillation)
+ Enlarge of chock point to the left apex due to LV dilations,
+ Lung auscultation: Crackle if APO or acute bronchitis.

D. ***Test***:

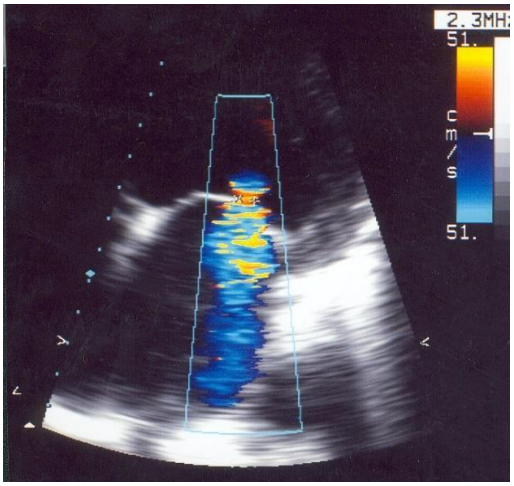
1. ***ECG***: Sinus rhythm or Sinus tachycardia, or Afib,

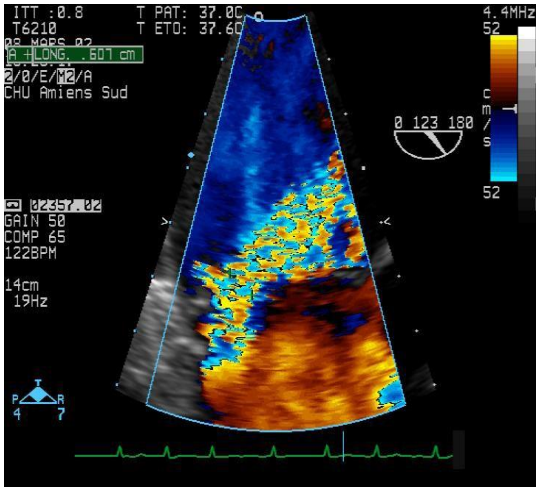


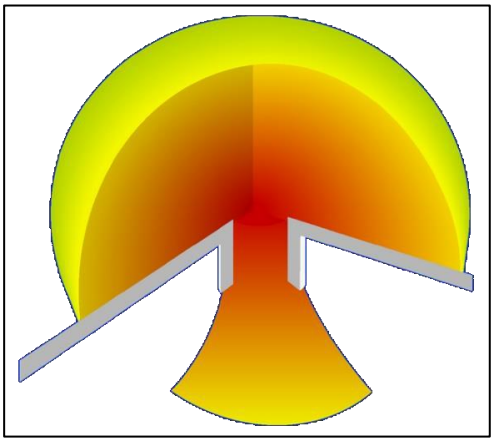


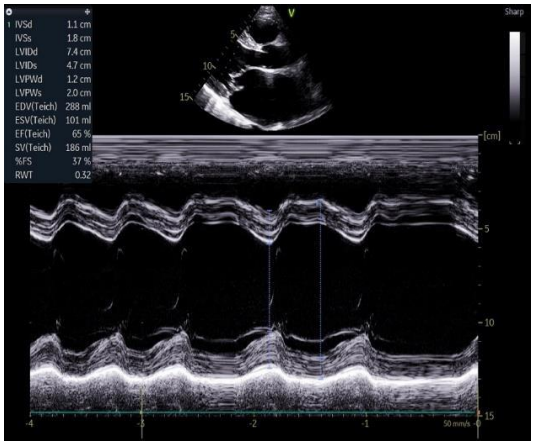
2. ***Echocardiolgraphie***: (Key exman to diagnose MR)

- Quantification of severity of MR by PISA
- Certified etiologie of MR
- Evaluation of LV function and LV dilation,
- Estimatate PAP,
- Selected patient for indications interventional surgery and opened heart surgery.









3. ***Chest X-ray***:

- A chest X-ray is a picture of the heart and lungs. It can show whether the heart is enlarged, which can be a sign of certain types of heart valve disease.





4, Blood test: CBC, Diabetes screanning (Fasting Glucose, HbA1C), Kidney function (Iono, urea, creat), Uric acide, TC, HDL, LD, TG, liver functions (Transaminases, GGT, Bilirubines, PAL, Albumine), TSH, T4, Cortisol, Calcium, Magnesium,

VI. DIFFERENTIAL DIAGNOSIS

- Aortic stenosis (AS)
- Tricuspid Regurgitation (TR)
- Obstructive Hypertrophic cardiomyopathy (OHCM)
- Congestive heart failure

VII. MANAGEMENT: MR IS LONG TERM TOLERANCE

- ***Mild to Moderate***: Follow up and prevention of endocarditis and RAA.
- ***Sever chronic MR symptomatic***:
- ***Medical treatment***:
  - ***Prevention of endocarditis and RAA***.
    - ***Sinus rhythm***:

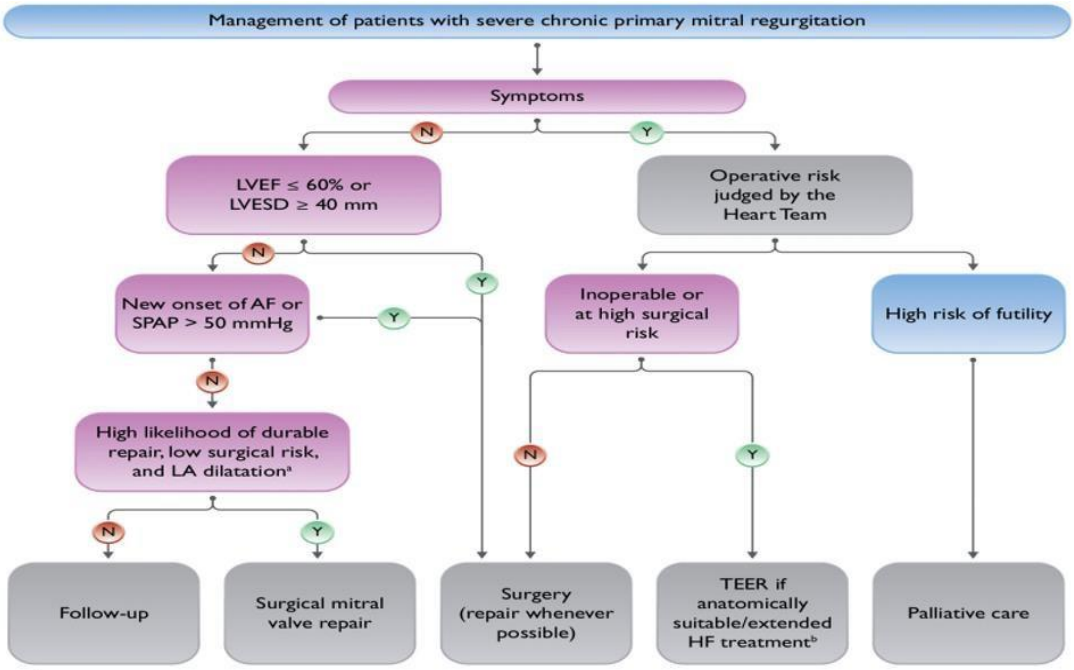
    + Volume overload: Loupe diuretic (Furosemide) +/- MRA (Spironolactone or Eplenone)
    + LV remodeling and LV dysfunction or LV dilated: HF management,
    + Thrombo-embolic prevention: Antiplatelet: ASP-81/day
    - ***Afib or Flutter: Antithrombotic***:

    + Heparin standart or henoxaparin, Antivitamin-K: Warfarin, Sintrom, or NOAC. etc.
    + Heart rate controle: Digoxine, Betablocker etc.
    + Volume overload: Loupe diuretic (Furosemide) +/- MRA (Spironolactone or Eplenone),
    + LV remodeling, LV dysfunction, LV dilated: HV management.

- ***Surgery***:
  - The first choice is conservative surgery: mitral valves repair if feasible, Mitral Valve Annuloplasthies:

- ***MVR*** (Biologic or Mechanical) (see Algorithm),
  + *Biologic MVR*:
  . Sinus rhythm: Antiplatelet, ASP-81/day
  . AFib or Flutter: Antivitamin-K: Warfarin, Sintrom, etc
  . Optimal management of HF,
  + ***Mechacnical MVR***:
  . Antivitamin-K: Warfarin, Sintrom, etc.
  . Optimal management of HF,
  + ***Interventional repair*** (Mitral valve clip) if contra-indication for opened heart surgery.

Algorithm:



VIII. SPECIAL CASES

- Pregnancy (see VHD with pregnancy)
- Associated with others valvular heart diseases, may have concomitant surgery.
- Coronary Heart Disease may need PCI or CABG,
- Stroke (see stroke management with VHD)
- MI with mechanical complications

IX. EVOLUTION AND PROGNOSIS

- MR long term tolerance
- Severe MR if no medical management evolute to be HF, supraventricular and ventricular arrhythmia, bad prognosis,
- Severe MR:
  - Even though optimal medial management evolute to be HF and other complication
  - Surgery on time good prognostic (see algorithm).

X. COMPLICATION

- HF, Acute Pulmonary Oedema (APO),
- Supraventriculaer arrhythmia: Afib, Flutter,
- Ventricular arrhythmias: Ventricular tachycardia (VT), Ventricular Fibrillation (VF),

XI. PREVENTION AND RECOMMENDATION

- Prevention of endocarditis, RAA by good management pharyngitis and other infectious diseases,
- Closely follow up, optimal management of HF, surgery indication on time.

XII. REFERENCES

1. ESC 2021 guideline on the management of valvular heart disease,
2. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38:2739-91.
3. Freed LA, Levy D, Levine RA, Larson MG, Evans JC, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical outcome of mitral-valve prolapse. N Engl J Med. 1999;341:1-7.
4. Guilherme L, Fae K, Oshiro SE, Tanaka AC, Pomerantzeff PM, Kalil J. Molecular pathogenesis of rheumatic fever and rheumatic heart disease. Expert Rev Mol Med. 2005;7:1-15.
5. Carapetis JR, McDonald M, Wilson NJ. Acute rheumatic fever. Lancet. 2005;366:155-68.
6. Thompson CR, Buller CE, Sleeper LA, Antonelli TA, Webb JG, Jaber WA, et al. Cardiogenic shock due to acute severe mitral regurgitation complicating acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we use emergently revascularize Occluded Coronaries in cardiogenic shocK? J Am Coll Cardiol. 2000;36:1104-9.
7. Seguela PE, Houyel L, Acar P. Congenital malformations of the mitral valve. Arch Cardiovasc Dis. 2011;104:465-79.
8. Kaski JP, Wolfenden J, Josen M, Daubeney PE, Shinebourne EA. Can atrioventricular septal defects exist with intact septal structures? Heart. 2006;92:832-5.
9. Piper C, Hetzer R, Korfer R, Bergemann R, Horstkotte D. The importance of secondary mitral valve involvement in primary aortic valve endocarditis; the mitral kissing vegetation. Eur Heart J. 2002;23:79-86.
10. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36:3075-128.

MITRAL STENOSIS (MS)

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I. DEFINITION

Mitral stenosis (MS) is a form of valvular heart disease, characterized by narrowing of mitral valve orifice in diastole. Today, the most common cause of MS is rheumatic fever, but the stenosis usually appears clinically relevant only after several decades.

II. EPIDEMIOLOGY

The prevalence of rheumatic disease in developed countries is declining, with an estimated incidence of 1 in 100000. The prevalence is higher in developing nations than in US. In Cambodia, the prevalence is more than 35 case per 100000.

III. ETIOLOGY

- Rheumatic fever more than 95%,
- Calcification of mitral valve leaflets,
- Congenital heart disease,
- Mitral annular calcification,
- Endomyocardial fibroelastosis,
- Malignant carcinoid syndrome,
- Myxom of mitral valves
- Systemic lupus erythematosus, Whipple disease, Fabry disease, and rheumatoid arthritis.

IV. PHYSIOPATHOLOGY

- The normal mitral valve orifice area is 4 to 6cm2. If mitral valve areas less then 2cm2 cause and impediment to the blood flow from the LA int LV. This creates a presser gradient across the MV. As the gradient across the MV increases, the LV requires the atrial kick to fill with blood.
- MS causes an increase int LA pressure. The normal LV diastolic pressure is 5 mmHg. A pressure gradient across the MV of 20 mmHg due to severe MS will cause a LA pressure of about 25 mmHg. This LA pressure is transmitted to the pulmonary vasculature resulting in pulmonary hypertension.
- A LA pressure remains elevated, the LA will increase in size. As the LA increases in size, there is a greater chance of developing Afib. If Afib develops, the atrial kick is lost.
- Thus, the LV filling depends on the atrial kick in severe MS. With the loss of the atrial kick, there is a decrease in cardiac output and sudden development of CHF.
- MS progresses slowly from initial signs of mitral stenosis to NYHA functional class II symptoms to Afib to NYHA functional class III or IV symptoms.

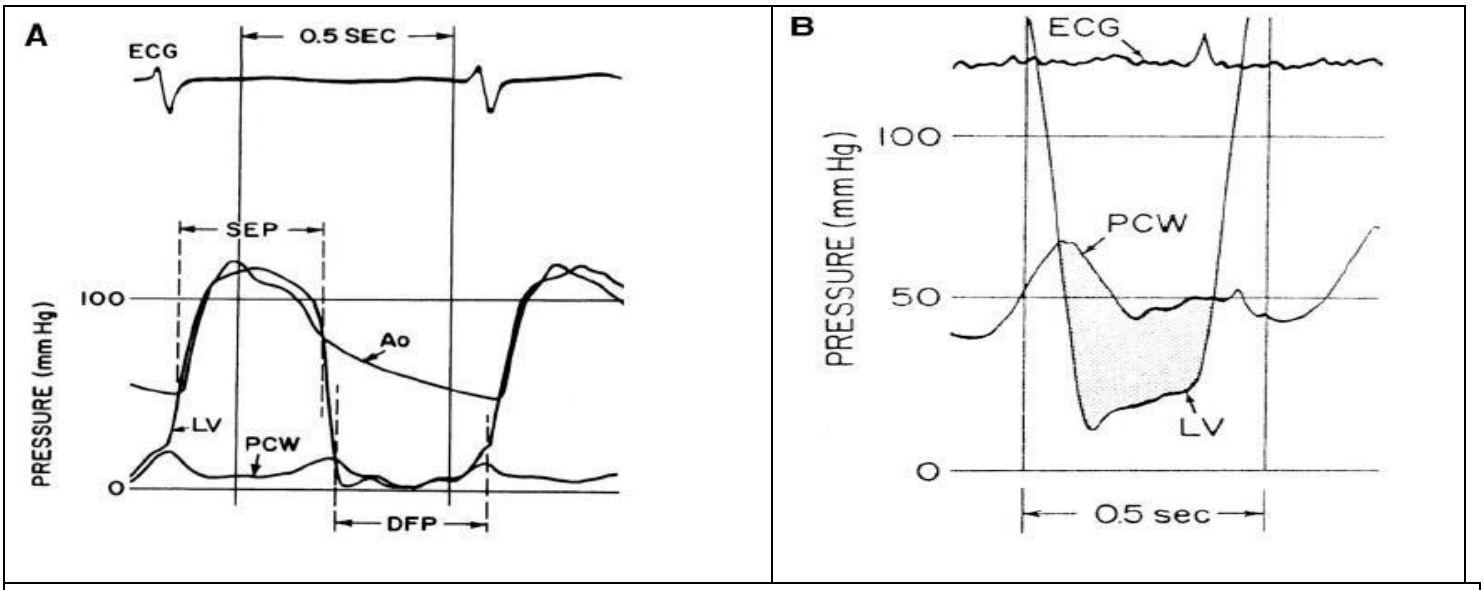


Figure 1. A, Normal left ventricular (LV), left atrial, and aortic (Ao) pressure tracings are shown. DFP indicates diastolic filling period; SEP, systolic ejection period. Taken from Carabello and Grossman[7] with permission. B, Pressure gradient between pulmonary capillary wedge pressure (PCW) and left ventricle (LV) is shown for patient with MS. In this figure, left ventricular end-diastolic pressure is atypically elevated, consistent with coincident mitral regurgitation. Reproduced from Carabello and Grossman[7] with permission.

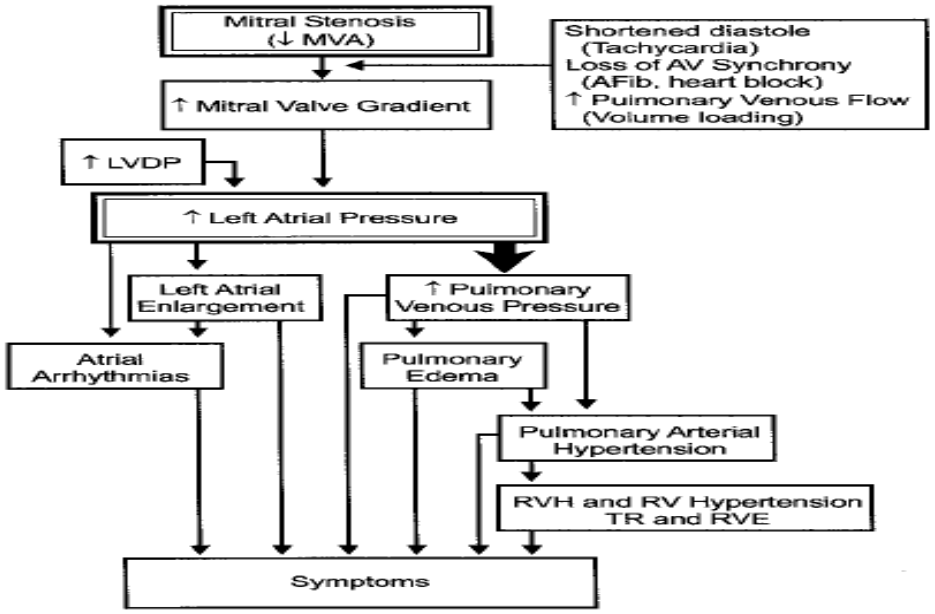


Figure 2. Pathophysiology of MS. Important factors in determining outcomes are the severity of MS and severity of LA hypertension. RVH indicates right ventricular hypertrophy; RV, right ventricular; TR, tricuspid regurgitation; and RVE, right ventricular enlargement.

A. Natural History and Prognosis of Severe MS

Natural History and Prognosis of Severe MS[3]	
Symptoms	10-Year Survival (%)
None (class I)	84
Mild (early class II)	34–42
Moderate-severe (late class II, class III)	40
Class IV	0
At 1 year	42
At 5 years	10

Class indicates New York Heart Association Functional class.

C. ***Anatomy pathology***:

Mitral Valve Anatomy According to the Wilkins Score

Grade 1

- Mobility: Highly mobile valve with only leaflet tips restricted
- Thickening: Leaflet near normal in thickness (4 mm to 5 mm)
- Calcification: A single area of increased echo brightness
- Subvalvular Thickening: Minimal thickening just below the mitral leaflets

Grade 2

- Mobility: Leaflet mid to base portions have normal mobility
- Thickening: Mid leaflets normal, considerable thickening of margins (5 to 8 mm)
- Calcification: Scattered areas of brightness confirmed to leaflet margins
- Subvalvular Thickening: Thickening of chordal structures extending to one of the chordal lengths

Grade 3

- Mobility: Valve continues to move forward in diastole, mainly from the base
- Thickening: Thickening extending through the entire leaflet (5 mm to 8 mm)
- Calcification: Brightness extending into the mid portions of the leaflets
- Subvalvular Thickening: Thickening extended to the distal third of the chords

Grade 4

- Mobility: No or minimal forward movement of the leaflets in diastole
- Thickening: Considerable thickening of all leaflet tissue (more than 8 mm to 10 mm)
- Calcification: Extensive brightness throughout much of the leaflet tissue
- Subvalvular Thickening: Extensive thickening and shortening of all chordal structures extending down to the papillary muscles.

V. DIAGNOSIS

A. Clinical presentation:

a. Symptoms: MS is 20 to 40 years after an episode of rheumatic fever

- The most common symptoms are orthopnea, and paroxysmal nocturnal dyspnea,
- Palpitations, chest pain, hemoptysis, thromboembolism when the LA is increased
- Ascites, edema and hepatomegaly if right side HF develops.
- There is also an increase in symptoms of fatigue and weakness with exercise and pregnancy.

b. Signs:

- Heart Auscultation:

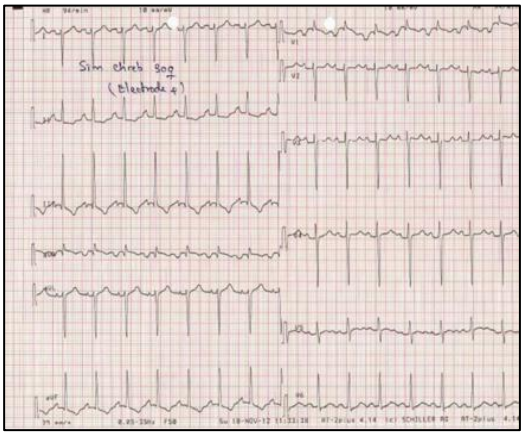
. Normal sinus rhythm: diastolic murmur, Eclat zB1 and B2

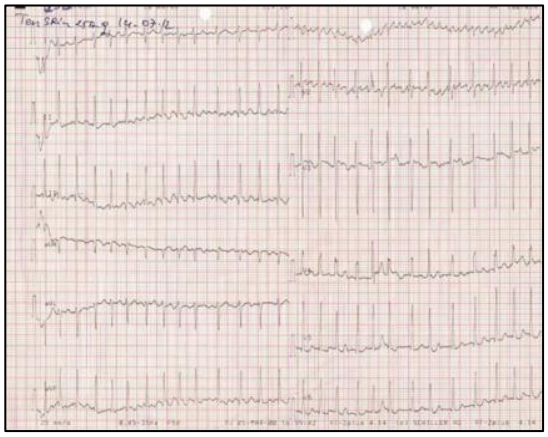
. In irregular heart beat and tachycardia: difficult.

- Palpitation, cat shacking,
- Lung auscultation: crackle, sibilente,
- Right heart failure signs,

B. Test:

a. ***ECG***: Sinus rhythm or Sinus tachycardia, or Afib,





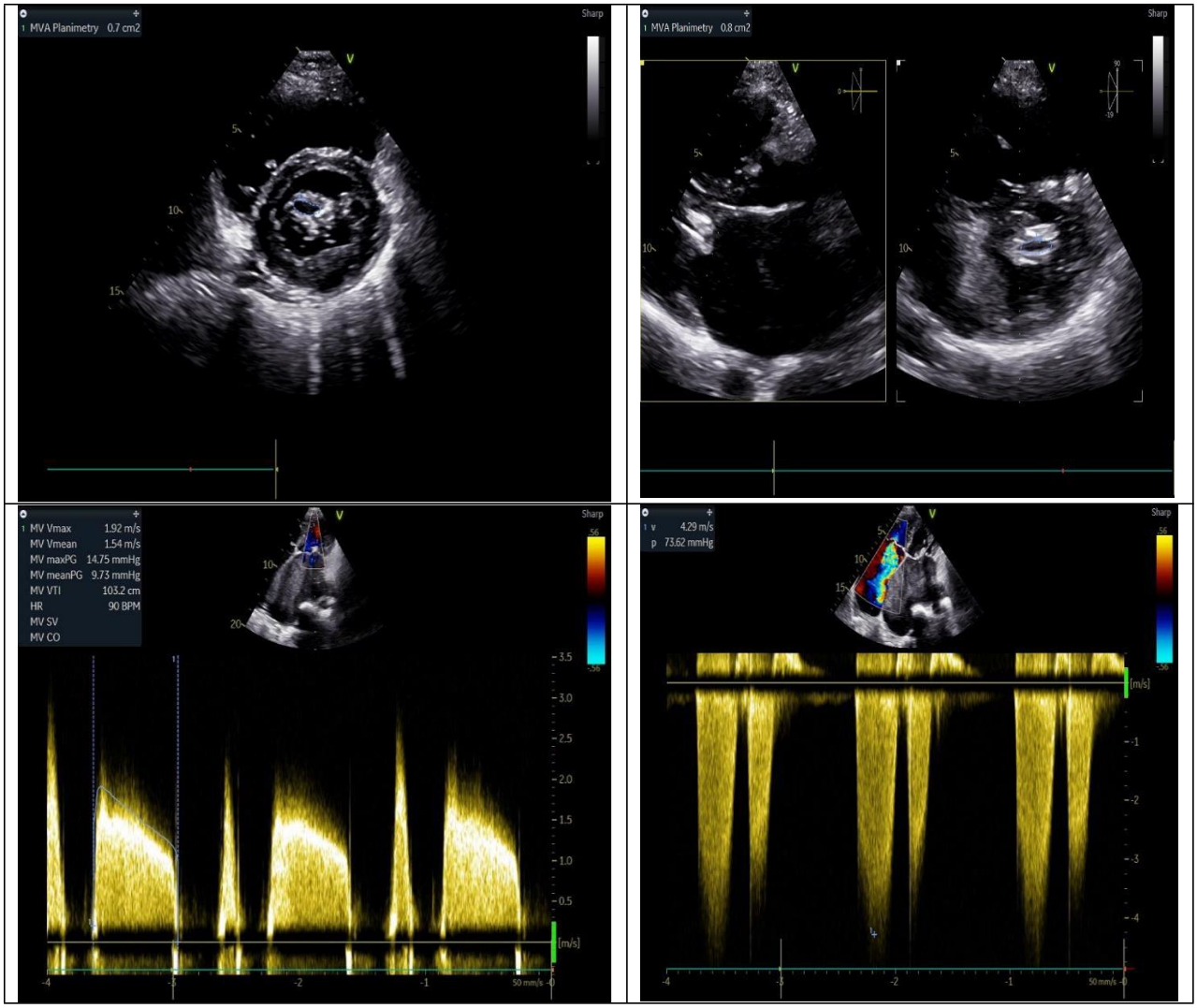
b. ***Heart ultrasound***: key diagnosis of MS

. Quatification of severity of MS,

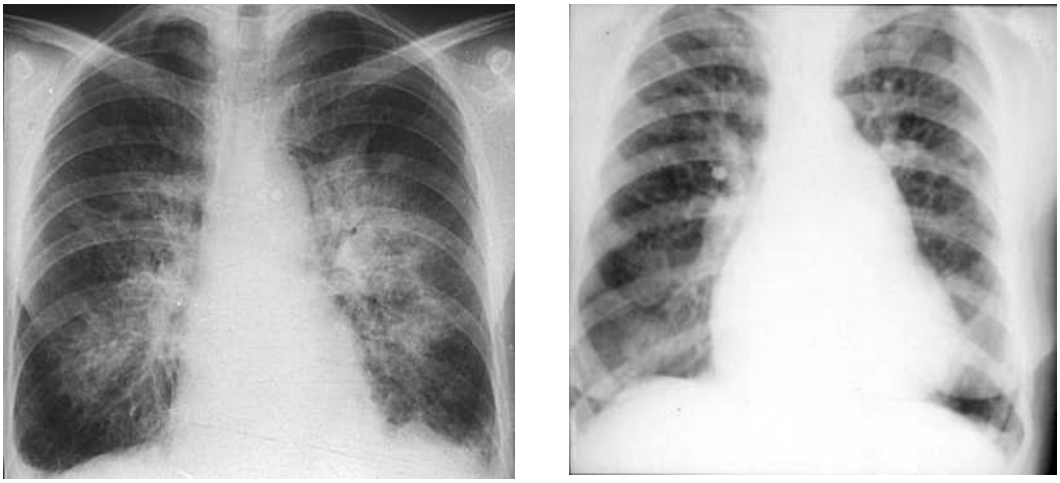
. Certified etiology, of MS

. Estimated of PAP,

. Selection patient for surgery indications



c. ***Chest X-ray***:
. A chest X-ray is a picture of the heart and lungs. It can show whether the heart is enlarged, which can be a sign of certain types of heart valve disease.



d. ***Blood test***: CBC, Diabetes screanning (Fasting Glucose, HbA1C), Kidney function (Iono, urea, creat), Uric acide, TC, HDL, LD, TG, liver functions

(Transaminases, GGT, Bilirubines, PAL, Albumine), TSH, T4, Cortisol, Calcium, Magnesium,

VI. DIFFERENTIAL DIAGNOSIS

- Aortic stenosis (AS)
- Tricuspid Regurgitation (TR)
- Obstructive Hypertrophic cardiomyopathy (OHCM)
- Management: MR is long term tolerance
- Mild to Moderate: Follow up and prevention of RAA,
- Sever MR symptomatic (send to the reference heart center).

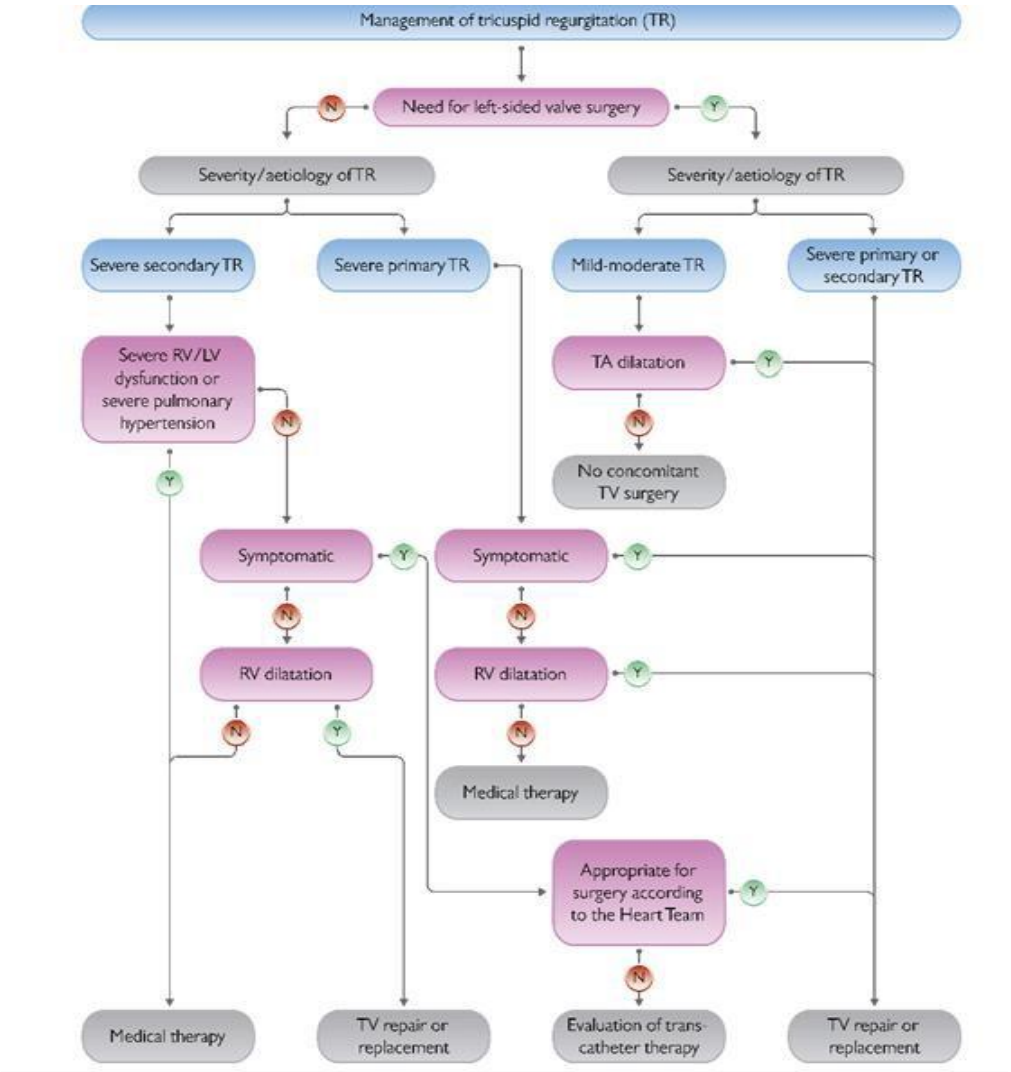
VII. MANGEMENT

1. Prevention recurrent of Acute Rheumatic Fever and Endocarditis (See ARF and Endocarditis)
2. Mild and moderated MS, MSA ≥1.5cm2: Medical treatment and preventrion
   - Prevention recurrent of Acute Rheumatic Fever and Endodcarditis,
   - Sinus rhythm: Rhythm and rate control by betablocker, systemic thrombo-embolic prevention by anti-agregent plaquettar, ex. Aspirin-81mg or Clopidogrel-75/day,
   - Afib: Rate control with Anticoagulant, AVK ex. Warfarin or Sintrom,
3. Sever MS, MSA <1.5cm^2
   - Asymptomatic patient: medical treatment, prevention of thrombo-embolic and endocarditis.
   - Symptoms or any complications related with MS:
     - Surgery indications: (see algorhythm)
   - Percutaneous balloon valvular Plasty if favorable (See Wilking and Cormier Classification and surgical selection)
   - Opened heart commissurotomy if favorable (See Wilking and Cormier Classification and surgical selection)
   - Mitral valve replacement:
     - Mechanical valve replacement: Under life anticoagulations, AVK
     - Biologic valve replacement: Aspirin if SR, anticoagulation AVK if Afib.

Medical treatment:

- Volume over load: Lope diuretic + MRA
- Sinus tachycardia:
  - Betablocker: propranolol, atenolol, bisoprolol, metoprolol.
  - Thrombo-embolic prevention: Antiplatelet: ASP-81 or CLOPIDOGREL/day.
- Afib or Flutter: Antithrombotic: Heparin standart or henoxaparin, Antivitamin-K: Varfarin, Sintrom. Heart rate controle: Digoxine, Betablocker (propranolol, atenolol, bisoprolol, meteprolol)

4. Algorithm



VIII. SPECIAL CASES

- Pregnancy:
  - Mild to moderate MS, MSA≥ 1.5cm2: can keep pregnancy, have child bird, systemic embolic prevention,
  - Severe MS, MSA< 1.5cm2, Grdmean:15mmHg, PAPs > 50mmHg with symptoms relate to MS: Should have pregnancy Abortions,
- Stroke: It is a seriously conditions and most frequently ischemic stroke,
  - Mild to moderate MS, MSA≥ 1.5cm2: undergone ASP-81 associate Clopidogrel-75/day.
  - Severe MS, MSA < 1.5cm2, with Sinus rhythm or Afib: undergone AVK (Varfarin or Coumadin).

IX. COMPLICATION

- Arrhythmia: Atrial flutter, Afib.
- Systemic thrombo-embolism: Ischemic stroke, others organism ischemic,
- Heart failures: Left heart failure and right heart failure,
- Signs of pulmonary effusions, frequency fo bronchitis,
- Infectious endocarditis.

X. EVOLUTION AND PROGNOSIS

Bad prognosis if bad management and follow up,

XI. PREVENTION AND RECOMMENDATION

- Prevention: Acute rheumatism and endocarditis,
- Recommendation:
  - Mild to moderated MS: see medical treatments,
  - Sever MS: Serious medical treatment and surgery on times.

XII. REFERENCES

1. ESC 2021 guideline in the management of valvular heart disease.
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006 Sep 16;368(9540):1005-11.
3. Généreux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, Pibarot P, Bax JJ, Bonow RO, Leon MB. Natural History, Diagnostic Approaches, and Therapeutic Strategies for Patients With Asymptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2016 May 17;67(19):2263-2288.
4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. (2017). AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Jul 11;70(2):252-289.
5. Lafitte S, Perlant M, Reant P, Serri K, Douard H, DeMaria A, Roudaut R. Impact of impaired myocardial deformations on exercise tolerance and prognosis in patients with asymptomatic aortic stenosis. Eur J Echocardiogr. 2009 May;10(3):414-9.
6. Dahl JS, Videbæk L, Poulsen MK, Rudbæk TR, Pellikka PA, Møller JE. Global strain in severe aortic valve stenosis: relation to clinical outcome after aortic valve replacement. Circ Cardiovasc Imaging. 2012 Sep 01;5(5):613-20.
7. Lancellotti P, Donal E, Magne J, Moonen M, O'Connor K, Daubert JC, Pierard LA. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart. 2010 Sep;96(17):1364-71.
8. Magne J, Lancellotti P, Piérard LA. Exercise testing in asymptomatic severe aortic stenosis. JACC Cardiovasc Imaging. 2014 Feb;7(2):188-99.
9. Otto CM, Prendergast B. Aortic-valve stenosis--from patients at risk to severe valve obstruction. N Engl J Med. 2014 Aug 21;371(8):744-56.
10. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. /AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 10;129(23):e521-643.

MANAGEMENT AND SURVEILLANCE OF PROSTHETIC VALVES

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I. DEFINITION

Prosthetic heart valves are designed to replicate the function of native valves by maintaining unidirectional blood flow and can be separated into two broad categories, mechanical and bioprosthetic (also called tissue) valves, each with different advantages and disadvantages.

Mechanical heart valves (MHV) are made entirely from non-biological (artificial) materials including metals (titanium, cobalt), pyrolytic carbon, and polymers in order to provide mechanical stability and durability.

Bioprosthetic valves (BPV) are, at least in part, made from animal (e.g., porcine, bovine or equine) (heterograft or xenograft) or human (homograft or allograft) tissue mounted onto a metal or polymer supporting structure with three pillars (also called struts or posts) and have a trileaflet configuration that resembles the geometry of a native aortic valve.

II. SELECTION OF PROSTHETIC VALVES

The choice between a mechanical and a bioprosthetic valve is a complex decision based on prosthetic valve characteristics, patient-related factors (e.g., comorbidities) and patient preferences such as wishes and expectations.

Table 1. Factors to be considered for the choice of prosthetic heart valve

In favor of a bioprosthesis	In favor of a mechanical valve
For AVR: age >65 years	For AVR: age <60/50 years
For MVR: age >70/65 years	For MVR: age <65 years
Anticoagulation contraindicated, not desired, or cannot be monitored	Other indication for anticoagulation (e.g., atrial fibrillation)
Desired pregnancy Limited life expectancy	Small aortic root size (preclusion of future transcatheter valve-in-valve [VIV] implantation for failed aortic bioprosthesis)
Patient preference (avoidance of risk or inconvenience of anticoagulation)	Patient preference (avoidance of risk of reintervention)

III. BASELINE ASSESSMENT AND FOLLOW-UP

All patients with prosthetic valves require lifelong follow-up to detect early deterioration in prosthetic function or ventricular function, or progressive disease of another heart valve. Clinical assessment should be performed **yearly** or as soon as possible if new cardiac symptoms occur. TTE should be performed if **any new symptoms occur** or if complications are suspected. After transcatheter, as well as surgical implantation of a BHV, echocardiography, including measurement of transprosthetic gradients, should be performed within 30 days after valve implantation (i.e. baseline), at 1 year, and annually thereafter.

Many clinicians in the United States use 4–6-week INR follow-up intervals for these patients. However, the 2012 American College of Chest Physicians' guidelines suggested a 12-week INR follow-up interval may be appropriate.

IV. ANTITHROMBOTIC THERAPY

1. Mechanical heart valves

The term antithrombotic therapy refers to anticoagulant, antiplatelet therapy or both. All mechanical valves require lifelong oral anticoagulation using a vitamin K antagonist (VKA) (Class I). It is preferable to specify a single international normalised ratio (INR) target median value for each patient and to concede that the acceptable range includes 0.5 INR units either side of this target. There are no data to support the use of non-vitamin K oral anticoagulants (NOACs) in patients with MHVs.

Table 2 Target international normalized ratio for mechanical prostheses

Prosthesis thrombogenicity	**Patient-related risk factors**[a]	
	None	**≥1 risk factor**
Low[b]	2.5	3.0
Medium[c]	3.0	3.5
High[d]	3.5	4.0

AF = atrial fibrillation; LVEF = left ventricular ejection fraction.

a Mitral or tricuspid valve replacement; previous thromboembolism; AF; mitral stenosis of any degree; LVEF <35%.

b Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical, Sorin Bicarbon.

c Other bileaflet valves with insufficient data.

d Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork-Shiley and other tilting-disc valves.

2. Adjunctive antithrombotic pharmacotherapy in bioprosthetic valves

- VKA for 3 months should be considered in all patients with a mitral or tricuspid BHV and ASA or VKA should be considered for 3 months after surgical implantation of an aortic bioprosthesis.
- OAC is recommended lifelong for patients with surgical BHVs who have other indications for anticoagulation. The evidence supporting the use of NOACs in preference to VKA has increased.

3. Algorithm

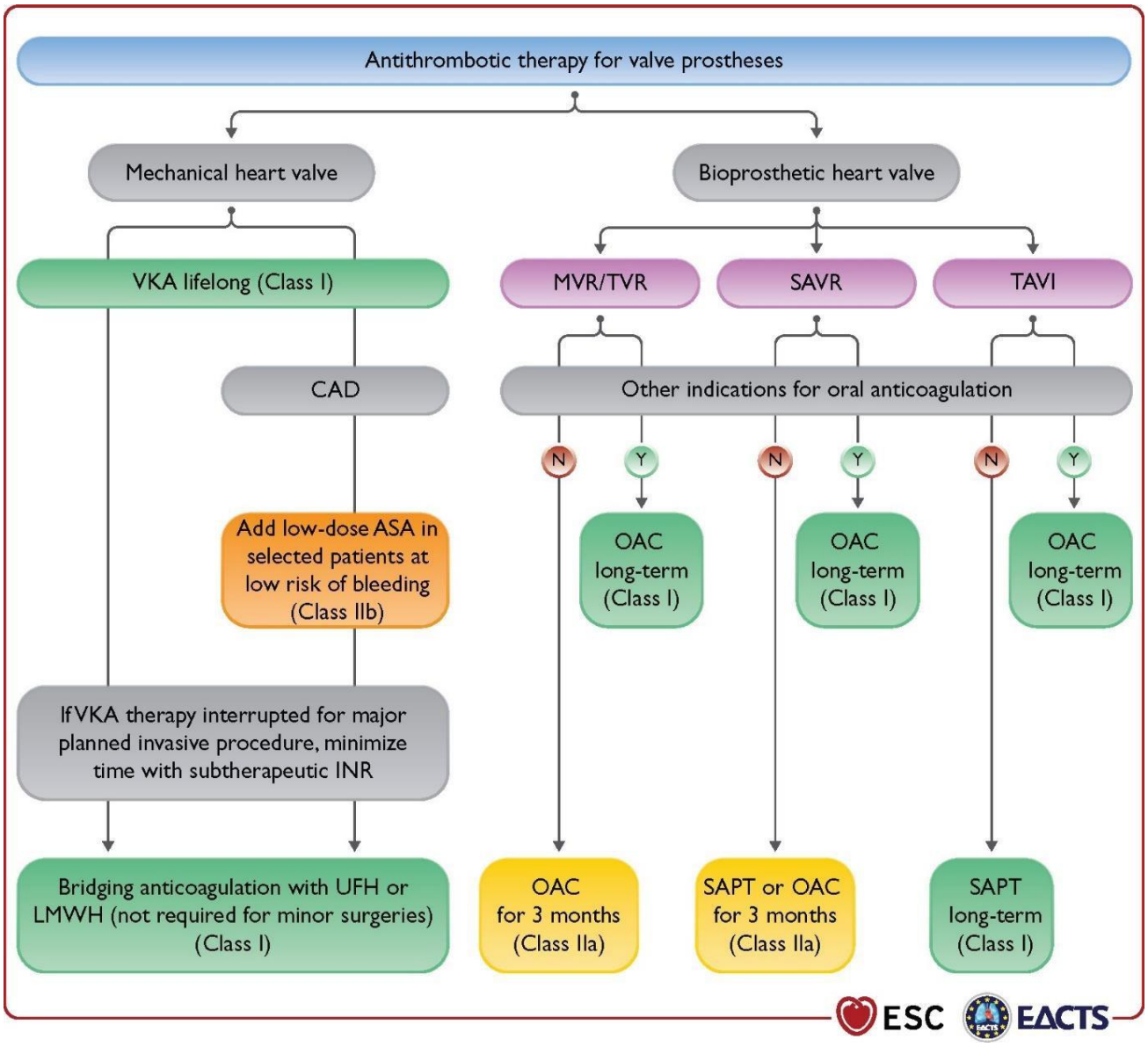


Figure 1 Antithrombotic therapy for valve prostheses. AF=atrial fibrillation; ASA= acetylsalicylic acid; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; INR = international normalized ratio; LMWH = low-molecular-weight heparin; LV = left ventricle/ left ventricular; MHV = mechanical heart valve; MVR = mitral valve replacement or repair; AC=oral anticoagulation; SAPT = single antiplatelet therapy; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation; TVR = tricuspid valve replacement or repair; UFH = unfractionated heparin; VKA = vitamin K antagonist.

Color coding corresponds to class of recommendation.

V. SPECIAL CASES

- **Combination of oral anticoagulant (OAC) with antiplatelet drugs**: this combination may be considered in patients with coexistent atherosclerotic (e.g., peripheral artery, coronary artery or cerebrovascular) disease (Class IIb)
- **Interruption of anticoagulant therapy for planned invasive procedure**: bridging therapy during interruption of oral anticoagulation for planned invasive procedures is a complex issue (discussed in "Vitamin K antagonism in surgery" section)
- **Management of vitamin K antagonist (VKA) overdose and bleeding (Table 3)**

INR >4.5 with bleeding	▪ The VKA should be discontinued ▪ 10 mg vitamin K should be administrated by slow i.v, infusion and repeated every 12 h if needed ▪ Until the anticoagulation effect is reversed, administration of prothrombin complex concentration (PCC) and/or fresh frozen plasma (FFP) therapy should be initiated according to body weight and pre-treatment INR. ▪ Monitored by re-check of INR at 30 min and every 4–6 h until normalization. ▪ The optimal time to restart anticoagulation should be discussed in relation to location of the bleeding event and interventions performed to stop bleeding and/or to treat an underlying cause.
INR > 10 without bleeding	▪ The use of PCC and/or FFP therapy is not recommended ▪ The VKA must be stopped ▪ oral vitamin K (2.5–5 mg) prescribed, while the INR must be monitored on a daily base for 2 weeks
INR 4.5 to 10 without bleeding	▪ The VKA should be stopped temporarily, and a small dose of oral vitamin K (1–2 mg) can be considered on an individual basis balancing between the risks
INR <4.5 and asymptomatic	▪ Requiring careful down-titration and/or skipping one or more doses. ▪ In all patients with MHVs, VKAs must be resumed once the INR achieves the therapeutic range or is slightly elevated

- **Mechanic heart valves (MHV) in pregnancy**:
    - The need for anticoagulation increases maternal and foetal mortality and morbidity due to the risk of MHV thrombosis and high risk of bleeding during pregnancy and delivery.
    - The potentially teratogenic VKAs cross the placenta and have a dose-dependent relationship with adverse outcomes, including foetal wastage and embryopathy.
    - It is very challenging to manage the anticoagulant during pregnancy for the safety of mother and child as well as avoiding the complications.

VI. COMPLICATIONS

- Structural failure (bioprosthetic valves): resulting in thickening, calcification, tearing, or disruption of the prosthetic valve (PV) with eventual haemodynamic dysfunction, manifesting as stenosis, regurgitation or a combination of both.
- Thrombosis and thromboembolism: leading to prosthetic valve dysfunction and embolism.
- Pannus formation: leading to prosthetic valve dysfunction
- Paraprosthetic regurgitation
- Bleeding related to antithrombotic therapy
- Intravascular haemolysis
- Infectious endocarditis
- Heart failure

VII. PATIENT EDUCATION

Patients should be educated about

- Prosthetic valve outcomes,
- The need for proper care (including optimal dental care, the need for antibiotic prophylaxis for dental procedures, and when required, appropriate antithrombotic therapy)
- Seeking prompt medical attention for any new sign or symptom that might be related to a valve complication such as a significant change in the audible click of a mechanical prosthesis, persistent or recurrent fever, decrease in exercise tolerance, ischemic cerebral events, or palpitations.
- The relation of VKA and diet
- Follow-up and checking PT and INR regularly with his/her doctor.
- Not to start, stop, or change the dose of any medicine or supplement without checking with his/her doctor.
- Telling his/her doctor, nurse, and pharmacist about all medicines he/she takes. This includes prescription or over-the-counter medicines, natural products, and vitamins. (As in Cambodia, prescribed-VKA patient should not take other medication without consulting his/her doctor due to medication interaction).
- Birth control and if she has an accidental pregnancy, should inform her follow-up doctor and not to stop taking VKA without consultation.

VIII. REFERENCES

1. Dr. Roland R. Brandt, FESC, & Prof. Philippe Pibarot , FESC. (2021, June 2). Prosthetic heart valves: Part 2 - Antithrombotic Management. ESC European Society of Cardiology. https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-20/prosthetic-heart-valves-part-2-antithrombotic-management
2. Porter, A. L., Margolis, A. R., Staresinic, C. E., Nagy, M. W., Schoen, R. R., (2018). Feasibility and safety of a 12-week INR follow-up protocol over 2 years in an anticoagulation clinic: a single-arm prospective cohort study. Journal of Thrombosis and Thrombolysis, 47(2), 200–208. https://doi.org/10.1007/s11239-018-1760-9
3. Overview of the management of patients with prosthetic heart valves - UpToDate. (n.d.). UpToDate. https://www.uptodate.com/contents/overview-of-the-management-of-patients-with-prosthetic-heart-valves

DEEP VENOUS THROMBOSIS

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I. DEFINITION

Deep venous thrombosis (DVT) is the formation of blood clot (thrombus) in a deep vein, typically in the legs.

II. EPIDEMIOLOGY

DVT is a significant global health issue, affecting around 1 in 1000 people annually. The incidence increases with age and risk factors include immobility, surgery, trauma, cancer, and genetic clotting disorders. DVT is more common in women due to risk factors like pregnancy and oral contraceptive use.

III. ETIOLOGY

The etiology of DVT involves a combination of factors that promote blood clotting in the veins. These include **immobility** (e.g after surgery or long flights), **trauma** to the vein, **hypercoagulability** (due to genetic disorders like Factor V Leiden), and **vascular injury**. Additional risk factors include **cancer**, use of **oral contraceptives**, **pregnancy** and **obesity**.

IV. PATHOPHYSIOLOGY

The pathophysiology of DVT involves Virchow's triad, which consists of three key mechanisms: **venous stasis**, **endothelial injury**, and **hypercoagulability**. Venous stasis, often caused by prolonged immobility, reduces blood flow, promoting clot formation. Endothelial injury from trauma or surgery triggers clotting at the injury site, while hypercoagulability – whether from genetic disorders, cancer or hormonal changes – increases the blood's tendency to clot. Together, these factors lead to thrombus formation in deep veins, usually in the legs.

V. DIAGNOSIS

1. Clinical assessment:
    - Assess symptoms (leg pain, swelling) and use a clinical prediction tool like the **two-level modified Well's Score** (Annex 1) to determine the likelihood of DVT
2. D-dimer Test:
    - For patients with **DVT unlikely**, a **D-dimer** blood test is performed. If the D-dimer is negative, DVT is ruled out. If positive, further imaging is required.
3. Imaging with Venous Ultrasound:
    - For patients with **DVT likely** or **positive D-dimer**, compression venous ultrasound is the first-line imaging test.
4. Further Imaging:
    - If the ultrasound results are unclear or DVT involves unusual locations (e.g. pelvic veins), advanced imaging like **CT venography** or **MR venography** may be used.

5. Follow-up:
    - In patients where initial tests are inconclusive but suspicion remains, **repeat ultrasound after 5 – 7 days may be performed to confirm or exclude DVT.**

VI. DIFFERENTIAL DIAGNOSIS

Several conditions that present with similar symptoms such as leg pain and swelling:

1. Cellulitis: a bacterial skin infection that cause redness and swelling
2. Muscle strain or tear: injury to muscle can lead to localized pain and swelling
3. Baker's cyst: a fluid-filled cyst behind the knee that can rupture, causing pain and swelling
4. Lymphedema: swelling due to lymphatic obstruction can mimic DVT
5. Chronic venous insufficiency: persist swelling and skin changes due to poor vein function, often confused with acute DVT

VII. MANAGEMENT

1. Initial assessment: risk stratification is crucial. Categorize patients as low, intermediate or high risk based on clinical presentation and underlying conditions
2. Initial treatment (first 5 – 21 days)
    - Initiate anticoagulation in most patients unless contraindicated
    - Direct oral anticoagulants (DOACs) such as apixaban or rivaroxaban are preferred for most **non-cancer patients**
    - **LMWH (Low molecular weight heparin)** or **unfractionated heparin (UFH)** is used for certain patients (e.g. cancer, renal impairment, high bleeding risk).
    - **VKA (Vitamin K antagonists): second-line therapy. VKA** are often considered when DOACs are contra-indicated or unsuitable, such as
        - In patients with severe renal impairment (eGFR < 30 ml/min)
        - In patients on certain medications that interact with DOACs, reducing their efficacy or increase bleeding
    - **Compression stockings** are recommended to reduce symptoms like swelling and prevent post-thrombotic syndrome.

Table 1: Key points about LMWH for DVT treatment

Key points about LMWH for DVT treatment	
Administration	Subcutaneous injection (S/C)
LMWH	Enoxaparin (Lovenox®) 20mg, 40 mg, 60 mg
Dosing protocol	1 mg/kg twice daily

Table 2: Key points about UFH for DVT treatment

Key points about UFH for DVT treatment	
Administration	IV bolus followed by continuous infusion
Dosing protocol	• Initial bolus: 80 units/kg (usually 5000 – 10000 units) • Continuous infusion: 18 units/kg/h, adjusted based on aPTT results (target: 1.5 – 2.5 times normal value)
Monitoring	aPTT measured every 6 hours initially to ensure target level
Reversal (antidote)	Protamine sulfate

Table 3: Key points about VKA for DVT treatment

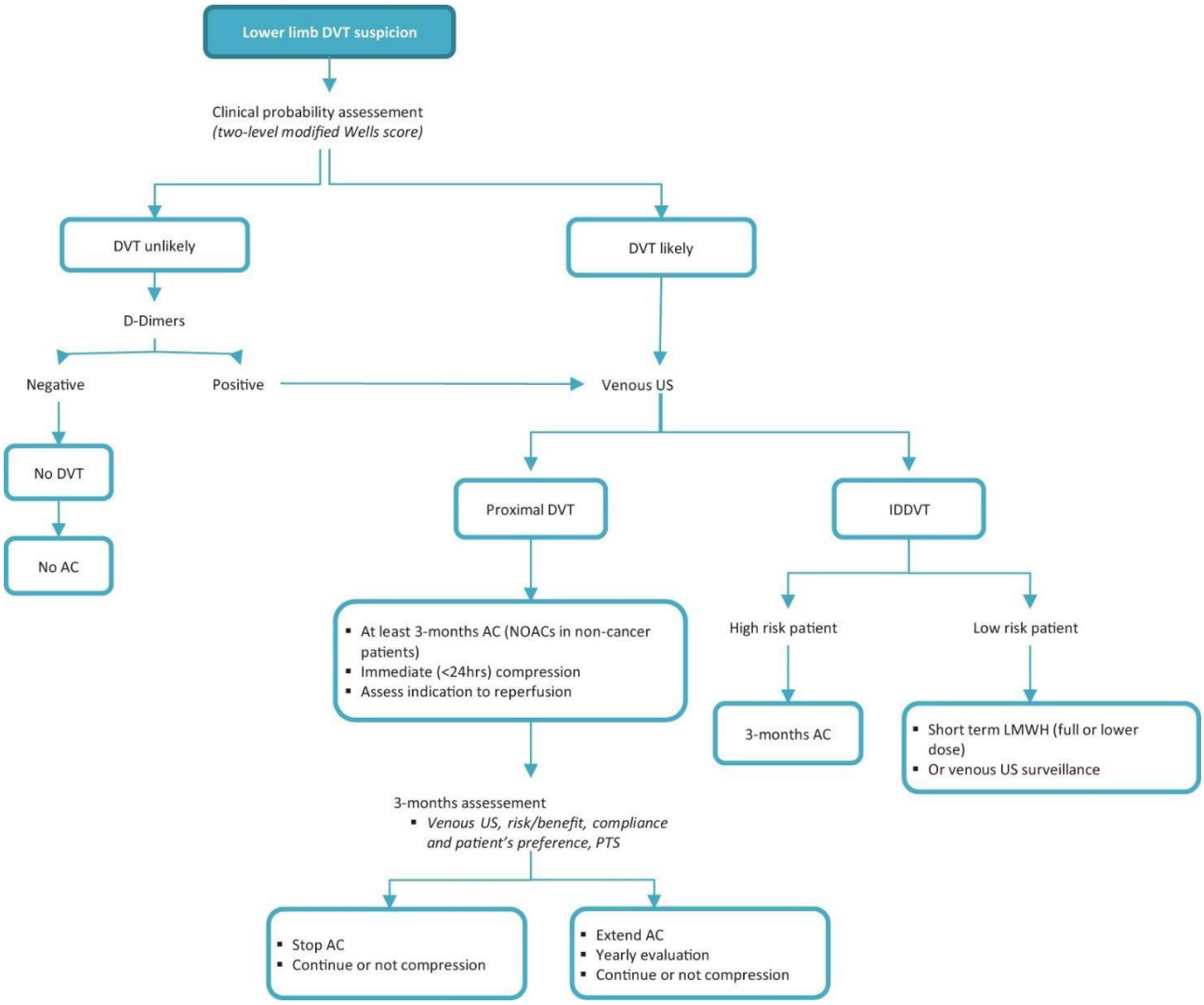
Key points about VKA for DVT treatment	
Overlap with heparin	UFH or LMWH is used for at least 5 days until the INR reaches the therapeutic range (2 – 3) for 2 consecutive days
Agents	• Wafarin (COUMADINE®) • Acenocumarol (SINTROM®)
Monitoring	Frequent INR checks during initiation, then less often (monthly) once stable
Maintenance dose	Adjusted based on INR
Reversal agent	Vitamin K

Table 4: Key points about DOAC for DVT treatment

Key points about DOAC for DVT treatment	
DOAC Agents	• Apixaban • Rivaroxaban • Dabigatran • Edoxaban
Dosing protocol	• Apixaban: **initial dose 10 mg twice daily for 7 days**, then 5 mg twice daily • Rivaroxaban: **initial dose 15 mg twice daily for 21 days**, then 20 mg once daily • Dabigatran: initial treatment with parenteral anticoagulation (e.g LMWH) for 5 – 10 days, then switch to 150 mg twice daily • Edoxaban: initial treatment with parenteral anticoagulation (e.g LMWH) for 5 – 10 days, then switch to 60 mg once daily

3. Long-term management (first 3 – 6 months)
    - Continue anticoagulant to prevent clot extension and recurrence. The choice of anticoagulant is based on patient's characteristic
        - **DOACs** are first-line for **non-cancer patients**
        - **LMWH** is preferred in **cancer patients**
    - Monitor for bleeding risks
4. Extended treatment (> 6 months)
    - For patients at **high - risk of recurrence** (e.g. those with active cancer, recurrent DVT, or persistent risk factors), anticoagulation may be extended indefinitely, balancing the risk of bleeding
    - For patients with lower recurrence risk, anticoagulation may be stopped after 3 – 6 months, with follow-up imaging to assess for clot resolution.

5. Algorithm for deep venous thrombosis assessment and management



VIII. SPECIAL CASES

- **Pregnancy-Related DVT:** due to physiological changes and compression of pelvic veins. Use Low molecular weight heparin (LMWH) for treatment.
- **Cancer-Related DVT**: due to increased coagulability associated with malignancy, treatment (chemotherapy) and immobility. Management often involves long-term anticoagulation with LMWH or DOACs.
- **Post-surgical DVT:** Common in orthopedic and abdominal surgeries. Prophylactic measures (e.g. early mobilization, compression stockings) and anticoagulation may be initiated perioperatively.
- **Upper extremity DVT:** often associated with central venous catheters or repetitive trauma. Management focus on catheter removal and anticoagulation.
- **May-Thurner Syndrome:** compression of the left common iliac vein by the right common iliac artery leading to DVT. Management includes stenting or surgical intervention alongside anticoagulation.

IX. EVOLUTION AND PROGNOSIS

- Immediate risk: DVT can lead to serious complications such as pulmonary embolism (PE) especially in acute phase
- Long-term outcomes: many patients may experience resolution of symptoms, but some develop post-thrombotic syndrome (PTS), characterized by chronic pain and swelling
- Recurrence: the risk of recurrent DVT varies based on individual risk factors (e.g. cancer, history of thrombosis), with rates ranging from 10 – 30% in 10 years
- Appropriate anticoagulation and monitoring improve outcomes, reducing the risk of complications and recurrences.

X. COMPLICATIONS

- Pulmonary embolism (PE)
- Post-thrombotic syndrome (PTS): resulting from damage to veins and valves
- Recurrent DVT
- Chronic venous insufficiency: long-term damage to veins lead to varicoses veins and skin ulcer
- Phlegmasia Cerulea Dolens: a rare, severe condition where extensive thrombosis causes blue discoloration of the limb, leading to tissue ischemia and necrosis.
- Venous gangrene: a rare but critical complication (death of tissue due to compromised blood flow)

XI. PREVENTION AND RECOMMENDATION

- Identify individuals at high risk (e.g. surgery patients, those with cancer, or prolonged immobilization) to tailor prevention strategies
- Use compression stocking to promote venous return during hospitalization or surgery
- Pharmacological prophylaxis: administer anticoagulant (LMWH or DOACs) for high-risk patients
- Early mobilization: encourage early mobilization after surgery or during prolonged hospitalization
- Patient education: inform patients about DVT symptoms and the important of prevention measures particularly after surgery or during long travel.

XII. REFERENCES

1. Theng Youdaline, MD, Sok Chour, MD. (2013). Clinical Practice Guideline for Medicine. Ministry of Health. Part 1: Page; 161-167
2. Diagnosis and Management of acute deep vein thrombosis: a joint consensus document from European Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function. European Heart Journal, Volume 39, Issue 47, 2018, Pages 4208 – 4218
3. Second consensus document on diagnosis and management of acute deep venous thrombosis: updated document elaborated by the ESC working Group on aorta and peripheral vascular disease and the ESC working Group on pulmonary circulation and right ventricular function. European Journal of Preventive Cardiology, Volume 22, Issue 8, May 2022, Pages 1248 – 1263
4. Kahn, S. R., Lim, W., Dunn, A., et al. (2021). "Antithrombotic Therapy for VTE Disease: A Guide for Patients and Their Caregivers." *Chest*, 159(3), 1114-1132. ACCP Guidelines.

5. Venous thrombo-embolic disease: diagnosis, management and thrombophilia testing. NICE Guideline [NG 158], 2020. Available: https://www.nice.org.uk/guidance/ng158

Annex 1: The Wells Score

Clinical variable	**Points**
Active cancer (treatment ongoing or within previous 6 months or palliative)	+1
Paralysis, paresis or recent plaster immobilization of the lower extremities	+1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swelling	+1
Calf swelling at least 3 cm larger than that on the asymptomatic leg (measured 10 cm below the tibial tuberosity)	+1
Pitting edema confined to the symptomatic leg	+1
Collateral superficial veins (non varicose)	+1
Previously documented DVT	+1
Alternative diagnosis at least as likely as DVT	-2
3-level Wells score	
Low	<1
Intermediate	1-2
High	>2
2-level Wells score	
Unlikely	≤1
Likely	≥2

PREVENTION OF DEEP VENOUS THROMBOSIS

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I. INTRODUCTION

The prevention of deep venous thrombosis (DVT), a common and potentially serious condition, is a critical component of clinical care.

Effective DVT prevention begins with identifying patients at risk:

1. **Risk factors:**
    - Medical conditions: Cancer, heart failure, stroke, acute infection
    - Immobilization: Prolong bed rest, paralysis, or travel
    - Surgery: orthopedic (hip and knee) or major abdominal/pelvic surgeries
    - Previous DVT or pulmonary embolism (PE)
    - Thrombophilias: inherited or acquired conditions (e.g. Factor V leiden, antiphospholipid syndrome)
    - Others: obesity (BMI > 30), pregnancy, hormonal therapy (oral contraceptives, or hormonal replacement)
2. **Assessment tools**
    - **Padua Prediciton Score** (for **hospitalized medical patients**)
    - **Caprini Risk Score (for surgical patients)**
    - **IMPROVE Bleeding Risk Score** (risk assessment for bleeding)

II. RISK ASSESSMENT AND PROPHYLACTIC RECOMMENDATION FOR MEDICAL PATIENTS

1. PADUA prediction score (PPS)

Padua Risk Assessment Model for Medical Patients PPS ≥ 4 (High Risk)	
Baseline features	**Score**
An active cancer	**3**
Previous VTE	**3**
Reduced Mobility (bedrest ≥ 3 days)	**3**
Already know thrombophilic condition	**3**
Recent (< 1 month) trauma and / or surgery	**2**
Age 70 years and above	**1**
Heart and / or respiratory failure	**1**
Acute myocardial infarction or ischemic stroke	**1**
Acute infection and / or rheumatologic disorder	**1**
Obesity BMI > 30 kg/m^2	**1**
Ongoing hormonal therapy	**1**

2, Risk Stratification and Prophylactic Recommendation of Medical Patients

Risk Stratification and Prophylactic Recommendation	
Category	**Recommendation**
Low Risk (PPS < 4)	Early mobilization or mechanical prophylaxis
High Risk (PPS ≥ 4)	Pharmacological prophylaxis (e.g : LMWH, UFH)

III. RISK ASSESSMENT AND PROPHYLACTIC RECOMMENDATION FOR SURGICAL PATIENTS

1. CAPRINI Risk Score

1-point Factors Age 41 – 60 Minor surgery Varicose veins Swelling in the legs Obesity BMI > 30 History of prior major surgery (within 1 month) Pregnancy or post-partum status Use of oral contraceptives or hormone replacement therapy Sepsis (< 1 month) Serious lung disease (< 1 month) Acute myocardial infarction < 1 month Congestive heart failure < 1 month History of inflammatory bowel disease	**2-point Factors** Age 61 – 74 Arthroscopic surgery Major open surgery (> 45 min) Laparoscopic surgery (> 45 min) Malignancy (current or previous) Confined to bed (> 72 h) Immobilizing plaster cast
3-point Factors Age ≥ 75 History of DVT /PE Positive Family history of thrombosis Factor V Leiden mutation Elevated serum homocysteine Heparin-induced thrombocytopenia (HIT)	**5-point Factors** Stroke (< 1 month) Elective lower-extremity arthroplasty Hip, pelvic or leg fracture (< 1 month) Acute spinal cord injury with paralysis (< 1 month)

2. Risk stratification and prophylactic recommendation of surgical patients

Total Score	Risk level	Prophylaxis Recommendation
0	Low	Early ambulation
1 – 2	Moderate	Mechanical prophylaxis
3 – 4	High	LMWH, UFH, DOAC
≥ 5	Highest	Combined mechanical and pharmacological prophylaxis

IV. ISK ASSESSMENT FOR BLEEDING

1. **Improve** Bleeding Risk Score
   The IMPROVE bleeding risk score is a validated tool for assessing the risk of bleeding in hospitalized patients who may require pharmacological prophylaxis for DVT / PE

Risk Factor	Points
Active gastroduodenal ulcer	4
Bleeding within 3 months before admission	4
Platelet count < 50 x 10^9 /L	4
Age ≥ 85 years	3
Hepatic failure (INR > 1.5)	2
Severe renal failure (eGFR < 30 ml/min)	2
ICU or critical care unit stay	2
Central venous catheter	1
Rheumatic disease	1
Current cancer	1
Male sex	1

2. Scoring and Risk category
   - Score ≥ 7 : High risk of bleeding (pharmacological prophylaxis should be used cautiously or avoided). Mechanical prophylaxis may be alternative.
   - Score < 7: Low risk of bleeding (pharmacological prophylaxis is safe and recommended)

V. METHOD OF PROPHYLAXIS

1. Mechanical Prophylaxis:
   Mechanical methods promote venous blood flow and are primarily used for patients at high bleeding risk or as an adjunct to pharmacological prophylaxis
   - Intermittent pneumatic compression (IPC): inflatable sleeve applied to the legs to promote venous return and useful in surgical and ICU patients with high bleeding risk
   - Graduated Compression Stocking (GCS): Elastic stockings that apply pressure to the legs, reducing venous stasis.
2. Pharmacological prophylaxis
   - Low molecular weight heparin (LMWH):
     - **Enoxaparin 40 mg (SC) daily**
     - Enoxaparin 20 mg (SC) daily (for renal impairment with eGFR 15 – 30 ml/min)
   - Unfractionated Heparin (UFH): **5000 units (SC) every 8 – 12 h,** preferred in patients with severe renal impairment (eGFR< 30 ml/min)
   - Direct Oral Anticoagulant (DOA):
     - Rivaroxaban: 10 mg orally once daily (avoid if eGFR < 15 ml/min)
     - Apixaban: 2.5 mg orally twice daily (avoid if eGFR < 15 ml/min)
     - Dabigatran: 110 mg orally on the first day, then 220 mg once daily (avoid if eGFR < 30 ml/min).

VI. TIMING AND INITIATION OF PROPHYLAXIS

1. Medical patients

- Indication: prophylaxis is indicated for hospitalized medical patients with a Padua Prediction Score ≥ 4
- Timing:
  - Initiate on admission and continue throughout hospitalization
  - Avoid prophylaxis in patients with active bleeding or high bleeding risk
- Option: LMWH is preferred (Enoxaparin)

2. Surgical patients

Clinical situation	Prophylactic agents	Timing of initiation
General Surgery	LMWH: Enoxaparin 40 mg OD	12 – 24 h post-op
Orthopedics Hip/Knee replacement Hip Fracture	LMWH: Enoxaparin 40 mg OD	12 – 24 h post-op
	Rivaroxaban 10 mg OD	6 – 10 h post-op

VII. DURATION OF PROPHYLAXIS

1. Medical patients

- Duration: Until the patient is fully ambulatory or discharged from hospital
- Extended prophylaxis: not routinely recommended after hospital discharge unless they are at very high risk of venous thrombo-embolism and low risk of bleeding

2. Surgical patients

Indication	**Duration**
Major General Surgery	Until hospital discharge (7 – 10 days)
Orthopedic Surgery Hip/Knee Replacement Hip Fracture repair	Minimum duration: 10 – 14 days Extended duration: **up to 35 days** post-operatively is recommended

VIII. REFERENCES

1. Kearon C, Akl EA, Ornelas J, et al. "Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report." Chest. 2016;149(2):315-352
2. Schünemann HJ, Cushman M, Burnett AE, et al. "American Society of Hematology 2018 Guidelines for Management of Venous Thromboembolism: Prophylaxis for Hospitalized and Non-hospitalized Medical Patients." Blood Adv. 2018;2(22):3198-3225.
3. NICE Guideline NG89: "Venous Thromboembolism in Over 16s: Reducing the Risk of Hospital-Acquired Deep Vein Thrombosis or Pulmonary Embolism."

INFECTIOUS ENDOCARDITIS

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I. DEFINITION

Infectious Endocarditis (IE) refers to infection of the endocardial surface of the heart; it usually refers to infection of one or more heart valves or infection of an intracardiac device.

II. EPIDEMIOLOGY

- The incidence of infective endocarditis is estimated between 30 and 80 cases per million inhabitants and per year in the general population in industrialized countries.
- Incidence increases after the age of 60 and Staphylococcus is now the most frequent responsible microorganism.
- Infective endocarditis was native (NVE) in 1764 (56.6%) patients, prosthetic (PVIE) in 939 (30.1%), and device-related (CDRIE) in 308 (9.9%). Infective endocarditis was community-acquired in 2046 (65.66%) patients.

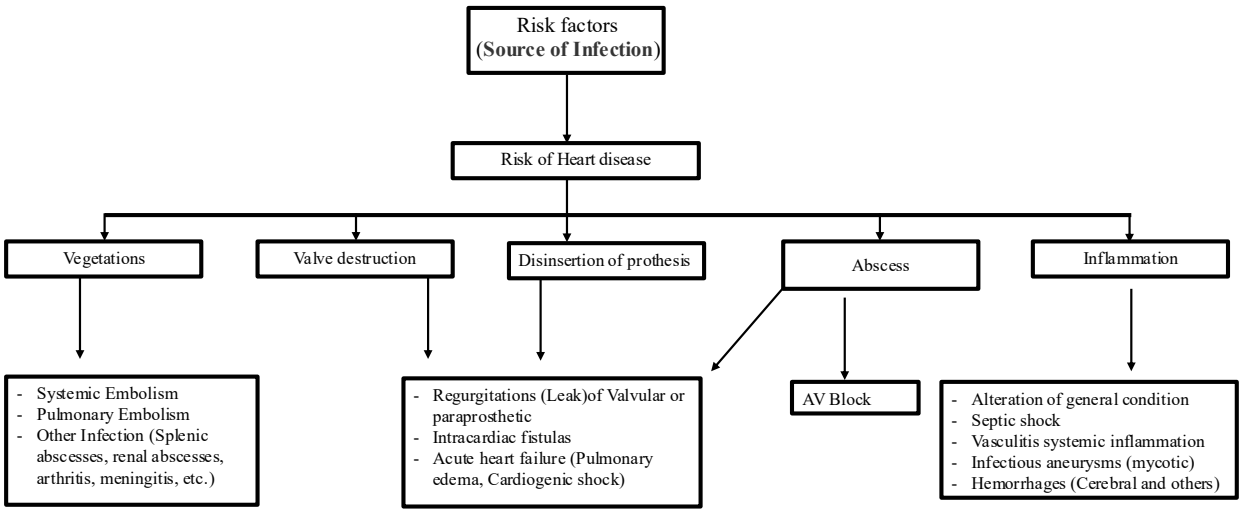
III. ETIOLOGY AND RISK FACTORS

- Risk factors for native valve infective endocarditis (IE) include cardiac factors or non-cardiac risk factors.
- It is most often from bacteria and more rarely a fungus from

Bacteria	Source of Infection
Staphylococcus aureus	Skin
Oral Streptococcus, HACEK	Oral, dental
Group D Streptococcus	Gastro-intestinal tract (Coloscopy)
Enterococcus	Gastro-intestinal tract (Coloscopy), Urinary tract

Cardiac risk factors	Non-cardiac risk factors
• Previous infective endocarditis • Valvular heart disease • Prosthetic heart valve • Central venous or arterial catheter • Transvenous cardiac implantable electronic device • Congenital heart disease	• Central venous catheter • People who inject drugs • Immunosuppression • Recent dental or surgical procedures • Recent hospitalization Haemodialysis

IV. PATHOPHYSIOLOGY



V. DIAGNOSIS

1. Clinical Manifestations

- **Symptoms**: Fever is the most common symptom of IE
    - It is often associated with chills, anorexia, and weight loss.
    - Other common symptoms: Malaise, headache, myalgias, arthralgias, night sweats, abdominal pain, tooth pain and dyspnea.
- **Signs**: A new or changing cardiac
    - Supportive signs: splenomegaly, petechiae or splinter hemorrhages.
    - **Relatively uncommon manifestations highly suggestive of IE:**
        - Janeway lesions
        - Osler nodes
        - Roth spots

2. Investigation for Endocarditis

- Blood cultures: At least two sets of blood cultures should be obtained from separate venipuncture sites prior to initiation of antibiotic therapy.
- Cardiac imaging:
    - Transthoracic echocardiography (TTE) is the first diagnostic test for patients with suspected IE.
    - Transesophageal echocardiography (TEE) has higher sensitivity than TTE and is better for detection of cardiac complications.
    - **Cardiac CT**: May be helpful for cases in which definitive evidence of IE and its complications cannot be demonstrated with TEE, and/or for planning surgery in patients with extra valvular complications.
    - Additional evaluation for IE source or complications: ECG, chest radiography, other radiographic imaging tailored to clinical manifestations, and dental evaluation.

3. Definitions of the 2023 European Society of Cardiology modified diagnostic criteria of infective endocarditis

Major criteria
1. Blood cultures positive for IE (a) Typical microorganisms consistent with IE from two separate blood cultures: Oral streptococci, Streptococcus gallolyticus (formerly S. bovis), HACEK group, S. aureus, E. faecalis. (b) Microorganisms consistent with IE from continuously positive blood cultures: • ≥ 2 positive blood cultures of blood samples drawn >12 h apart. • All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart). (c) Single positive blood culture for C. burnetii or phase I IgG antibody titre >1:800. 2. Imaging positive for IE: Valvular, perivalvular/periprosthetic and foreign material anatomic and metabolic lesions characteristic of IE detected by any of the following imaging techniques: • Echocardiography (TTE and TOE) • Cardiac CT • [18F]-FDG-PET/CT(A) • WBC SPECT/CT
Minor criteria
Predisposing conditions (i.e. predisposing heart condition at high or intermediate risk of IE or PWIDs) Fever defined as temperature >38°C Embolic vascular dissemination (including those asymptomatic detected by imaging only): • Major systemic and pulmonary emboli/infarcts and abscesses. • Haematogenous osteoarticular septic complications (i.e. spondylodiscitis). • Mycotic aneurysms • Intracranial ischaemic/haemorrhagic lesions • Conjunctival haemorrhages • Janeway's lesions Immunological phenomena: • Glomerulonephritis • Osler nodes and Roth spots • Rheumatoid factor Microbiological evidence: • Positive blood culture but does not meet a major criterion as noted above. • Serological evidence of active infection with organism consistent with IE.
IE Classification (at admission and during follow-up)
Definite: • 2 major criteria. • 1 major criterion and at least 3 minor criteria. • 5 minor criteria. Possible: • 1 major criterion and 1 or 2 minor criteria. • 3–4 minor criteria. Rejected: • Does not meet criteria for definite or possible at admission with or without a firm alternative diagnosis.

VI. DIFFERENTIAL DIAGNOSIS

The differential diagnosis for endocarditis is broad and should be considered based on two clinical categories: presence of bacteremia in the absence of valvular vegetation and presence of valvular vegetation(s) in the absence of bacteremia.

Presence of bacteremia in the absence of valvular vegetation	Presence of valvular vegetation(s) in the absence of bacteremia
• Intravascular catheter infection • Cardiac device infection • Prosthetic joint infection • Hematogenous osteomyelitis • Septic thrombophlebitis • Infected arterial aneurysm	• Culture-negative endocarditis or sterile vegetation(s) (marantic endocarditis or Libman-Sachs endocarditis) due to a noninfectious etiology or antiphospholipid syndrome.

VII. MANAGEMENT

1. Antimicrobial therapy:

- Penicillin-susceptible oral streptococci and Streptococcus gallolyticus group and Oral streptococci and Streptococcus gallolyticus group susceptible, increased exposure or resistant to penicillin

Recommendations		Class[a]	Level[b]
Penicillin-susceptible oral streptococci and *Streptococcus gallolyticus* group			
Standard treatment: 4-week duration in NVE or 6-week duration in PVE			
In patients with IE due to oral streptococci and *S. gallolyticus* group, penicillin G, amoxicillin, or ceftriaxone are recommended for 4 (in NVE) or 6 weeks (in PVE), using the following doses:[277,278]		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million[c] U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Paediatric antibiotic dosage and route			
Penicillin G	200 000 U/kg/day i.v. in 4–6 divided doses		
Amoxicillin	100–200[c] mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg/day i.v. in 1 dose		
Standard treatment: 2-week duration (not applicable to PVE)			
2-week treatment with penicillin G, amoxicillin, ceftriaxone combined with gentamicin is recommended only for the treatment of non-complicated NVE due to oral streptococci and *S. gallolyticus* in patients with normal renal function using the following doses:[277,278]		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million[c] U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		

continue

Paediatric antibiotic dosage and route			
Penicillin G	200 000 U/kg/day i.v. in 4–6 divided doses		
Amoxicillin	100–200 mg/kg/day[c] i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose or 3 equally divided doses[d]		
Allergy to beta-lactams			
In patients allergic to beta-lactams and with IE due to oral streptococci and *S. gallolyticus*, vancomycin for 4 weeks in NVE or for 6 weeks in PVE is recommended using the following doses:[292]		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 or 3 equally divided doses[e]		
Oral streptococci and *Streptococcus gallolyticus* group susceptible, increased exposure or resistant to penicillin			
In patients with NVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 4 weeks in combination with gentamicin for 2 weeks is recommended using the following doses:[285–290]		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	12 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
In patients with PVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:[285–290]		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	12 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
Allergy to beta-lactams			
In patients with NVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 4 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
In patients with PVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		

- Recommendations for antibiotic treatment of infective endocarditis due to Staphylococcus spp

IE, infective endocarditis; i.m., intramuscular; i.v., intravenous; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; U, units. a Class of recommendation. b Level of evidence. c The starting recommended doses are the lower doses which can be scalable to the highest doses. d Maximum doses 240 mg/day. High doses are associated with increased risk of nephrotoxicity. Renal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, pre-dose (trough) concentrations should be

- Recommendations for antibiotic treatment of IE due to Staphylococcus spp

Recommendations		Class[a]	Level[b]
IE caused by methicillin-susceptible staphylococci			
In patients with NVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin is recommended for 4–6 weeks using the following doses:[264,314,316–318]		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin[c]	12 g/day i.v. in 4–6 doses		
Cefazolin[e]	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin[c]	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin[e]	300–600 mg/kg/day in 3–4 doses		
In patients with PVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:[264,314,316–318,320]		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin[c]	12 g/day i.v. in 4–6 doses		
Cefazolin	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin[c]	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin	300–600 mg/kg/day in 3–4 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Allergy to beta-lactams			
In patients with NVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin for 4–6 weeks is recommended using the following doses:[322–327]		I	B
Adult antibiotic dosage and route			
Cefazolin[e]	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
Cefazolin[e]	300–600 mg/kg/day in 3–4 doses		
In patients with PVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin combined with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:[344]		I	B
Adult antibiotic dosage and route			
Cefazolin[e]	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Cefazolin[e]	300–600 mg/kg/day in 3–4 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
In patients with NVE due to methicillin-susceptible staphylococci who are allergic to penicillin, daptomycin combined with ceftaroline or fosfomycin may be considered.[322–327]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		
In patients with PVE due to methicillin-susceptible staphylococci who are allergic to penicillin, daptomycin combined with ceftaroline or fosfomycin or gentamicin with rifampin for at least 6 weeks and gentamicin for 2 weeks may be considered using the following doses:[344]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		

IE caused by methicillin-resistant staphylococci			
In patients with NVE due to methicillin-resistant staphylococci, vancomycin is recommended for 4–6 weeks using the following doses:[345]		I	B
Adult antibiotic dosage and route			
Vancomycin[h]	30–60 mg/kg/day i.v. in 2–3 doses		
Paediatric antibiotic dosage and route			
Vancomycin[h]	30 mg/kg/day i.v. in 2–3 equally divided doses		
In patients with PVE due to methicillin-resistant staphylococci, vancomycin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Vancomycin[h]	30–60 mg/kg/day i.v. in 2–3 doses		
Rifampin	900–1200 mg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Vancomycin[h]	30 mg/kg/day i.v. in 2–3 equally divided doses		
Rifampin	20 mg/kg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
In patients with NVE due to methicillin-resistant staphylococci, daptomycin combined with cloxacillin, ceftaroline or fosfomycin may be considered using the following doses:[335,345–349]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Cloxacillin[c]	12 g/day i.v. in 6 doses		
OR	OR		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		

IE, infective endocarditis; i.m., intramuscular; i.v., intravenous; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; U, units. a Class of recommendation. b Level of evidence. c Cloxacillin is not recommended if the patient has penicillin allergy. d Maximum doses 240 mg/day. High doses are associated with increased risk of nephrotoxicity. Renal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, pre-dose (trough) concentrations should be

- Recommendations for antibiotic treatment of infective endocarditis due to Enterococcus spp

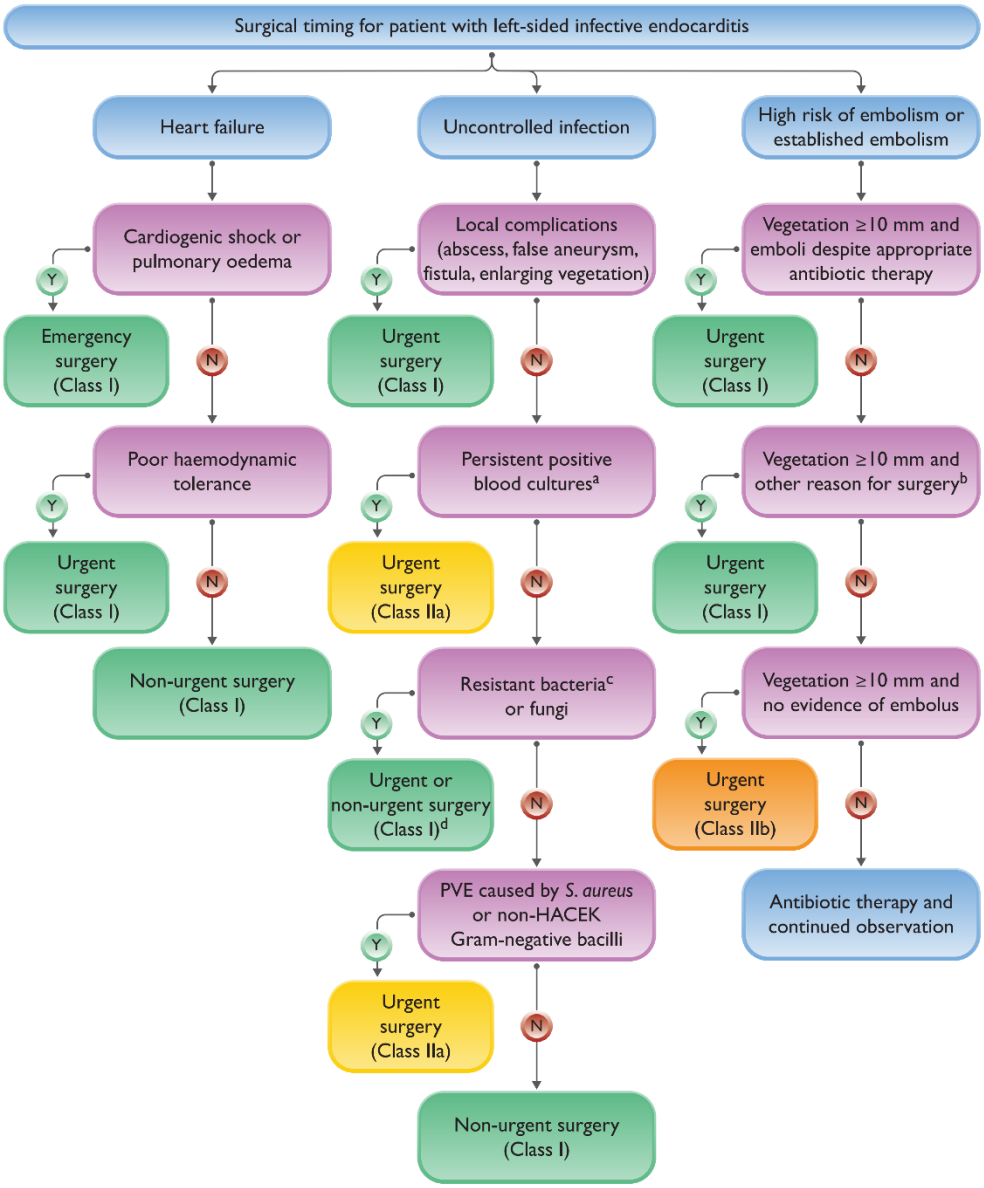
Recommendations		Class[a]	Level[b]
Beta-lactam and gentamicin-susceptible strains			
In patients with NVE due to non-HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended using the following doses:[355,360,361]		I	B
Adult antibiotic dosage and route			
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Ceftriaxone	100 mg/kg i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		
In patients with PVE and patients with complicated NVE or >3 months of symptoms due to non-HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended using the following doses:[355,360,361]		I	B
Adult antibiotic dosage and route			
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg/day i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		

High-level aminoglycoside resistance[d]			
In patients with NVE or PVE due to HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin and ceftriaxone for 6 weeks is recommended using the following doses:[355,360,361]		I	B
Adult antibiotic dosage and route			
Ampicillin	12 g/day i.v. in 4–6 doses		
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. or i.m. in 2 doses		
Beta-lactam resistant *Enterococcus* spp. (*E. faecium*)[e]			
In patients with IE due to beta-lactam resistant *Enterococcus* spp. (*E. faecium*), vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:[358,359,369]		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2–3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Vancomycin-resistant *Enterococcus* spp.[f]			
In patients with IE due to vancomycin-resistant *Enterococcus* spp., daptomycin combined with beta-lactams (ampicillin, ertapenem, or ceftaroline) or fosfomycin is recommended using the following doses:[369]		I	C
Adult antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	12 g/day i.v. in 4 doses		
Ceftaroline	1800 mg/day i.v. in 3 doses		
Ertapenem[g]	2 g/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose (age-adjusted)		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	2–3 g/day i.v. in 1 dose		
Ceftaroline	24–36 mg/kg/day in 3 doses		
Ertapenem[g]	1 g/day i.v. or i.m. in 1 dose [if younger than 12 years, 15 mg/kg/dose (to a maximum of 500 mg) twice daily]		

HLAR, high-level aminoglycoside resistance; IE, Infective endocarditis; i.m., intramuscular; i.v., intravenous; NVE, native valve endocarditis; PBP, Penicillin-binding protein; PVE, prosthetic valve endocarditis. a Class of recommendation. b Level of evidence. c Maximum doses 240 mg/day. High doses are associated with increased risk of nephrotoxicity. Renal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, pre-dose (trough) concentrations should be

2. Indications and timing of surgery in the presence of heart failure in infective endocarditis:

Timing of surgical intervention in patients with IE complicated by HF should be decided by the Endocarditis Team, although surgery should not be delayed by Endocarditis Team discussions in patients requiring emergency operations. The presence of HF leads to recommendation for surgery in the majority of patients and is the principal indication for urgent surgery in IE patients.



Proposed surgical timing for infective endocarditis. HACEK, Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella; PVE, prosthet ic valve endocarditis. Surgery timing: emergency, within 24 h. Urgent, within 3–5 days. Non-urgent, within same hospital admission. a Despite appropriate antibiotic therapy for >1 week and control of septic embolic foci. b E.g. patients with significant valvular dysfunction that is, or is not, a direct result of endo carditis process. c S. aureus (methicillin resistant and non-methicillin resistant), vancomycin-resistant enterococci, non-HACEK Gram-negative bacteria and fungi. d Urgent for S. aureus, non-urgent for others.

VIII. EVOLUTION AND PROGNOSIS

- Relapse is a repeat episode of IE caused by the same microorganism and represents a failure of treatment and mandates a search for a persistent focus of infection and an evaluation towards surgical therapy.
- Reinfection is an infection caused by a different microorganism, usually more than 6 months after the initial episode.
- Once antibiotic treatment has been completed, blood cultures should be performed.

- Patients discharged after the first episode of IE should remain under close surveillance for potential long-term complications.

IX. COMPLICATIONS

Complications of infective endocarditis (IE) include cardiac, metastatic, neurologic, renal, musculoskeletal, and pulmonary complications as well as complications related to systemic infection (including embolization, metastatic infection, and mycotic aneurysm). More than one complication can occur simultaneously.

Cardiac complications	Metastatic infection
- Heart failure - Perivalvular abscess - Pericarditis (suppurative or nonsuppurative) - Intracardiac fistula (eg, aorta-atrial or aorta-ventricular)	- Forms of metastatic infection include Septic embolization, metastatic abscess, and mycotic aneurysm. - Emboli can occlude or damage virtually any vessel in the systemic or pulmonary arterial circulation: • Stroke • Paralysis (due to embolic infarction of either the brain or spinal cord) • Blindness (due to embolism or due to endophthalmitis as a result of bacteremic seeding) • Ischemia of the extremities • Splenic or renal infarction • Pulmonary embolism • Acute myocardial infarction

X. PREVENTION AND RECOMMENDATION

Measures for prevention of IE include:

- Maintenance of oral hygiene
- Antibiotic prophylaxis prior to invasive dental or invasive oral procedures
- Timely treatment of infections with pathogens likely to cause endocarditis
- Antibiotic prophylaxis prior to surgery reduces the risk of surgical site infection, as discussed separately, and has been postulated to reduce the risk of subsequent endocarditis.
- Closure of a patent ductus arteriosus or ventricular septal defect.

XI. REFERENCES

1. Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, et al. EURO-ENDO Investigators. Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. Eur Heart J. 2019 Oct 14;40(39):3222-3232. doi: 10.1093/eurheartj/ehz620. Erratum in: Eur Heart J. 2020 Jun 7;41(22):2091. doi: 10.1093/eurheartj/ehz803. PMID: 31504413.
2. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet. 2016 Feb 27;387(10021):882-93. doi: 10.1016/S0140-6736(15)00067-7. Epub 2015 Sep 1. PMID: 26341945.
3. Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H, et al. ESC Scientific Document Group. 2023 ESC Guidelines for the management of endocarditis. Eur Heart J. 2023 Oct 14;44(39):3948-4042. doi: 10.1093/eurheartj/ehad193. Erratum in: Eur Heart J. 2023 Dec 1;44(45):4780. doi: 10.1093/eurheartj/ehad625. Erratum in: Eur Heart J. 2024 Jan 1;45(1):56. doi: 10.1093/eurheartj/ehad776. PMID: 37622656.
4. Fowler VG, Durack DT, Selton-Suty C, et al. The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria. Clin Infect Dis 2023; 77:518.

INFECTIOUS ENDOCARDITIS

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I. DEFINITION

Infectious Endocarditis (IE) refers to infection of the endocardial surface of the heart; it usually refers to infection of one or more heart valves or infection of an intracardiac device.

II. EPIDEMIOLOGY

- The incidence of infective endocarditis is estimated between 30 and 80 cases per million inhabitants and per year in the general population in industrialized countries.
- Incidence increases after the age of 60 and Staphylococcus is now the most frequent responsible microorganism.
- Infective endocarditis was native (NVE) in 1764 (56.6%) patients, prosthetic (PVIE) in 939 (30.1%), and device-related (CDRIE) in 308 (9.9%). Infective endocarditis was community-acquired in 2046 (65.66%) patients.

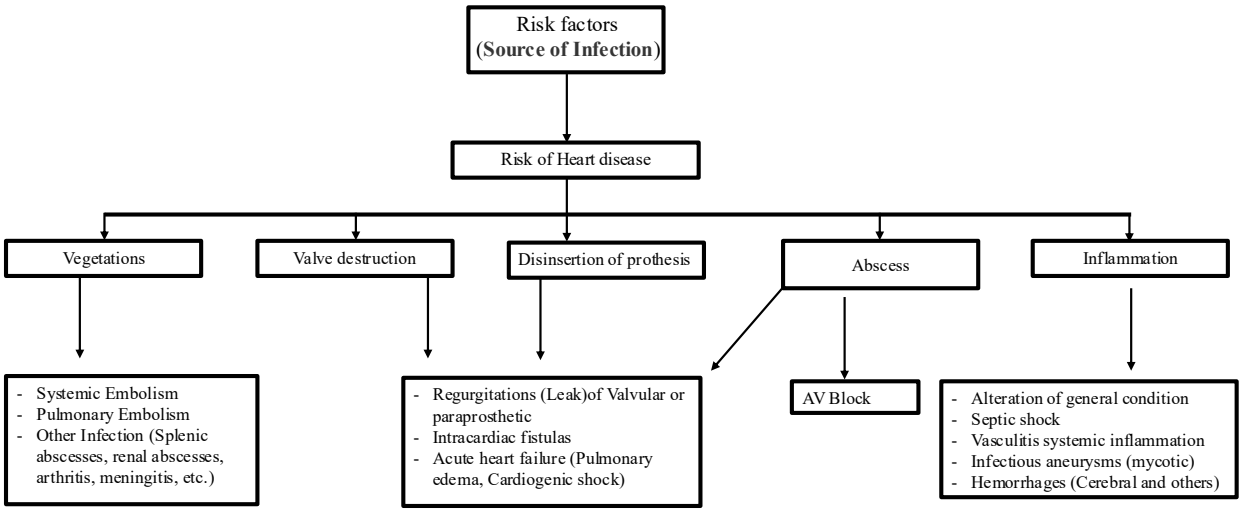
III. ETIOLOGY AND RISK FACTORS

- Risk factors for native valve infective endocarditis (IE) include cardiac factors or non-cardiac risk factors.
- It is most often from bacteria and more rarely a fungus from

Bacteria	Source of Infection
Staphylococcus aureus	Skin
Oral Streptococcus, HACEK	Oral, dental
Group D Streptococcus	Gastro-intestinal tract (Coloscopy)
Enterococcus	Gastro-intestinal tract (Coloscopy), Urinary tract

Cardiac risk factors	Non-cardiac risk factors
• Previous infective endocarditis • Valvular heart disease • Prosthetic heart valve • Central venous or arterial catheter • Transvenous cardiac implantable electronic device • Congenital heart disease	• Central venous catheter • People who inject drugs • Immunosuppression • Recent dental or surgical procedures • Recent hospitalization Haemodialysis

IV. PATHOPHYSIOLOGY



V. DIAGNOSIS

1. Clinical Manifestations

- **Symptoms**: Fever is the most common symptom of IE
    - It is often associated with chills, anorexia, and weight loss.
    - Other common symptoms: Malaise, headache, myalgias, arthralgias, night sweats, abdominal pain, tooth pain and dyspnea.
- **Signs**: A new or changing cardiac
    - Supportive signs: splenomegaly, petechiae or splinter hemorrhages.
    - Relatively uncommon manifestations highly suggestive of IE:
        - Janeway lesions
        - Osler nodes
        - Roth spots

2. Investigation for Endocarditis

- Blood cultures: At least two sets of blood cultures should be obtained from separate venipuncture sites prior to initiation of antibiotic therapy.
- Cardiac imaging:
    - Transthoracic echocardiography (TTE) is the first diagnostic test for patients with suspected IE.
    - Transesophageal echocardiography (TEE) has higher sensitivity than TTE and is better for detection of cardiac complications.
    - Cardiac CT: May be helpful for cases in which definitive evidence of IE and its complications cannot be demonstrated with TEE, and/or for planning surgery in patients with extra valvular complications.
    - Additional evaluation for IE source or complications: ECG, chest radiography, other radiographic imaging tailored to clinical manifestations, and dental evaluation.

3. Definitions of the 2023 European Society of Cardiology modified diagnostic criteria of infective endocarditis

Major criteria
1. Blood cultures positive for IE (a) Typical microorganisms consistent with IE from two separate blood cultures: Oral streptococci, Streptococcus gallolyticus (formerly S. bovis), HACEK group, S. aureus, E. faecalis. (b) Microorganisms consistent with IE from continuously positive blood cultures: • ≥ 2 positive blood cultures of blood samples drawn >12 h apart. • 3 j ≥4 w w ≥1 apart). (c) Single positive blood culture for C. burnetii or phase I IgG antibody titre >1:800. 2. Imaging positive for IE: Valvular, perivalvular/periprosthetic and foreign material anatomic and metabolic lesions characteristic of IE detected by any of the following imaging techniques: • Echocardiography (TTE and TOE) • Cardiac CT • [18F]-FDG-PET/CT(A) • WBC SPECT/CT
Minor criteria
Predisposing conditions (i.e. predisposing heart condition at high or intermediate risk of IE or PWIDs) Fever defined as temperature >38°C Embolic vascular dissemination (including those asymptomatic detected by imaging only): • Major systemic and pulmonary emboli/infarcts and abscesses. • Haematogenous osteoarticular septic complications (i.e. spondylodiscitis). • Mycotic aneurysms • Intracranial ischaemic/haemorrhagic lesions • Conjunctival haemorrhages • J w ’ Immunological phenomena: • Glomerulonephritis • Osler nodes and Roth spots • Rheumatoid factor Microbiological evidence: • Positive blood culture but does not meet a major criterion as noted above. • Serological evidence of active infection with organism consistent with IE.
IE Classification (at admission and during follow-up)
Definite: • 2 major criteria. • 1 major criterion and at least 3 minor criteria. • 5 minor criteria. Possible: • 1 major criterion and 1 or 2 minor criteria. • 3–4 minor criteria. Rejected: • Does not meet criteria for definite or possible at admission with or without a firm alternative diagnosis.

VI. DIFFERENTIAL DIAGNOSIS

The differential diagnosis for endocarditis is broad and should be considered based on two clinical categories: presence of bacteremia in the absence of valvular vegetation and presence of valvular vegetation(s) in the absence of bacteremia.

Presence of bacteremia in the absence of valvular vegetation	Presence of valvular vegetation(s) in the absence of bacteremia
• Intravascular catheter infection • Cardiac device infection • Prosthetic joint infection • Hematogenous osteomyelitis • Septic thrombophlebitis • Infected arterial aneurysm	• Culture-negative endocarditis or sterile vegetation(s) (marantic endocarditis or Libman-Sachs endocarditis) due to a noninfectious etiology or antiphospholipid syndrome.

VII. MANAGEMENT

1. Antimicrobial therapy:

- Penicillin-susceptible oral streptococci and Streptococcus gallolyticus group and Oral streptococci and Streptococcus gallolyticus group susceptible, increased exposure or resistant to penicillin

Recommendations		Class[a]	Level[b]
Penicillin-susceptible oral streptococci and *Streptococcus gallolyticus* group			
Standard treatment: 4-week duration in NVE or 6-week duration in PVE			
In patients with IE due to oral streptococci and *S. gallolyticus* group, penicillin G, amoxicillin, or ceftriaxone are recommended for 4 (in NVE) or 6 weeks (in PVE), using the following doses:[277,278]		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million[c] U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Paediatric antibiotic dosage and route			
Penicillin G	200 000 U/kg/day i.v. in 4–6 divided doses		
Amoxicillin	100–200[c] mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg/day i.v. in 1 dose		
Standard treatment: 2-week duration (not applicable to PVE)			
2-week treatment with penicillin G, amoxicillin, ceftriaxone combined with gentamicin is recommended only for the treatment of non-complicated NVE due to oral streptococci and *S. gallolyticus* in patients with normal renal function using the following doses:[277,278]		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million[c] U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		

Continue

Paediatric antibiotic dosage and route			
Penicillin G	200 000 U/kg/day i.v. in 4–6 divided doses		
Amoxicillin	100–200 mg/kg/day[c] i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose or 3 equally divided doses[d]		
Allergy to beta-lactams			
In patients allergic to beta-lactams and with IE due to oral streptococci and *S. gallolyticus*, vancomycin for 4 weeks in NVE or for 6 weeks in PVE is recommended using the following doses:[292]		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 or 3 equally divided doses[e]		
Oral streptococci and *Streptococcus gallolyticus* group susceptible, increased exposure or resistant to penicillin			
In patients with NVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 4 weeks in combination with gentamicin for 2 weeks is recommended using the following doses:[285–290]		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	12 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
In patients with PVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:[285–290]		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	12 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
Allergy to beta-lactams			
In patients with NVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 4 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
In patients with PVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		

IE, infective endocarditis; i.m., intramuscular; i.v., intravenous; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; U, units. a Class of recommendation. b Level of evidence. c The starting recommended doses are the lower doses which can be scalable to the highest doses. d Maximum doses 240 mg/day. High doses are associated with increased risk of nephrotoxicity. Renal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, pre-dose (trough) concentrations should be

- Recommendations for antibiotic treatment of IE due to Staphylococcus spp

Recommendations		Class[a]	Level[b]
IE caused by methicillin-susceptible staphylococci			
In patients with NVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin is recommended for 4–6 weeks using the following doses:[264,314,316–318]		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin[c]	12 g/day i.v. in 4–6 doses		
Cefazolin[e]	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin[c]	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin[e]	300–600 mg/kg/day in 3–4 doses		
In patients with PVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:[264,314,316–318,320]		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin[c]	12 g/day i.v. in 4–6 doses		
Cefazolin	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin[c]	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin	300–600 mg/kg/day in 3–4 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Allergy to beta-lactams			
In patients with NVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin for 4–6 weeks is recommended using the following doses:[322–327]		I	B
Adult antibiotic dosage and route			
Cefazolin[e]	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
Cefazolin[e]	300–600 mg/kg/day in 3–4 doses		
In patients with PVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin combined with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:[344]		I	B
Adult antibiotic dosage and route			
Cefazolin[e]	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Cefazolin[e]	300–600 mg/kg/day in 3–4 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
In patients with NVE due to methicillin-susceptible staphylococci who are allergic to penicillin, daptomycin combined with ceftaroline or fosfomycin may be considered.[322–327]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		
In patients with PVE due to methicillin-susceptible staphylococci who are allergic to penicillin, daptomycin combined with ceftaroline or fosfomycin or gentamicin with rifampin for at least 6 weeks and gentamicin for 2 weeks may be considered using the following doses:[344]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		

IE caused by methicillin-resistant staphylococci			
In patients with NVE due to methicillin-resistant staphylococci, vancomycin is recommended for 4–6 weeks using the following doses:[345]		I	B
Adult antibiotic dosage and route			
Vancomycin[h]	30–60 mg/kg/day i.v. in 2–3 doses		
Paediatric antibiotic dosage and route			
Vancomycin[h]	30 mg/kg/day i.v. in 2–3 equally divided doses		
In patients with PVE due to methicillin-resistant staphylococci, vancomycin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Vancomycin[h]	30–60 mg/kg/day i.v. in 2–3 doses		
Rifampin	900–1200 mg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Vancomycin[h]	30 mg/kg/day i.v. in 2–3 equally divided doses		
Rifampin	20 mg/kg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
In patients with NVE due to methicillin-resistant staphylococci, daptomycin combined with cloxacillin, ceftaroline or fosfomycin may be considered using the following doses:[335,345–349]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Cloxacillin[c]	12 g/day i.v. in 6 doses		
OR	OR		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		

IE, infective endocarditis; i.m., intramuscular; i.v., intravenous; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; U, units. a Class of recommendation. b Level of evidence. c Cloxacillin is not recommended if the patient has penicillin allergy. d Maximum doses 240 mg/day. High doses are associated with increased risk of nephrotoxicity. Renal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, pre-dose (trough) concentrations should be

- Recommendations for antibiotic treatment of infective endocarditis due to Enterococcus spp

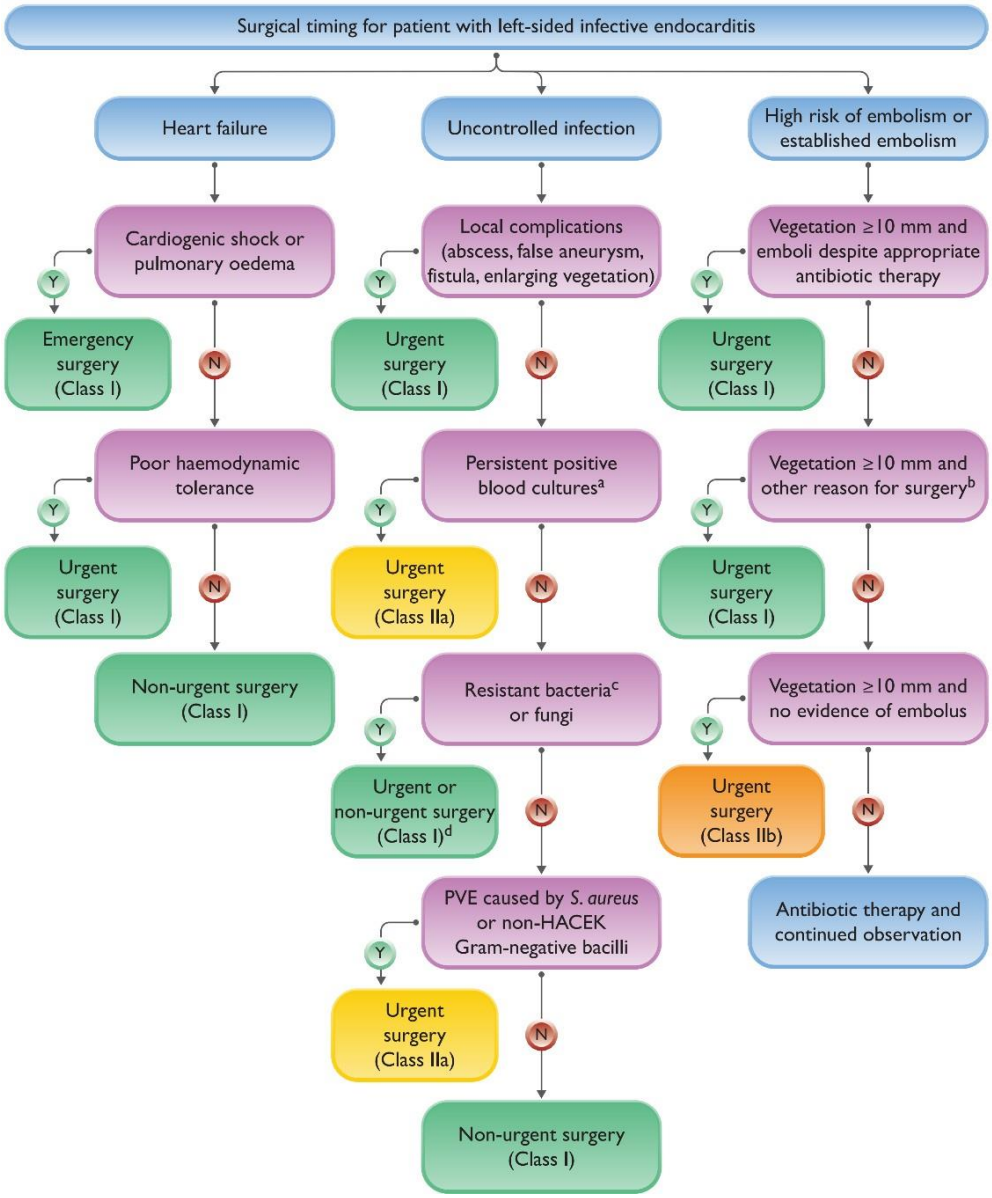
Recommendations		Class[a]	Level[b]
Beta-lactam and gentamicin-susceptible strains			
In patients with NVE due to non-HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended using the following doses:[355,360,361]		I	B
Adult antibiotic dosage and route			
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Ceftriaxone	100 mg/kg i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		
In patients with PVE and patients with complicated NVE or >3 months of symptoms due to non-HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended using the following doses:[355,360,361]		I	B
Adult antibiotic dosage and route			
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg/day i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		

High-level aminoglycoside resistance[d]			
In patients with NVE or PVE due to HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin and ceftriaxone for 6 weeks is recommended using the following doses:[355,360,361]		I	B
Adult antibiotic dosage and route			
Ampicillin	12 g/day i.v. in 4–6 doses		
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. or i.m. in 2 doses		
Beta-lactam resistant *Enterococcus* spp. (*E. faecium*)[e]			
In patients with IE due to beta-lactam resistant *Enterococcus* spp. (*E. faecium*), vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:[358,359,369]		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2–3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Vancomycin-resistant *Enterococcus* spp.[f]			
In patients with IE due to vancomycin-resistant *Enterococcus* spp., daptomycin combined with beta-lactams (ampicillin, ertapenem, or ceftaroline) or fosfomycin is recommended using the following doses:[369]		I	C
Adult antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	12 g/day i.v. in 4 doses		
Ceftaroline	1800 mg/day i.v. in 3 doses		
Ertapenem[g]	2 g/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose (age-adjusted)		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	2–3 g/day i.v. in 1 dose		
Ceftaroline	24–36 mg/kg/day in 3 doses		
Ertapenem[g]	1 g/day i.v. or i.m. in 1 dose [if younger than 12 years, 15 mg/kg/dose (to a maximum of 500 mg) twice daily]		

HLAR, high-level aminoglycoside resistance; IE, Infective endocarditis; i.m., intramuscular; i.v., intravenous; NVE, native valve endocarditis; PBP, Penicillin-binding protein; PVE, prosthetic valve endocarditis. a Class of recommendation. b Level of evidence. c Maximum doses 240 mg/day. High doses are associated with increased risk of nephrotoxicity. Renal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, pre-dose (trough) concentrations should be

2. Indications and timing of surgery in the presence of heart failure in infective endocarditis:

Timing of surgical intervention in patients with IE complicated by HF should be decided by the Endocarditis Team, although surgery should not be delayed by Endocarditis Team discussions in patients requiring emergency operations. The presence of HF leads to recommendation for surgery in the majority of patients and is the principal indication for urgent surgery in IE patients.



Proposed surgical timing for infective endocarditis. HACEK, Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella; PVE, prosthet ic valve endocarditis. Surgery timing: emergency, within 24 h. Urgent, within 3–5 days. Non-urgent, within same hospital admission. a Despite appropriate antibiotic therapy for >1 week and control of septic embolic foci. b E.g. patients with significant valvular dysfunction that is, or is not, a direct result of endo carditis process. c S. aureus (methicillin resistant and non-methicillin resistant), vancomycin-resistant enterococci, non-HACEK Gram-negative bacteria and fungi. d Urgent for S. aureus, non-urgent for others.

VIII. EVOLUTION AND PROGNOSIS

- Relapse is a repeat episode of IE caused by the same microorganism and represents a failure of treatment and mandates a search for a persistent focus of infection and an evaluation towards surgical therapy.
- Reinfection is an infection caused by a different microorganism, usually more than 6 months after the initial episode.
- Once antibiotic treatment has been completed, blood cultures should be performed.
- Patients discharged after the first episode of IE should remain under close surveillance for potential long-term complications.

IX. COMPLICATIONS

Complications of infective endocarditis (IE) include cardiac, metastatic, neurologic, renal, musculoskeletal, and pulmonary complications as well as complications related to systemic infection (including embolization, metastatic infection, and mycotic aneurysm). More than one complication can occur simultaneously.

Cardiac complications	Metastatic infection
- Heart failure - Perivalvular abscess - Pericarditis (suppurative or nonsuppurative) - Intracardiac fistula (eg, aorta-atrial or aorta-ventricular)	- Forms of metastatic infection include Septic embolization, metastatic abscess, and mycotic aneurysm. - Emboli can occlude or damage virtually any vessel in the systemic or pulmonary arterial circulation: • Stroke • Paralysis (due to embolic infarction of either the brain or spinal cord) • Blindness (due to embolism or due to endophthalmitis as a result of bacteremic seeding) • Ischemia of the extremities • Splenic or renal infarction • Pulmonary embolism • Acute myocardial infarction

X. PREVENTION AND RECOMMENDATION

Measures for prevention of IE include:

- Maintenance of oral hygiene
- Antibiotic prophylaxis prior to invasive dental or invasive oral procedures
- Timely treatment of infections with pathogens likely to cause endocarditis
- Antibiotic prophylaxis prior to surgery reduces the risk of surgical site infection, as discussed separately, and has been postulated to reduce the risk of subsequent endocarditis.
- Closure of a patent ductus arteriosus or ventricular septal defect.

XI. REFERENCES

1. Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, et al. EURO-ENDO Investigators. Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. Eur Heart J. 2019 Oct 14;40(39):3222-3232. doi: 10.1093/eurheartj/ehz620. Erratum in: Eur Heart J. 2020 Jun 7;41(22):2091. doi: 10.1093/eurheartj/ehz803. PMID: 31504413.

2. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet. 2016 Feb 27;387(10021):882-93. doi: 10.1016/S0140-6736(15)00067-7. Epub 2015 Sep 1.PMID: 26341945.

3. Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H, et al. ESC Scientific Document Group. 2023 ESC Guidelines for the management of endocarditis. Eur Heart J. 2023 Oct 14;44(39):3948-4042. doi: 10.1093/eurheartj/ehad193. Erratum in: Eur Heart J. 2023 Dec 1;44(45):4780. doi: 10.1093/eurheartj/ehad625. Erratum in: Eur Heart J. 2024 Jan 1;45(1):56. doi: 10.1093/eurheartj/ehad776. PMID: 37622656.

4. Fowler VG, Durack DT, Selton-Suty C, et al. The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria. Clin Infect Dis 2023; 77:518.

PERICARDITIS

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I. DEFINITION

Pericarditis refers to the inflammation of the pericardial layers with or without pericardial effusion.

Type of pericarditis

	Definition of Pericarditis According to the Time of Presentation
Acute	Even lasting <4 weeks
Incessant	Even lasting >4 to 6 weeks without remission But <3 months
Recurrent (20-30%)	Symptoms occur about 4 to 6 weeks after an episode of acute pericarditis with no symptoms in between
Chronic constrictive	Lasting >3 months

II. EPIDEMIOLOGY

Acute pericarditis is diagnosed in 0.2% of all cardiovascular in-hospital admissions and is responsible for 5% of emergency room admissions for chest pain.

III. ETIOLOGY

- Idiopathic is most common: presumed to be viral
- Infectious
    - Tuberculosis
    - Viral: Coxsackie virus A, B (most common), echovirus
    - Bacterial: S. pneumoniae, S. aureus
- Post-MI: acute (direct extension of myocardial inflammation, 1-7 d post-MI), Dressler's syndrome (autoimmune reaction, 2-8 weeks post-MI)
- Post-cardiac surgery (e.g. CABG), other trauma
- Metabolic: uraemia/CKD, hypothyroidism
- Neoplasm: Hodgkin's, breast, lung, renal cell carcinoma, melanoma
- Collagen vascular disease: SLE, polyarteritis, rheumatoid arthritis, scleroderma
- Other: drugs (e.g. hydralazine), radiation, infiltrative disease (sarcoid)

IV. PATHOPHYSIOLOGY

Due to the parietal layer's rich innervation, any inflammatory process mediated by an infectious, autoimmune or traumatic insult can result in severe retrosternal chest pain, as is commonly seen in acute pericarditis. This explains why the vast majority of presentations (>90%) have chest discomfort. In cases of pericardial effusion, the pericardial compliance can increase in response to slowly

accumulating fluid, allowing the pericardial sac to dilate over time without compressing the cardiac chambers. This means that the rate of fluid accumulation (and resulting pressure changes, as in pericardial compliance) is often more important than the volume in determining the hemodynamic sequela affecting the heart.

V. DIAGNOSIS

Symptoms

Chest pain is the most common symptom of pericarditis (>95%). It usually feels sharp or stabbing, and some patients having achy or pressure-like chest pain.

The pain:

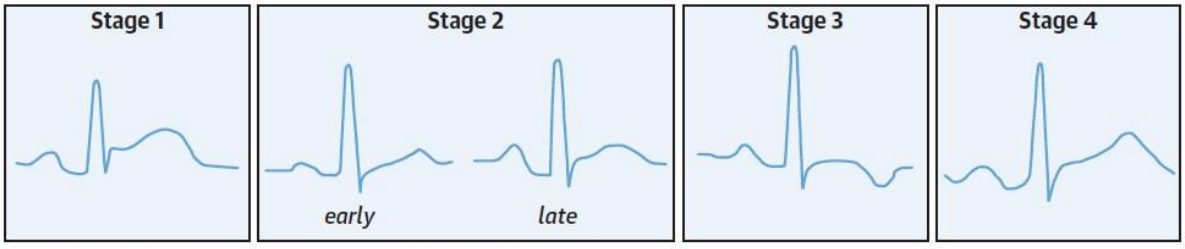
- Usually occurs behind the breastbone or on the left side of the chest
- Spread to the left shoulder and neck
- Get worse when coughing, lying down or taking a deep breath
- Get better when sitting up or leaning forward

Other signs and symptoms of pericarditis may include:

- Cough
- Fatigue or general feeling of weakness or being sick
- Leg swelling
- Low-grade fever
- Palpitation
- Shortness of breath when lying down
- Swelling of the belly (abdomen)

Investigations

- ECG: initially diffuse elevated ST segments ± depressed PR segment, the elevation in the ST segment is concave upwards → 2-5 d later ST isoelectric with T wave flattening and inversion
- Chest X-ray
- Heart ultrasound: performed to assess for pericardial effusion
- CT or MRI: when located pericardial effusion, pericardial thickening or masses, constrictive pericarditis



VI. DIFFERENTIAL DIAGNOSES

Common	Less common	Rare
Myocardial infarction Acute gastritis Gastroesophageal reflux disease Pleuritis Pneumonia	Esophageal spasm Pulmonary embolism Pneumothorax	Aortic dissection Esophageal rupture

VII. TREATMENT

- Anti-inflammatory agents (NSAIDs/ASA, steroids)
- Colchicine
- Treat the underlying disease

Drug	Dose	Duration
Aspirin*	750-1,000 mg every 8 h	1-2 weeks
Ibuprofen*	600-800 mg every 8 h	1-2 weeks
Colchicine	0.5-1.2 mg in one or divided doses	3 months

* Tapering once inflammatory markers have normalized

VIII. SPECIAL CASES

- Inpatient investigation and more intensive evaluation for a non-viral etiology should be considered where there is:
    - Any fever >38°C
    - Gradual onset
    - Large effusion (>20 mm) or tamponade
    - Lack of response to 1 week of non-steroidal anti-inflammatory drugs
    - Any history of trauma, immunosuppression/deficiency or oral anticoagulant use
- If pericarditis is caused by a bacterial infection, treatment may include antibiotics and drainage, if necessary.
- If pericarditis causes fluid buildup around the heart, a surgery or other procedure may be needed to drain the fluid (pericardiocentesis).

IX. EVOLUTION AND PROGNOSIS

The prognosis of acute pericarditis largely depends on the underlying aetiology. It is excellent in cases of idiopathic pericarditis. Prompt diagnosis and appropriate treatment of acute pericarditis may reduce the risk of acute complications and recurrences.

X. COMPLICATION

- Pericardial effusion
- Constrictive pericarditis
- Cardiac tamponade (this life-threatening condition requires emergency treatment)

XI. PREVENTION

Acute pericarditis can't be prevented. We can take steps to reduce your chance of having another acute episode, complications or chronic pericarditis. These steps include getting prompt treatment, following your treatment plan and getting ongoing medical care as needed.

XII. REFERENCE

1. https://my.clevelandclinic.org/health/diseases/17353-pericarditis
2. JACC Vol.75, No.1,2020 January 7/14, 2020: 76–92
3. NEJM 2023; 369:1522-1528
4. Clinical Medicine 2020 Vol20, No.1:48-51
5. Current Cardiology Reports (2022) 24:905–913
6. American Family Physician, vol89, num7, April 1-2014
7. Rev Assoc Med Bras 2015; 61(2):184-190
8. Dababneh E, Siddique MS. Pericarditis. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431080/
9. https://www.heart.org/en/health-topics/pericarditis/prevention-and-treatment-ofpericarditis#:~:text=Can%20pericarditis%20be%20prevented%3F,ongoing%20medical%20care%20as%20needed

Abbreviation:

ASA: aspirin
CABG: coronary artery bypass graft
CKD: chronic kidney disease
CT: computed tomography
DE: delayed enhancement
LV: left ventricle
MI: myocardial infarction
MRI: magnetic resonance imaging
NSAIDs: nonsteroidal anti-inflammatory drugs
PE: pericardial effusion

CONSTRICTIVE PERICARDITIS

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I. DEFINITION

Constrictive pericarditis (CP) is a chronic inflammatory process, often characterized by chronic scarring, fibrosis and calcification of the pericardium associated with diastolic dysfunction, eventually leading to low cardiac output and heart failure.

II. EPIDEMIOLOGY

Complication of acute CP is a relatively rare complication of viral or idiopathic acute pericarditis (<0.5%) but, in contrast, is relatively frequent for specific etiologies, especially bacterial. In Asian series, TB pericarditis is reported to be the underlying etiology in 20-80% of cases

III. ETIOLOGY

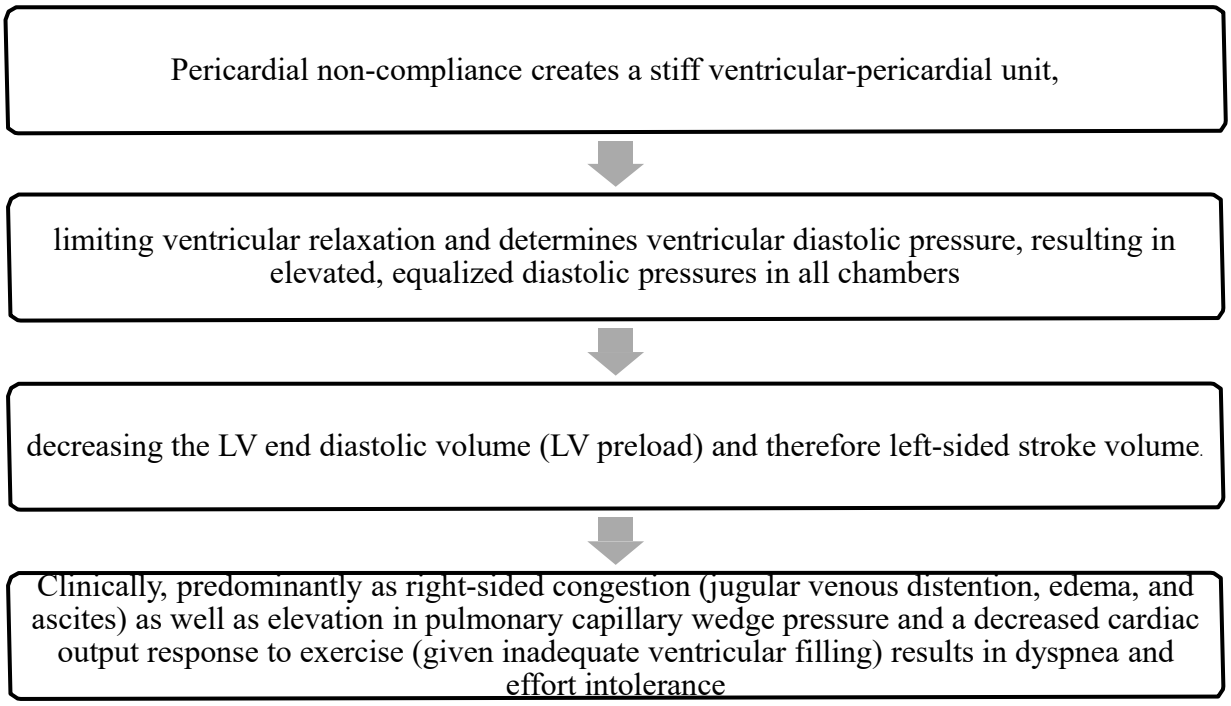
1. Common causes:

- Complication of acute idiopathic pericarditis
- Post cardiac surgery or post chest radiotherapy
- Infection (viral or bacterial)
  - **Tuberculosis**
  - Bacterial infections that lead to purulent pericarditis

2. Less common causes:

- Infection (fungal)
- Neoplasms
- Uremia
- Connective tissue disorders
- Drugs (e.g: procainamide and hydralazine)
- Trauma
- Myocardial infarction (with past medical history of Dressler syndrome and hemopericardium)

IV. PATHOPHYSIOLOGY



IV. DIAGNOSIS

1. **Initial assessment**:
   - The low prevalence of CP makes identifying key physical examination and historical features an important initial step in the diagnostic process.
   - History of cardiac surgery, radiation or **tuberculosis** should heighten clinical suspicion in the presence of edema, abdominal distention and exertional dyspnea.
   - In early stage: symptoms secondary to a reduction in cardiac output including fatigue and exertional dyspnea
   - In late stage, the filling pressures become significantly elevated, and systemic venous pressure rises, signs of overt RHF develop such as jugular venous distention, edema, ascites, pleural effusion.
   - Elevated jugular venous pressure (JVP) is present in virtually all patients:
     - Kussmaul's sign
     - Rapid x- and y-descents seen in the JVP of a patient with constrictive pericarditis. These are appreciated as rapid inward "flicking"/collapsing deflections in the presence of an elevated JVP.
   - Other findings: diastolic apex beat or diastolic precordial impulse, high-pitched early diastolic pericardial knock in heart auscultation.
2. **Investigations**:
   a. **Laboratory testing**: nonspecific in constrictive pericarditis.
   b. **Echocardiography**: As an initial diagnostic test, echocardiography can confirm the diagnosis of CP in most cases if pre-test probability is sufficiently high.
   - The pathognomonic finding is respirophasic septal shifting, detected by either M mode or 2D imaging and abnormal beat-to-beat septal motion, or "shudder," due to differential rapid early diastolic filling of the right and then left ventricle.

- The inferior vena cava is universally plethoric in the absence of hypovolemia; a sensitive but nonspecific feature of CP.
- The exaggerated respiratory preload changes are also exemplified by an inspiratory decrease in mitral valve inflow Doppler and an increase in tricuspid valve inflow Doppler.

c. **Cardiac radiology**:

- In CP, chest x-rays can demonstrate pericardial calcification, a pathognomonic finding in the presence of clinical heart failure and elevated JVP. Chest CT is more sensitive for pericardial calcification than chest x-ray.
- Chest CT and MRI allow for precise measurement of pericardial thickness, with MRI in particular demonstrating excellent accuracy (93%) in detection of pericardial thickening >4 mm.

Vl. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of constrictive pericarditis (CP) includes conditions with similar symptoms such as **restrictive cardiomyopathy**, **cardiac tamponade**, **systolic or diastolic congestive heart failure (CHF)**, **Right-sided valvular abnormalities**, **Right-sided atrial tumors**, and **Superior vena cava syndrome and nephrotic syndrome**. Theses can present with dyspnea, edema, ascites, pleural effusion, jugular vein distention mimicking CP. Careful evaluation of clinical history, laboratory finding and diagnostic imaging (echocardiography, cardiac CT or MRI) is essential to differentiate CP from these conditions.

Vll. MANAGEMENT

1. **Objective**:

- Improving cardiac function, reducing inflammation and congestion.
- The primary etiology be identified and managed accordingly
- The definitive cure for CP is primarily surgical in the form of complete pericardiectomy, where feasible.

2. **Critical signs**:

End-stage disease can include cachexia, markedly reduced resting cardiac output (cardiac index ≤1.2 L/m2 per min), hypoalbuminemia due to protein-losing enteropathy, and/or congestive hepatopathy including cardiac cirrhosis.

3. Outpatient management

Outpatient care may be appropriate during the early stages of the disease, particularly when the diagnosis is still uncertain and symptoms are relatively stable. It is important to emphasize and encourage a **low salt and fluid-restricted diet** as these are probably beneficial in order to avoid congestion and exacerbations of heart failure symptoms. Although no specific restrictions are needed, activity can often be severely limited by symptoms. However, decreased daily activities may be recommended in some patients.

4. **Pharmacologic therapy**:

Medical treatment may be considered as a trial of two to three months as conservative treatment if it is transient CP. The following specific treatment modalities should be considered for each of the special situations highlighted.

- **Subacute CP** may respond to **steroids** if treated before pericardial fibrosis develops.
- **Diuretics**, particularly loop diuretics, are the mainstay to **relieve congestion** and to optimise clinical volume status; however, they may decrease preload to the point of reducing cardiac output and thus **require closer monitoring.**
- Any other medications used to treat patients with CP should be specifically directed to the underlying aetiology of the pericardial disease.

- Any therapy directed towards the **causative disease**, e.g., antituberculosis therapy, is appropriate.
- CP-related complications require their own specific therapy as appropriate, e.g., atrial arrhythmias.
- In general, **beta-blockers** and **calcium channel blockers** should be **avoided.**
- Patients with advanced cardiac symptoms related to constriction may derive little benefit from surgery, as these are often the high surgical risk group.

Drug therapy in acute and recurrent pericarditis for adult patients

Drug	Antiinflammatory dose	Duration of initial or maintenance dose*	Tapering regimen
First-line therapy for most patients:[Δ]			
Aspirin	650 to 1000 mg orally 3 times daily	1 to 2 weeks	Decrease dose by about 250 mg per week
or			
Ibuprofen	600 to 800 mg orally 3 times daily[s]	1 to 2 weeks	Decrease dose by 200 mg per week
or			
Indomethacin	25 to 50 mg orally 3 times daily	1 to 2 weeks	Decrease dose by 25 mg per week
plus			
Colchicine	0.5 to 0.6 mg orally 2 times daily	3 months (acute) 6 months or more (recurrent)	Usually not tapered
Second-line therapy (for refractory cases or patients with a contraindication to NSAID therapy):			
Prednisone	0.2 to 0.5 mg/kg daily	2 to 4 weeks (acute or recurrent[†])	Gradual tapering over 2 to 3 months; refer to UpToDate topic review of treatment of acute pericarditis, section on glucocorticoids
plus			
Colchicine	0.5 to 0.6 mg	3 months or more	Usually not tapered
	orally 2 times daily	(acute) 6 months or more (recurrent) Colchicine is generally continued for 4 weeks or more after discontinuation of glucocorticoid	

5. **Pericardiectomy**

Pericardiectomy: a pericardiectomy remains the definitive therapy and a potential cure in most CP patients

Indication — We suggest pericardiectomy for patients with chronic constrictive pericarditis who meet all of the following criteria:

- Symptoms and signs have persisted despite at least 4 to 12 months of IL-1 inhibitor therapy.
- Symptoms are moderate to severe (New York Heart Association [NYHA] functional class III or IV (table 2).
- Constrictive pericarditis has not progressed to "end-stage." (See 'Patients unlikely to benefit from pericardiectomy' below.)
- There is no concomitant restrictive cardiomyopathy

Patients **unlikely** to benefit from pericardiectomy: Due to the complex nature of the surgery and the associated operative mortality, surgery should be carefully considered in patients who may not benefit from the procedure.

- Mild disease
- End-stage disease
- Mixed constrictive-restrictive disease
- Other high-risk groups – Mortality after pericardiectomy is also high in individuals with end-stage kidney disease or ventricular systolic dysfunction.

6. **Mortality risk factors of pericardiectomy**

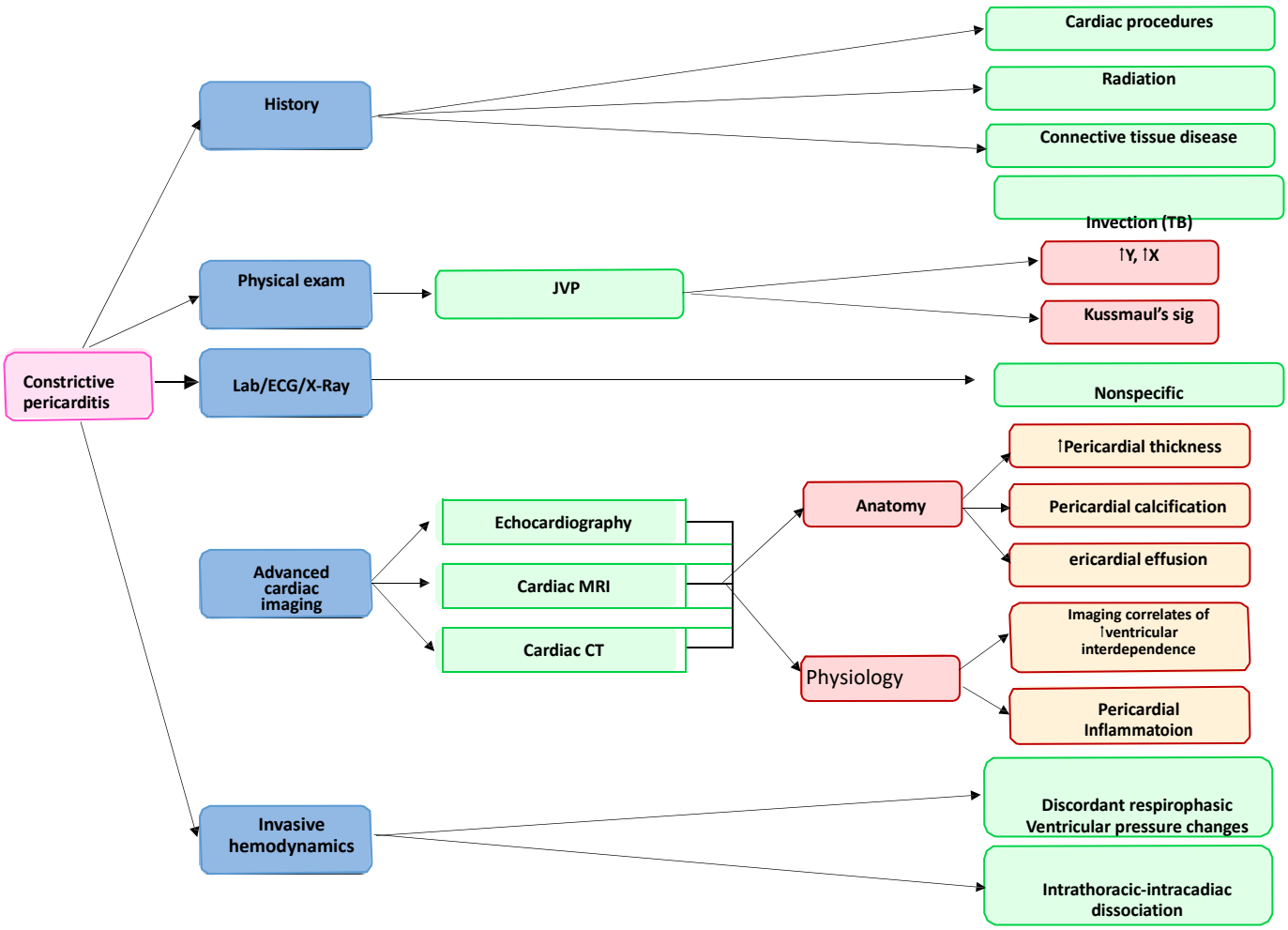
Detrimental outcomes of pericardiectomy include progressive heart failure or advanced heart failure symptoms (NYHA III-IV), sepsis, renal failure, respiratory failure, arrhythmia, prior mediastinal radiotherapy as the primary cause of constriction, and other concomitant severe comorbidities.

Preoperative myocardial atrophy or fibrosis is as well one of the causes of peri-operative mortality due to reduced ventricular mobility, particularly the RV free wall, are associated with acute RV dilatation related to subsequent increased preload to the RV, to increased venous return which then leads to acute RV failure and decreased cardiac output, function and subsequent death. Extensive pericardial calcification might have prognostic implications, which make pericardiectomy more extensive and complex.

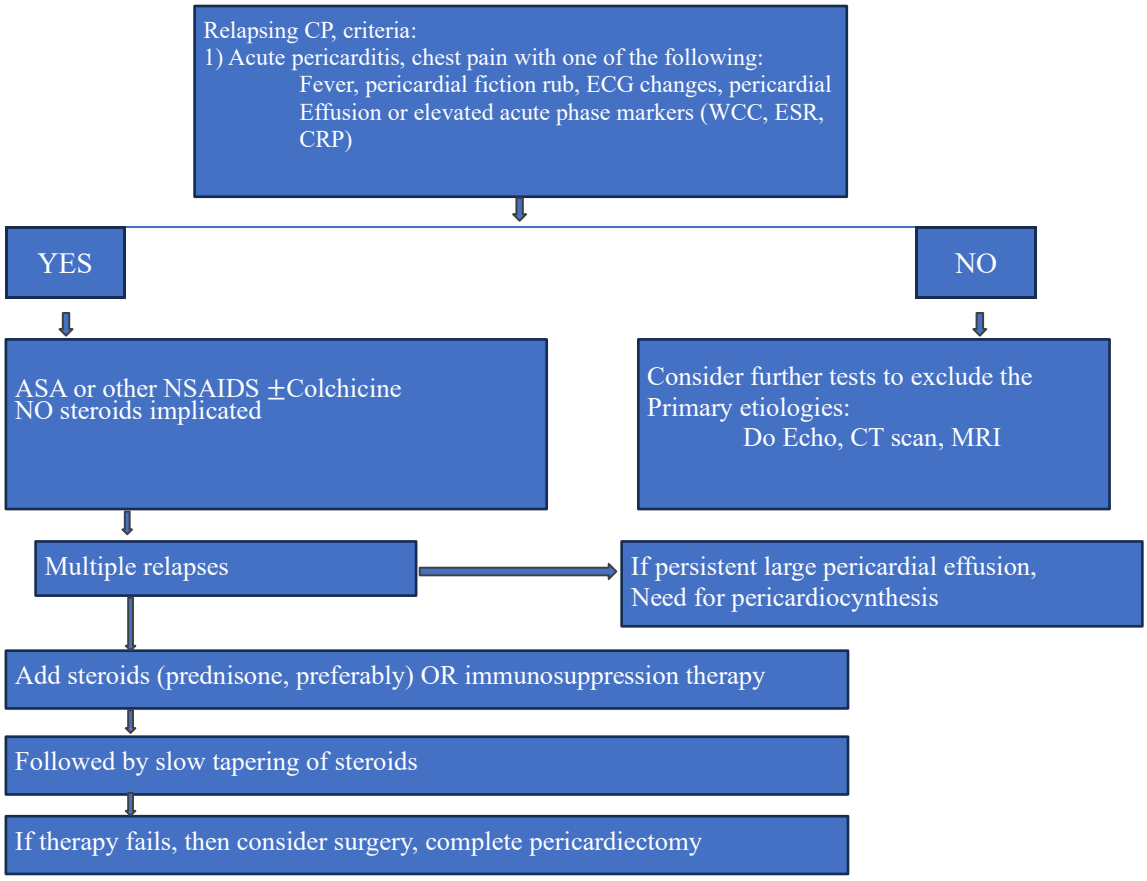
7. Algorithm

Diagnostic Algorithm for patient with suspected constrictive pericarditis

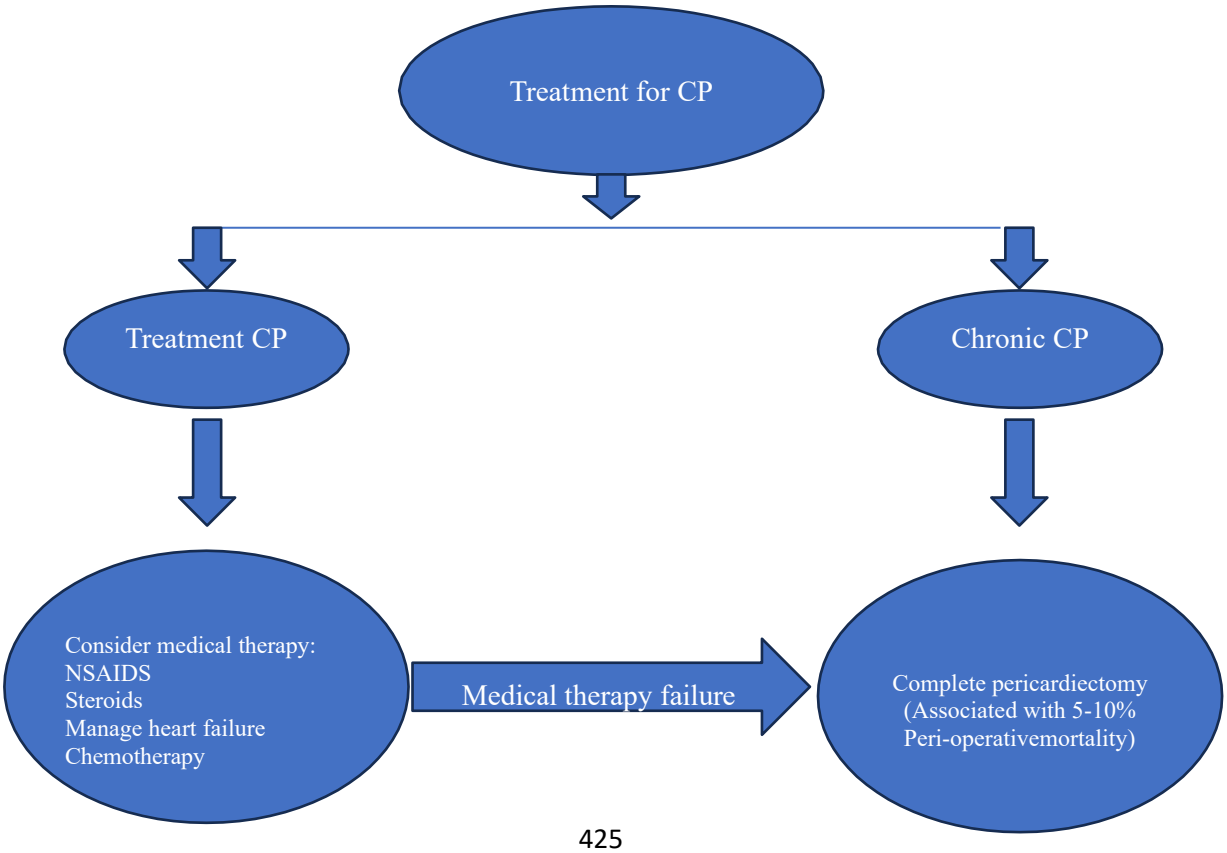
Figure 1



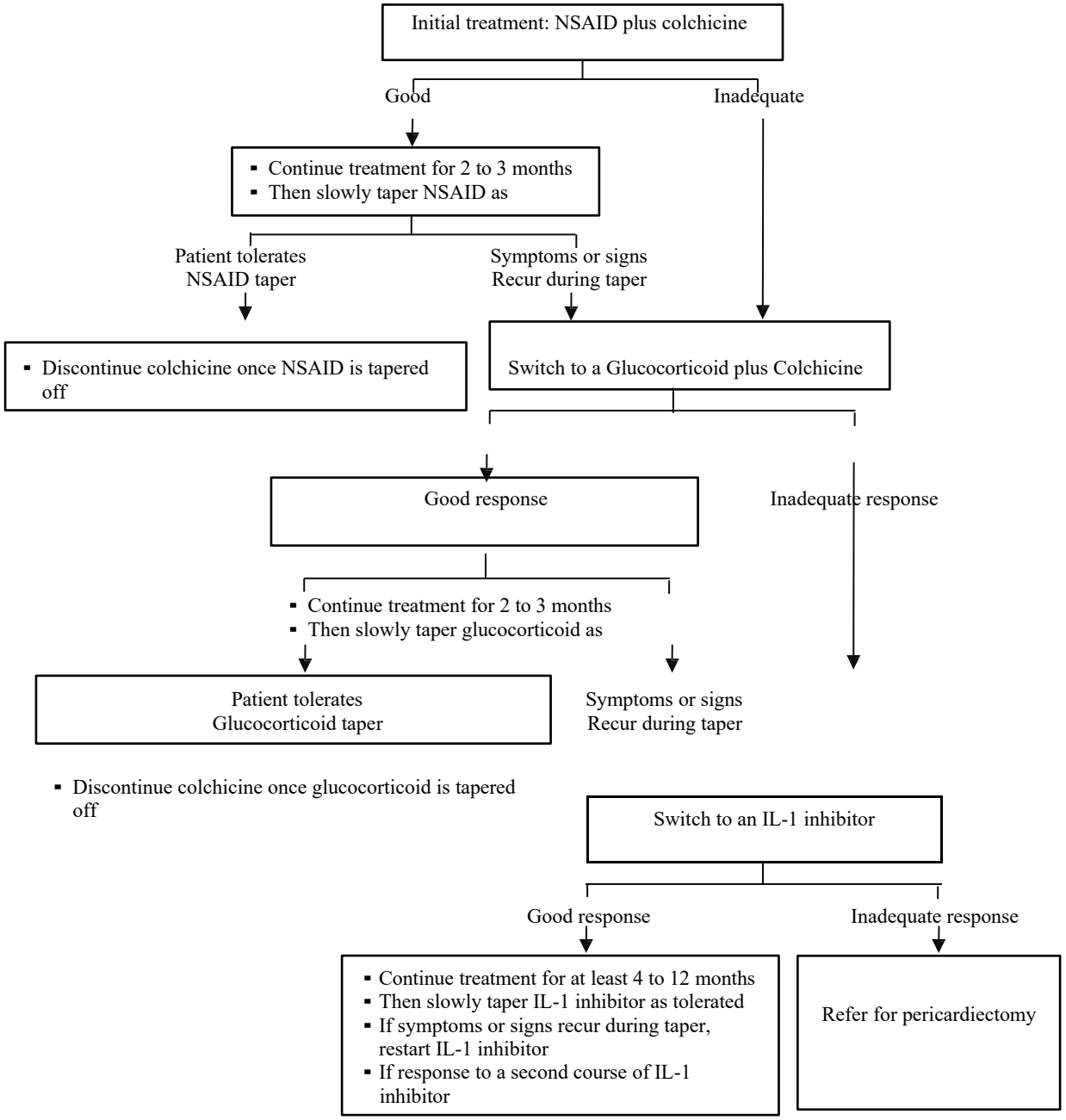
Diagnosis and therapeutic approach for relapsing pericarditis



Therapeutic overview for constrictive pericarditis



Approach to treatment of subacute constrictive pericarditis in adults



VIII. SPECIAL CASES

Due to high prevalence of Tuberculosis in Cambodia (WHO's estimated TB incidence in Cambodia is 302 per 100,000 population in 2018), in a case of constrictive pericarditis, Tuberculosis should be investigated as one of potential causes.

IX. EVOLUTION AND PROGNOSIS

Long-term survival after pericardiectomy for constrictive pericarditis is inferior to that of an age- and sex-matched population, although in many patients this is likely related to comorbid conditions. In one series, the 5- and 10-year survival rates were 78 and 57 percent, respectively.

X. PREVENTION AND RECOMMENDATION

The conditions which are primarily the leading causes of CP should be adequately managed to prevent the occurrence of CP as listing in Etiology Section above.

XI. COMPLICATIONS

Constrictive pericarditis if left untreated will lead to heart failure due to myocardial atrophy or fibrosis (diastolic et systolic dysfunction), Abnormal heart rhythm, liver and kidney dysfunction, which result in severe congestion in limbs, ascites, pleural effusion and dyspnea.

XII. REFERENCES

1. Adler, Y., Charron, P., Imazio, M., Badano, L., Barón-Esquivias, G., Bogaert, J., Brucato, A., Gueret, P., Klingel, K., Lionis, C., Maisch, B., Mayosi, B., Pavie, A., Ristić, A. D., Tenas, M. S., Seferovic, P., Swedberg, K., Tomkowski, W., Achenbach, S., . . . Codreanu, A. (2015). 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. European Heart Journal, 36(42), 2921–2964.
2. Matshela, M. R. (n.d.). Constrictive pericarditis: prevention and treatment. https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-15/Constrictive-pericarditis-prevention-and-treatment
3. Geske, J. B., & Reddy, Y. N. V. (2017, March 13). Pathophysiology and diagnosis of constrictive pericarditis. American College of Cardiology. https://www.acc.org/latest-in-cardiology/articles/2017/03/13/15/10/pathophysiology-and-diagnosis-of-constrictive-pericarditis
4. William M Edwards, J. (2021, March 23). Constrictive pericarditis differential diagnoses. Diseases & Conditions - Medscape Reference. https://emedicine.medscape.com/article/157096-differential?form=fpf&scode=msp&st=fpf&socialSite=google&icd=login_success_email_match_fpf
5. Hoit, B. D. (2024, June 3). Constrictive pericarditis: Management and prognosis. UpToDate. https://www.uptodate.com/contents/constrictive-pericarditis-management-and-prognosis
6. Imazio, M., Brucato, A., Maestroni, S., Cumetti, D., Belli, R., Trinchero, R., & Adler, Y. (2011). Risk of constrictive pericarditis after acute pericarditis. Circulation, 124(11), 1270–1275. https://doi.org/10.1161/circulationaha.111.018580
7. Edwards, W. M., Jr MD. (n.d.). Constrictive Pericarditis: Background, Pathophysiology, Etiology. https://emedicine.medscape.com/article/157096-overview#a5

MANAGEMENT OF CARDIOVASCULAR DISEASES DURING PREGNANCY

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I. INTRODUCTION

Today the number of pregnancy woman complicated by cardiovascular disease (CVD) is increasing worldwide. In western industrialized countries such patients represent 0.2-4% of all pregnancies. Counselling and management of women of childbearing age with suspected cardiac disease should start before pregnancy occurs; they should be managed by interdisciplinary teams; high risk patients should be treated in specialized centers; and diagnostic procedures and interventions should be performed by specialists with great expertise in the individual technique and experiences in treating pregnant patients.

II. EPIDEMIOLOGY

Hypertensive disorder are the most frequent cardiovascular events during pregnancy, occurring in 6-8% of all pregnancies.

In the western world, congenital heart disease is the most frequent cardiovascular disease present during pregnancy (75-82%). Congenital heart disease represents just 9-19% outside Europe and North America.

Rheumatic valvular disease dominates in non-western countries, including our country, Cambodia, comprising 56-89% of all cardiovascular disease in pregnancy.

Cardiomyopathies are rare, but represent sever causes of cardiovascular complication in pregnancy. Peripartum cardiomyopathy (PPCM) is the most common cause of severe complications.

III. HEMODYNAMIC, HEMOSTATIC AND METABOLIC ALTERATIONS DURING PREGNANCY

Pregnancy induces changes in the cardiovascular system to meet the increased metabolic demands of the mother and fetus: **increases in blood volume and cardiac output (CO)**, and **reductions in systemic vascular resistance and blood pressure (BP):**

- Plasma volume reaches a maximum of 40% above baseline at 24 weeks gestations.
- A 30-35% increase in CO in normal pregnancy
- Heart rate starts to rise at 20 weeks and increases until 32 weeks
- Systemic BP (SBP) typically falls early in gestation and diastolic BP (DBP) is usually 10mmHg below baseline in the second trimester: caused by active vasodilation. In the 3rd trimester, the DBP gradually increases and may normalized to non-pregnant values by term.
- The heart can increase its size by up to 30%

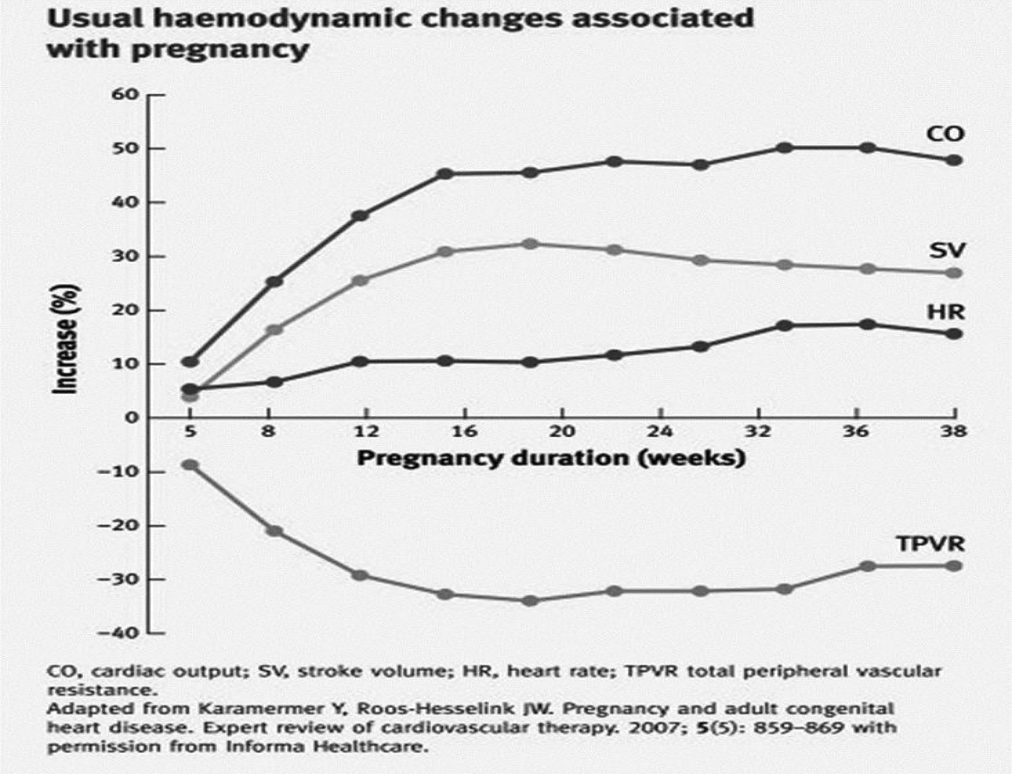


Figure 1. Hemodynamic changes in pregnancy

Hemostatic changes: *tend to hypercoagulability and increase risk of thrombo-embolic* due to increases in concentration of coagulation factors, fibrinogen, and platelet adhesiveness, as well as diminished fibrinolysis.

Maternal glucose and homeostasis may change and cholesterol levels increase in adaptation to fetal-maternal needs.

These changes can affect absorption, excretion, and bioavailability of all drugs.

Uterine contractions, positioning (left lateral vs. supine), pain, anxiety, exertion, bleeding and uterine involution cause significant hemodynamic changes during labor and post-partum.

IV. ARDIOVASCULAR DIAGNOSIS IN PREGNANCY

- **History and clinical investigation**
  - **Family history:**
    - Asking about possible sudden deaths in the family can identified some disease such as: Marfan syndrome, congenital heart disease, juvenile sudden death, long QT syndrome, catecholaminergic VT or Brugada syndrome.
    - Asking for the history or family history of hypertension or pre-eclampsia
  - **Clinical assessment:**
    - **dyspnea:** important for diagnosis a prognosis of valve lesions and for heart failure.
    - Auscultation: to detect ne murmur, changes in murmur
    - Oximetry: should be performed in patients with congenital heart disease

Table 1. How to differentiate common signs and symptoms of normal pregnancy versus those that are abnormal and indicative of underlying cardiac disease

	ROUTINE CARE	CAUTION*†	STOP†‡
	Reassurance	Nonemergent Evaluation	Prompt Evaluation Pregnancy Heart Team
History of CVD	None	None	Yes
Self-reported symptoms	None or mild	Yes	Yes
Shortness of breath	No interference with activities of daily living; with heavy exertion only	With moderate exertion, new-onset asthma, persistent cough, or moderate or severe OSA§	At rest; paroxysmal nocturnal dyspnea or orthopnea; bilateral chest infiltrates on CXR or refractory pneumonia
Chest pain	Reflux related that resolves with treatment	Atypical	At rest or with minimal exertion
Palpitations	Few seconds, self-limited	Brief, self-limited episodes; no lightheadedness or syncope	Associated with near syncope
Syncope	Dizziness only with prolonged standing or dehydration	Vasovagal	Exertional or unprovoked
Fatigue	Mild	Mild or moderate	Extreme
Vital signs	Normal		
HR (beats per minute)	<90	90–119	≥120
Systolic BP (mm Hg)	120–139	140–159	≥160 (or symptomatic low BP)
RR (per minute)	12–15	16–25	≥25
Oxygen saturation	>97%	95–97%	<95% (unless chronic)
Physical examination	Normal		
JVP	Not visible	Not visible	Visible >2 cm above clavicle
Heart	S3, barely audible soft systolic murmur	S3, systolic murmur	Loud systolic murmur, diastolic murmur, S4
Lungs	Clear	Clear	Wheezing, crackles, effusion
Edema	Mild	Moderate	Marked

- **Paraclinical investigation:**
  - ECG, Heart Ultrasound, proteinuria
  - Holter ECG (should be performed with known previous paroxysmal or persistent documented arrhythmia (VT, Afib or atrial flutter) or those reporting symptoms of palpitations.
  - TEE, Exercise testing may be indication in some special circumstances.
  - Radiation exposure: if possible, procedures should be delayed at least the completion of the period of major organogenesis (> 12 weeks after menses). There is no evidence of an increased fetal risk of congenital malformations, intellectual disability, growth restriction, or pregnancy lose at doses of radiation to the pregnant woman of < 50mGy.

V. INTERVENTION IN THE MOTHER DURING PREGNANCY

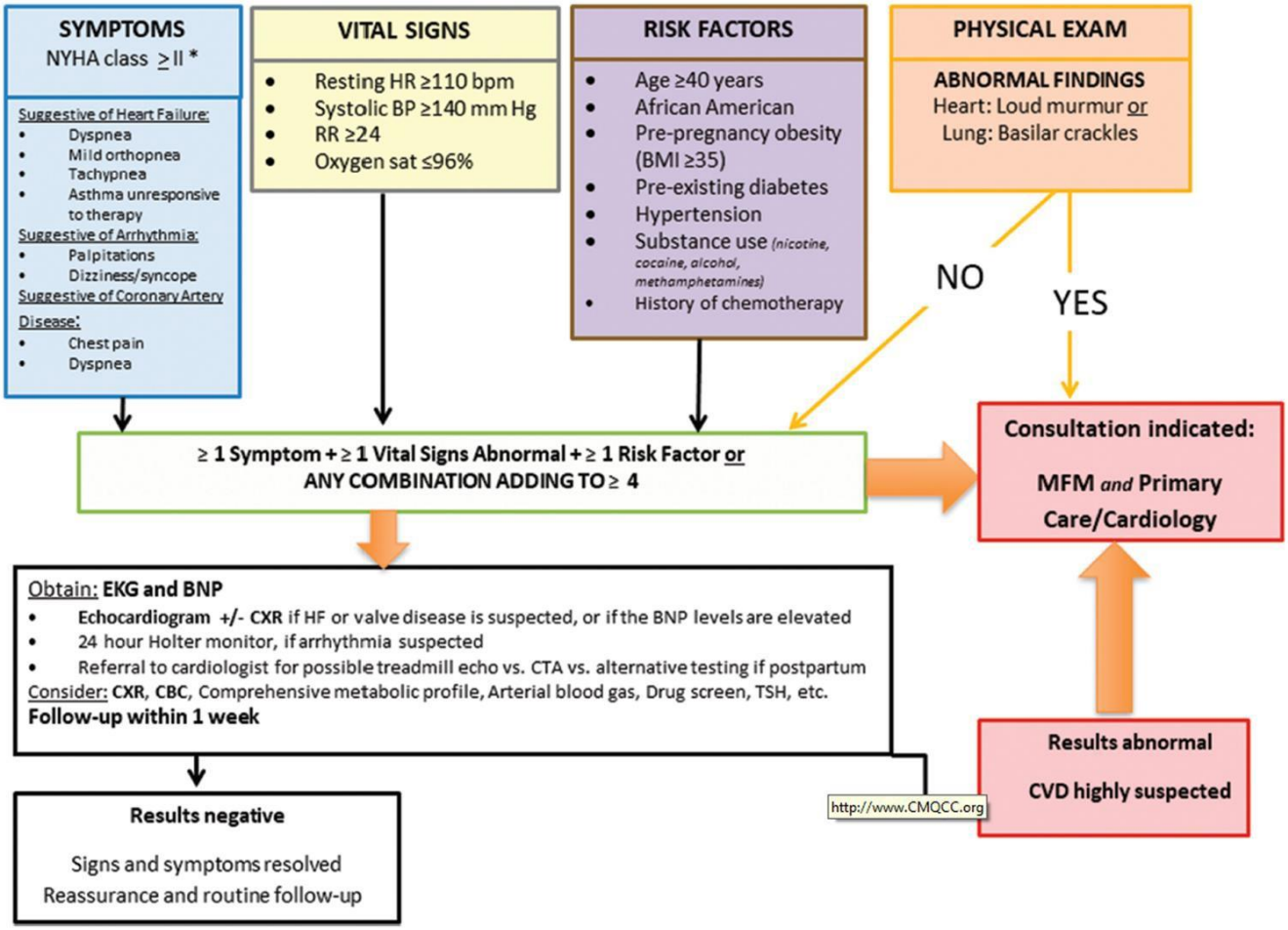


Figure 2. Cardiovascular disease assessment in pregnant and postpartum women

5.1. Percutaneous therapy

- the best time to intervene is considered to be after the fourth month in the second trimester: organogenesis is complete, the fetal thyroid is still inactive, and the volume of the uterus is still small (greater distance between the fetus and the chest).
- Fluoroscopy and cineangiography times should be short and the gravid uterus should be shielded from the radiation.
- Heparin should be given 40-70 U/Kg, keep ACT between 200-300s.

5.2. Cardiac surgery with cardiopulmonary bypass

- Cardiac surgery is recommended only when medical therapy or interventional procedures ail and the mother's life threatened.
- The best period for surgery is between the 13th and 28th week (surgery during the first trimester carries a higher risk of fetal malformations and during the third trimester is a higher incidence of pre-term delivery and maternal complication)
- Cesarean delivery may be considered before cardiopulmonary bypass if gestational age is > 26 weeks.
- Before surgery a full course (at least 24h) of corticosteroids should be administered to the mother, whenever possible.

- During cardiopulmonary bypass, fetal heart rate and uterine tone should be monitored in addition to standard patient monitoring.
- Keep pump flow > 2.5L/min/m2 and perfusion pressure > 70mmHg, maternal hematocrit > 28% is recommended to optimize the oxygen delivery.

VI. IMING AND MODE OF DELIVERY: RISK FOR MOTHER AND CHILD

6.1. Labor induction

- **Oxytocin and artificial rupture of the membrane are indicated when the Bishop score is favorable (avoiding long induction time)**
- Dinoprostone is contraindicated in active CVD (has profound effect on BP and risk of arrythmia)
- Mechanical methods such as a Foley catheter would be preferable to pharmacological agents, particularly in the patient with cyanosis where a drop in systemic vascular resistance and/or BP would be detrimental.

6.2. Vaginal or caesarean delivery?

- **The preferred mode of delivery is vaginal** and should be take place in a tertiary center with specialist multidisciplinary team care: less blood loses and infection risk, lower risk of venous thrombosis and thrombo-embolism.
- **Caesarean delivery is reserved for obstetric indications**: no consensus regarding absolute contraindications to vaginal delivery as this is very much dependent on maternal status and the time of delivery and the anticipated cardiopulmonary tolerance of the patient.
- **Caesarean delivery should be considered:**
    - For the patient on oral anticoagulants
    - Marfan syndrome and an aortic diameter > 45mm or between 40-45mm
    - Patients with acute or chronic aortic dissection
    - Patients in acute intractable heart failure
    - Women with sever aortic stenosis
    - Women with severe form of pulmonary hypertension (including Eisenmenger syndrome), or acute heart failure
    - Patient with mechanical heart valve prothesis

6.3. Anesthesia/analgesia and labor

- **Lumbar epidural analgesia is often recommendable**: it reduces pain related elevation of sympathetic activity, reduces the urge to push and provides anesthesia for surgery.
- However, it can cause systemic hypotension and must be used with caution in patients with obstructive valve lesion.
- **Labor position: the woman should be placed in a lateral decubitus position to attenuate the hemodynamic impact of uterine contractions**.
- **Delivery should be assisted by low forceps or vacuum extraction**, *without maternal pushing to avoid the unwanted effects of the Valsava manoeuvre.*

VII. ISK ESTIMATION: CONTRAINDICATION FOR PREGNANCY

- **Pre-pregnancy counselling**: a risk assessment should be performed prior to pregnancy and drugs reviewed so that those which are contra indicated in pregnancy can be stopped or changed to alternatives where possible
- **All women with heart disease should be assessed at least once before pregnancy and during pregnancy and hospital delivery should be advised**.

Table 2. Modified WHO risk classification

Risk Class	Risk of pregnancy by medical condition
I	No detectable increased risk of maternal mortality and no/mild increase in morbidity
II	Small increased risk of maternal mortality or moderate increase in morbidity
III	Significantly increased risk of maternal mortality or severe morbidity. Expert counseling required. If pregnancy is decided upon, if pregnancy decided upon, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth, and the puerperium.
IV	Extremely high risk of maternal mortality or sever morbidity, pregnancy contraindicated. If pregnancy occurs termination should be discussed. If pregnancy continues, care as for class III.

mWHO I

- Uncomplicated, small or mild pulmonary stenosis, PDA, mitral valve prolapses
- Successfully repaired simple lesion (ASD, VSD, PDA, anomalous pulmonary venous drainage)
- Atrial or ventricular ectopic beats, isolated.

⇨ *Risk is very low, cardiology follows up during pregnancy may be limited one or two visits.*

mWHO II (if otherwise well and uncomplicated)

- Unoperated ASD or VSD
- Repaired tetralogy of Fallot
- Most arrhythmias

mWHO II-III (depending on individual)

- Mild left ventricular impairment
- Hypertrophic cardiomyopathy
- Native or tissue VHD not considered WHO I or IV
- Marfan syndrome without aortic dilatation.
- Aorta < 45mm in aortic disease associated with bicuspid aortic valve
- Repaired coarctation

⇨ *Follow up every trimester is recommended.*

mWHO III

- Mechanical valve
- Systemic right ventricle
- Fontan circulation
- Cyanotic heart disease (unrepaired)
- Other complex congenital heart disease
- Aortic dilatation 40-45mm in Marfan syndrome

- Aortic dilatation 45-50mm in aortic disease associated with bicuspid aortic valve

⇨ *High risk of complications, follow up monthly or bi monthly during pregnancy with cardiologist and obstetrician is recommended.*

mWHO IV (pregnancy contraindicated)

- Pulmonary arterial hypertension of any cause
- Sever systemic ventricular dysfunction (LVEF < 30%, NYHA III – IV)
- Previous peripartum cardiomyopathy with any residual impairments of left ventricular function
- Sever mitral stenosis, sever symptomatic aortic stenosis
- Marfan syndrome with aorta dilated > 45mm.
- Aortic dilatation > 50mm in aortic disease associated with bicuspid aortic valve
- Native sever coarctation

⇨ *Advised against pregnancy, if pregnancy occurred consider termination of pregnancy. If they will not consider termination, monthly or bi-monthly review is recommended*.

VIII. ETHODS OF CONTRACEPTION

Monthly injectable that contain medroxyprogesterone acetate: *not recommended* in patient with *heart failure* because of risk of fluid retention.

Oral contraceptive containing 20mcg of ethinyl estradiol are safe in women with a low thrombogenic potential but not in women with complexes vascular disease.

Barrier method (condom) and IUD is the safest and most effective method in women with cyanotic congenital heart disease and pulmonary vascular disease (caution with this method: 5% of patients experience vasovagal reactions at the time of implant). It is contraindicated in cyanotic women with Ht > 55% (risk of intrinsic hemostatic defects that will cause excessive menstrual bleeding)

II. CONGENITAL HEART DISEASE AND PULMONARY HYPERTENSION

1. Maternal high-risk conditions (mWHO III-IV)

1.1. Pulmonary hypertension

Pulmonary hypertension defined as mean PAP ≥ 25mmHg at rest. It encompasses a group of disease with different pathophysiologies which include PAH, pulmonary hypertension related to left heart disease, to lung disease and/or hypoxia, chronic thrombo-embolic pulmonary hypertension, idiopathic, heritable forms of the disease as well as pulmonary hypertension associated with congenital heart disease, with or without previous corrective surgery.

☛ **Management:**

- If pregnancy occurs, termination should be offered.
- If patients choose to continue pregnancy despite the risk, they should be managed in a center with expertise in PAH with all therapeutic options available.
- Goal is to maintain circulating volume, avoid systemic hypotension, hypoxia and acidosis which may precipitate refractory heart failure.

- Supplemental oxygen therapy, IV prostacyclin or aerosolized iloprost are occasionally used antenatally and peripartum to improve hemodynamic during delivery.
- In patients who are already taking drug therapy for PAH before becoming pregnant, continuation of this therapy should be considered, but patients should be informed about the teratogenic effects of some therapies, such as bosentan.
- In the patients where the indication of anticoagulation outsides pregnancy is established, anticoagulation should be maintained during pregnancy.
- Type of the anticoagulation that can be used during pregnancy: UFH, LMWH, VKA need to be decided on an individual basis.
- In PAH associated with portal hypertension, anticoagulation is not recommended.

☛ **Delivery:**

- The mode of delivery should be individualized.
- Planned caesarean delivery and vaginal delivery are favored over emergency caesarean delivery.

1.2. Eisenmenger syndrome

☛ **Management:**

- If pregnancy occurs, termination should be offered (to be noted, termination also carries a risk)
- If patients choose to continue pregnancy despite the risk, care should be based in a specialist unit.
- Bed rest may be beneficial.
- Anticoagulant: prevention for thrombo-embolism should be considered after hematology review and investigations for blood hemostasis (anticoagulation should be use with caution, as patients with Eisenmenger syndrome are also prone to hemoptysis and thrombocytopenia).
- Diuretic should be used in patients with heart failure at the lowest effective dose (to avoid hemoconcentration and intravascular volume depletion)
- Supplement oral or IV iron: use in case of microcytosis and iron deficiency.

☛ **Delivery:**

- An early caesarean delivery should be planned if the maternal or fetal condition deteriorates.
- Incremental regional anesthesia may improve maternal outcome.

1.3. Cyanotic heart disease without pulmonary hypertension

☛ **Management:**

- Women with an oxygen saturation below 85% at rest should be advised against pregnancy.
- Restriction of physical activity and supplemental oxygen (monitoring oxygen are recommended)
- Use of compression stocking and avoiding the supine position to prevent venous stasis.

- Prophylactic heparin administration should be considered (after hematology review and investigations for blood hemostasis.
- Diuretic and iron therapy are indicated and manage in the same way as in patients with Eisenmenger syndrome.

☛ **Delivery:**

- Vaginal delivery is advised in most cases.
- If the maternal or fetal condition deteriorates, an early caesarean delivery should be planned.
- Incremental regional anesthesia may improve maternal outcome.

2. Maternal low and moderate risk conditions (mWHO I, II and III)

2.1. Atrial septal defect (ASD)

- Pregnancy is well tolerated by most women with an ASD
- The only contraindication is the presence of PAH or Eisenmenger syndrome
- Maternal risk includes: trombo-embolic complications ~ 5%, arrythmia especially in unrepair ASD, ASD closed at older age and the pregnant woman is > 30 years old.

☛ **Management:**

- Follow up twice during pregnancy is sufficient
- Catheter device closure can be performed during pregnancy but is only indicated when the condition of the mother is deteriorating
- Prevent of venous stasis with using of compression stockings and avoiding the supine position to reduce the risk of paradoxical embolism.
- Early ambulation after delivery, in case of prolonged bed rest, prophylactic heparin administration should be considered.

☛ **Delivery:**

- Spontaneous vaginal delivery is in most case appropriate.

2.2. Ventricular septal defect (VSD)

- For large VSD with pulmonary hypertension, manage as pulmonary hypertension
- Small peri membranous VSDs without left heart dilatation have a low risk of complications during pregnancy
- Follow up twice during pregnancy is sufficient and spontaneous vaginal delivery is appropriate.

2.3. Atrioventicular septal defect (AVSD)

- After correction, pregnancy is usually well tolerated when residual valve regurgitation is not severe and ventricular function is normal.
- Patients with severe (residual) left atrioventricular (AV) valve regurgitation with symptoms and/or impaired ventricular function should be treated surgically pre-pregnancy.

- AVSD with pulmonary hypertension => manage as pulmonary hypertension in above section.

☛ **Management**

- Follow up during pregnancy at least once each trimester.
- Clinical and echocardiographic follow up is indicated monthly or bimonthly in patients with moderate or severe valve regurgitation or impaired ventricular function.
- Prevention the risk of paradoxical thrombo-embolism.

☛ **Delivery:**

- Spontaneous vaginal delivery is in most case appropriate.

2.4. Coarctation of the Aorta (CoA)

- After repair, the pregnancy is often well tolerated.
- Those women with unrepaired native CoA and those repaired who have residual hypertension, residual CoA, or aortic aneurysms have an increased risk of aortic rupture and rupture of a cerebral aneurysm during pregnancy and delivery.

☛ **Management:**

- Close surveillance of BP is warranted, and regular follow up at lease every trimester is indicated.
- Hypertension: should be treated but avoid an aggressive treatment to avoid placental hypoperfusion.
- PCI for re-CoA is possible during pregnancy but it carries higher risk of aortic dissection than outside pregnancy. It should be performed if sever hypertension persists despite medical therapy and there is maternal or fetal compromise (the use of cover stent may lower the risk of dissection).

☛ **Delivery:**

- Spontaneous vaginal delivery is preferred with use of epidural anesthesia particularly in hypertensive patients.

2.5. Pulmonary valve stenosis and regurgitation

☛ **Management:**

- Mild and moderated PS are regarded low-risk lesions and follow up once every trimester is sufficient.
- In patient with sever PS, cardiac evaluation by echocardiography should be performed monthly or bi-monthly to determine clinical status and for surveillance of RV function.
- Percutaneous valvuloplasty can be undertaken in severely symptomatic PS not responding to medical therapy and bed rest during pregnancy or in severe pulmonary stenosis (peak Doopler gradient > 64m) Hg) pre-pregnancy.

☛ **Delivery:**

- Vaginal delivery is favored in patients with non-severe PS or sever PS in NYHA class I/II
- Caesarean section is considered in patients with severe PS and in NYHA class III/IV despite medical therapy and bed rest, in whom percutaneous pulmonary valvulotomy cannot be performed or has failed.

2.6 Tetralogy of Fallot

☛ **Management:**

- Follow up every trimester is sufficient in the majority of women
- In women with sever PR, monthly or bi-monthly cardiac evaluation with echocardiography is indicated.
- Diuretic and bed rest: if RV failure occurs during pregnancy
- Transcatheter valve implantation or early delivery should be considered in those who do not respond to conservative treatment.

☛ **Delivery:**

- The preferred mode of delivery is vaginal in almost all cases.

2.7 Ebstein's anomaly

- In women with Ebstein's anomaly without cyanosis and heart failure, pregnancy is often tolerated well.
- Symptomatic patients with cyanosis and/or heart failure should be treated before pregnancy or counselled against pregnancy.
- In severe symptomatic TR, repair should be considered pre-pregnancy.

☛ **Management:**

- Follow up
- Even sever TR with heart failure can usually be managed medically during pregnancy
- Prevention of paradoxical emboli (in case of interatrial shunting that can be develop shunt reversal and cyanosis)

☛ **Delivery:**

- The preferred mode of delivery is vaginal in almost all cases.

III. AORTIC DISEASE

Several heritable disorders affect the thoracic aorta, pre-disposing patients to both aneurysm formation and aortic dissection:

- Marfan syndrome
- Bicuspid aortic valve
- Ehlers-Danlos syndrome
- Turner syndrome

All women with genetically proven Marfan syndrome or other familial aortic pathology should have counselling on the risk of dissection and the recurrence risk, and have a complete evaluation including imaging of the entire aorta before pregnancy.

☛ **Management**

- Follow up: aortic diameter should be monitored by echocardiography at 4-12 weeks intervals throughout pregnancy and 6 months post-partum
- ß-blockers is recommended to use in patients with Marfan syndrome during pregnancy to prevent dissection.
- * Celiprolol is recommended in patients with Ehlers-Danlos syndrome type IV
- Fetal growth should be monitored when the mother is taking B-blockers.
- Intervention before pregnancy is recommended if ascending aorta ≥ 45mm in patients with Marfan syndrome or other syndromes with high risk of dissection, otherwise intervention should be done pre-pregnancy when the ascending aorta ≥ 50mm or > 27mm/m^2 for small woman.
- When progressive dilatation occurs during pregnancy, before the fetus is viable, aortic repair with the fetus in utero should be considered.
- When the fetus is viable, caesarean delivery followed directly by aortic surgery is recommended.

☛ **Delivery**

- **If the woman is taking ß-blockers during pregnancy they should be continue in the peripartum periods**
- If the ascending aorta diameter is 40-45mm, vaginal delivery with expedited second stage and regional anesthesia is advised to prevent BP peaks or Caesarean delivery could be considered based on the individual situations.
- **Caesarean section should be considered when the aortic diameter exceeds 45mm and should be performed early especially in women with Ehlers- Danlos syndrome type IV.**

Table 3. Different aortic pathology and its complication during pregnancy

	Marfan	Bicuspid aortic valve	LoeysDietz	Turner	Vascular Ehlers-Danlos
Location of aneurysm/dissection	Everywhere (sinus of Valsalva)	Ascending aorta	Everywhere	Ascending aorta, arch and descending aorta	Everywhere
Risk of dissection	High: 1-10%	Low: <1%	High: 1-10%	High: 1-10%	High: 1-10%
Comorbidity	Dural abnormalities, Mitral regurgitation, heart failure, arrhythmias	Aortic stenosis or regurgitation	Dural abnormalities, Mitral regurgitation.	Low height, infertility, hypertension, diabetes, bicuspid aortic valve, Coarctation	Dural abnormalities, uterine rupture
Advise not to become pregnant	Ascending aorta > 45mm (or >40mm in family history of dissection or sudden death)	Ascending aorta > 50mm	Ascending aorta > 45mm (or > 40mm in family history of dissection or sudden death)	ASI > 25mm/m^2	All patients

IV. ALVULAR HEART DISEASE

Rheumatic heart disease remains a major problem in developing countries. Stenotic valve disease carries a higher pregnancy risk than regurgitant lesion, and left sided valve disease have a higher complications rate than right sided valve lesions.

Specific problems, mainly related to anticoagulant therapy, are present in women with mechanical valve prostheses.

1. **Mitral stenosis**

- The risk of decompensation depends on the severity of MS.
- Heart failure occurs frequently in pregnant women with moderate to server MS (valve area < 1.5cm2), particularly during the second and third trimesters, even in previously asymptomatic women.
- AF carries the additional risk of thrombo-embolic events.

☛ **Management**

- All patients with moderate to severe MS even when asymptomatic should be counselled against pregnancy.
- Intervention should be performed pre-pregnancy, favoring percutaneous interventions.
- Clinical and echocardiographic follow up is indicated monthly or bi-monthly depending on hemodynamic tolerance for moderate to server MS. For mild MS, evaluation is recommended every trimester and prior to delivery.
- **In patients with symptoms or pulmonary hypertension** (estimated systolic PAP > 50mmHg), ***restricted activities and B1-selective blockers are recommended***.
- **Diuretics** ***are recommended (avoiding high dose) when congestive symptoms persist despite B-blockers***
- **Therapeutic anticoagulation** is recommended in the case of paroxysmal or permanent AF, left atrial thrombosis, or prior embolism or spontaneous echocardiographic contrast in the LA, large left atrium (≥ 40mL/m2), low CO or congestive heart failure.

☛ **Intervention**

- Percutaneous mitral commissurotomy is preferable performed after 20 weeks gestations.
- It is indicated in women with ***NYHA class III/IV and/or estimated systolic PAP > 50mmHg despite optimal medical treatment***, in the absence of contraindications and if patient characteristics are suitable.

☛ **Delivery**

- Vaginal delivery: in patient with mild MS and in patients with moderate to server MS in NYHA class I/II without pulmonary hypertension.
- Caesarean section: in patients with moderate or severe MS who are in NYHA class III/IV or have pulmonary hypertension despite medical therapy.

2. Valvular aortic stenosis

` Cardiac morbidity during pregnancy is related to severity of AS and symptoms. Asymptomatic mild or moderate AS, pregnancy is well tolerated. Also, patients with severe AS, may sustain pregnancy well, as long as they remain asymptomatic during exercise testing and have a normal BP response during exercise.

☛ **Management**

- All symptomatic patients with severe AS or asymptomatic patients with impaired LV function (LVEF < 50%) or a pathological exercise test should be counselled against pregnancy.
- Valvuloplasty or surgery should be performed pre-pregnancy.

- Regardless of symptoms, pre-pregnancy surgery should be considered in patients with ascending aorta > 50mm (27.5mm/m^2).
- Monthly or bimonthly cardiac evaluation including echocardiography are advised to determine symptom status, progression of AS, or other complications.
- **Restricted activities** are indicated for patients developing signs or symptoms of heart failure during pregnancy.
- **Diuretic**s are indicated in case of congestive symptoms.
- **ß-blocker** or a **non-dihydropyridine calcium channel antagonist** or **digoxin** should be considered for rate control in AF.

☛ **Intervention**

- Percutaneous valvuloplasty is indicated in severely symptomatic patients not responding to medical therapy in non-calcified valves with minimal regurgitation.
- If this is not possible and patients have life-threatening symptoms, valve replacement should be considered after early delivery by caesarean section.

☛ **Delivery**

- In severe AS=> caesarean delivery should be preferred with endotracheal intubation and general anesthesia.
- In non-sever AS=> vaginal delivery is favored, avoiding a decrease in peripheral vascular resistance during regional anesthesia and analgesia.

3. Mitral and aortic regurgitation

Left sided regurgitant valve lesions carry a lower pregnancy risk than stenotic valve lesion because the decreased systemic vascular resistance reduces regurgitant volume.

Sever regurgitation with LV dysfunction is poorly tolerated, as is acute severe regurgitation.

☛ **Management**

- Pre-pregnancy valve repair surgery should be done in patients with severe regurgitation and symptoms or compromised LV function or LV dilatation.
- Follow up every trimester in mild/moderate regurgitation and more often in sever regurgitation (needed to be individualized)
- Symptoms of fluid overload can usually be managed medically
- In acute sever regurgitation with therapy-refractory heart failure, surgery sometimes is unavoidable.

☛ **Delivery**

- Vaginal delivery is preferable, in symptomatic patients, epidural anesthesia and shortened second stage is advisable.

4. Valvular atrial fibrillation

Prevention of thrombo-embolic risk is important. UFH / LMWH can be used in the first and last trimester.

LMWH should be given in weigh adjusted therapeutic dose (twice daily) until 36h prior to delivery.

OACs (VKA) or LMWH can be used in the 2nd trimester.

INR should be kept between 2.0 and 2.5 (to minimize the risk for the fetus).

5. Bio prothesis

Pregnancy is generally well tolerated in women with a fell functioning bio prothesis. Pre-pregnancy assessment and counselling as well as follow up, medical treatment, and indications for intervention are comparable with those for pregnancies with native valve dysfunction.

6. Mechanical prosthesis and anticoagulation

Concerning of women with mechanical prothesis include increased risk of valve thrombosis, of hemorrhage complications and of offspring complications (miscarriage and hemorrhagic complications).

For the management of anticoagulant in mechanical valve during pregnancy, please see following schema (Figure 3, Figure 4 and Table 4).

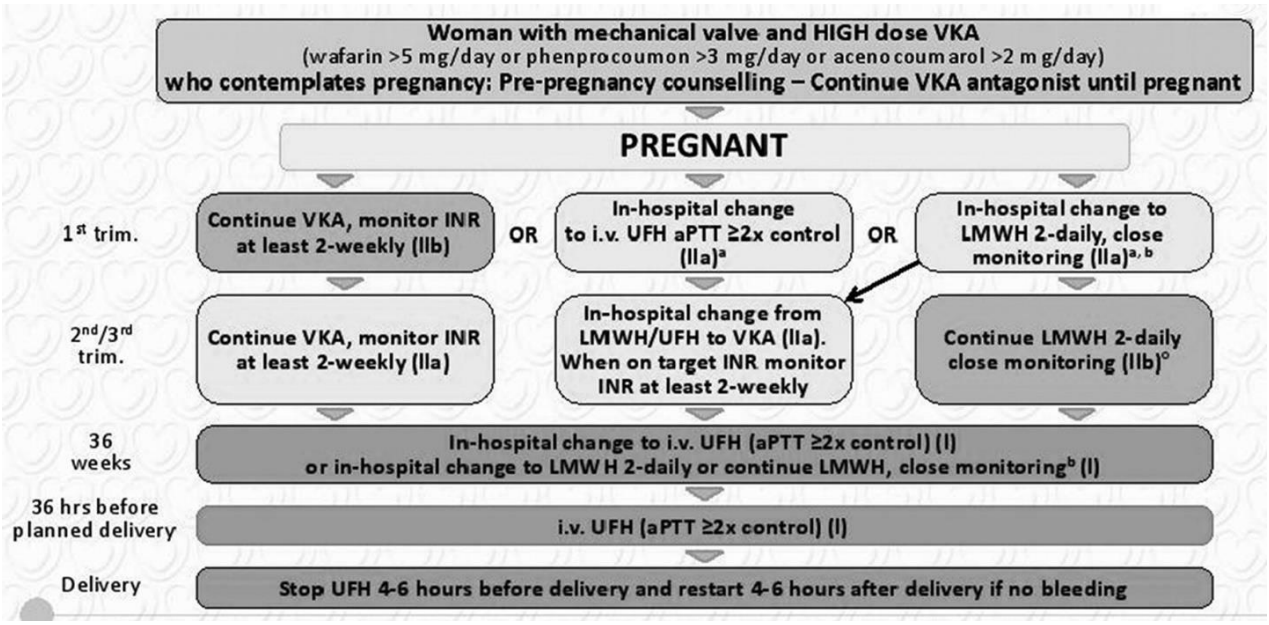


Figure 3. Management of anticoagulation in mechanical valve and high dose VKA

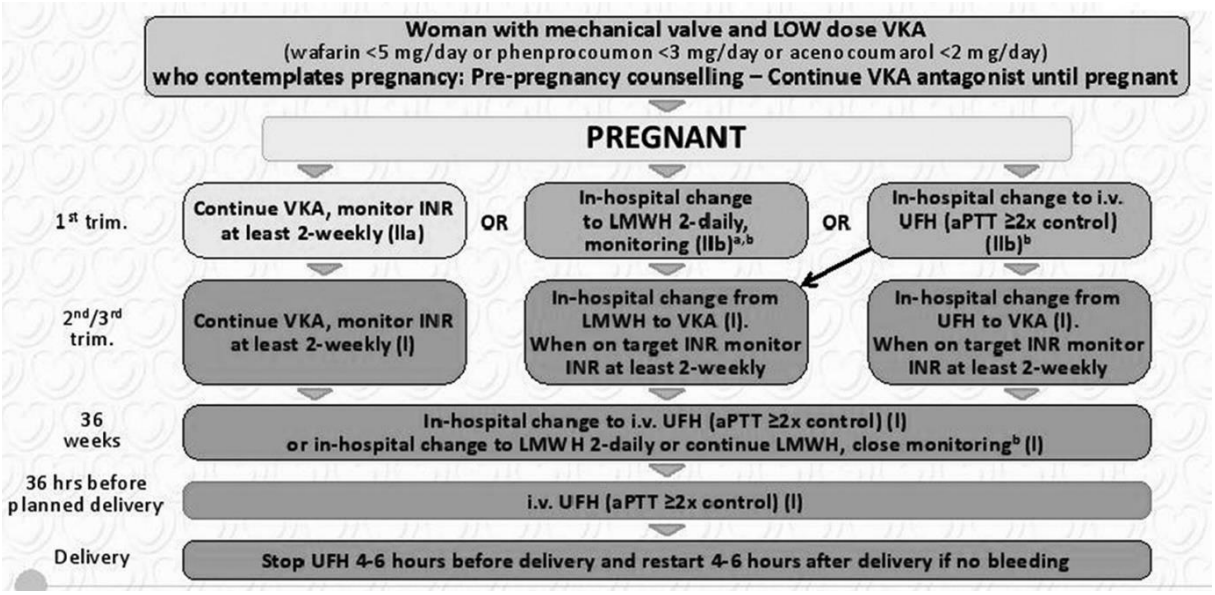


Figure 4. Management of anticoagulation in mechanical valve and low dose VKA

Table 4. INR target for mechanical valve prothesis

Prothesis Thrombogenicity	Risk factors	
	None	≥ 1
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

☛ **Delivery**

- Planned vaginal delivery is usually preferred with prior switch to heparin.
- A planned cesarean section may be considered in patient with high risk of valve thrombosis (aim to keep the time without OACs as short as possible).
- Caesarean delivery should be performed if labor onset occurs while the patient is still on OACs.

V. CORONARY ARTERY DISEASE AND ACUTE CORONARY SYNDROME

ECG and measurements of troponin level are recommended when a pregnant woman has a chest pain.

Primary coronary angioplasty is recommended as the preferred reperfusion therapy for STEMI during pregnancy. The safety of DES in pregnant woman is still unknow and they should be avoided because it requires prolonged DAPT.

In **non-ST-elevation ACS / NSTEMI**, an *invasive management should be considered in only patient with risk criteria*, otherwise a **conservative management should be considered**.

The use of ACEi / ARBs and renin inhibitor is contraindicated during pregnancy.

ß-blockers and low dose aspirin are considered to be *relatively safe*.

Clopidogrel should only be used when strictly needed (after stenting) and for the shortest duration possible.

Breastfeeding is not recommended in mother who take antiplatelet agents other than low dose aspirin due to lack of data.

VI. ARDIOMYOPATHIES AND HEART FAILURE

It is recommended to **treat women with HF during pregnancy according to current guideline for non-pregnant patients**, *respecting contraindications for some drugs in pregnancy*

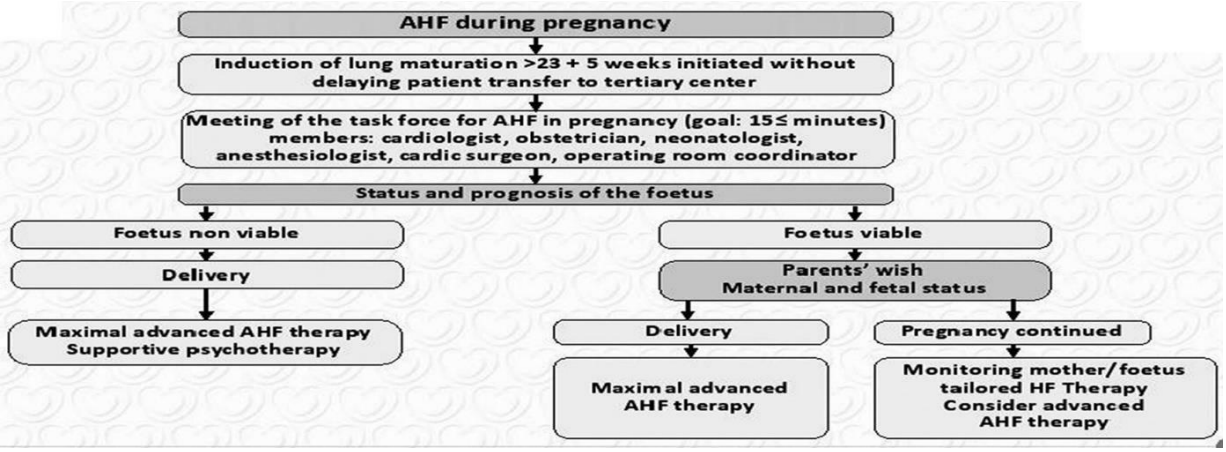


Figure 5. Rapid interdisciplinary workup and treatment of mother and foetus

In patients with PPCM and DCM, subsequent pregnancy is not recommended if LVEF does not normalize, counselling for recurrent risk during subsequent pregnancy is recommended in all cases, even after recovery of LV function.

In this case **bromocriptine treatment may be considered to stop lactation** and **enhance recovery (LV function).**

Due to the high metabolic demands of lactation and breastfeeding, preventing lactation may be considered in patients with severe heart failure.

ß-blocker is recommended to continue in women who used theme before pregnancy or **install them with caution in heart failure, in HCM or in arrythmia.**

Cardioversion should be considered for persistent atrial fibrillation.

Therapeutic anticoagulation with LMWH or VKA according to stage of pregnancy is recommended for patients with atrial fibrillation or with intracardiac thrombus detected by imaging or with evidence of systemic embolism.

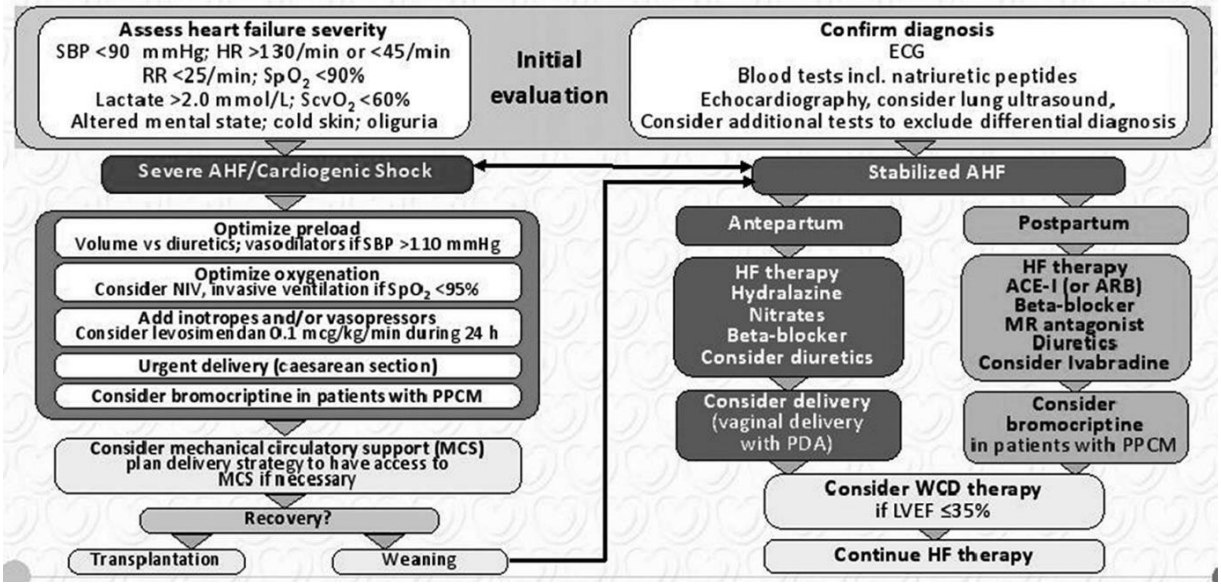


Figure 6. Management of acute heart failure during/after pregnancy

VII. RRTHMIAS

1. SVT and AF
   - **Acute management**
     - Stable hemodynamic => vagal maneuvers followed by adenosine if these fail (other drugs: beta -1- selective blockers should be considered if adenosine fail or not available)
     - Instable hemodynamic => immediate electrical cardioversion
   - **Long term management**
     - SVT without pre-excitation: ß1 selective blockers or verapamil
     - SVT in patients with WPW syndrome: flecainide or propafenone
     - Digoxin and verapamil should be considered for rate control of AT or AF if beta blocker fails
     - Catheter ablation with electroanatomical system should be considered in experiences centers in case of drug-refractory and poorly tolerated SVT.

   PS: *Atenolol should not be used for any arrhythmias*
2. Ventricular tachyarrhythmias
   - **Acute management**

- **Immediate electrical cardioversion** is recommended for sustained both unstable and stable VT.
- For acute conversion of sustained, hemodynamically stable, monomorphic VT, a beta blocker, sotalol, flecainide, procainamide or overdrive ventricular pacing should be considered.

 Long term management

- In patients with long QT syndrome or catecholaminergic polymorphic VT or idiopathic VT: **ß-Blockers** are recommended.
- **VERAPAMIL** also can be used for the prevention of idiopathic sustained VT if associated with severe symptoms or hemodynamic compromise. **Sotalol and Flecainide** could be use if other drugs fail.
- **ICD (preferable one chamber)** is recommended prior to pregnancy if clinically indicated but also during pregnancy, especially if the foetus is beyond 8 weeks of gestation, if indication emerges.

Table 5. Risk of arrythmia with hemodynamic compromise at delivery

Low risk	PSVT, AF, idiopathic VT, low-risk LQTS, WPW syndrome
Medium risk	Unstable SVT, VT, ICD carriers, VT and structural heart disease, Brugada syndrome; moderate risk: LQTS, catecholaminergic polymorphic VT
High risk for life threatening arrythmia	Unstable VT in structural heart disease/ congenital heart disease, unstable VT/TdP in high risk LQTS patients, short QT syndrome, high risk catecholaminergic polymorphic VT

Table 6. Surveillance levels at time of delivery in women with arrythmia

Descriptions of action to be planned	**Surveillance level**		
	Low	**Medium**	**High**
Consult cardiologist	☑		
Consultation with multidisciplinary team including arrythmologists at specialized center		☑	☑
Mode and location of delivery as advised by obstetricians.	☑	☑	
Cesarean delivery recommended			☑
Monitor cardiac rhythm (telemetry, external rhythm monitor)		☑	☑
Intravenous line		☑	☑
Arterial line			☑
Prepare for intravenous administration of adenosine		☑	
Prepare for intravenous administration of betablocker		☑	☑
Prepare for intravenous administration of selected antiarrhythmic drugs			☑
External cardioverter defibrillator at site		☑	☑
Delivery at thoracic operating theatre			☑
Prepare for transfer to cardiac intensive care unit post-partum if needed			☑

3. Bradyarrhythmias

 Sinus node dysfunction:

- sinus bradycardia may appear as a reflex cardiac slowing (Valsava maneuver) during delivery.

- Rare case of bradycardia cause symptoms of hypotension, **if occur => change the position of the mother to a left lateral decubitus position.**
- **For persistent symptoms, a temporary pacemaker maybe necessary.**

 AV blocks
- 1st degree AV block can be observed during pregnancy in the absence of underlying heart disease
- **Temporary pacing during pregnancy is recommended in selected women with complete heart block and symptoms due to the risk of bradycardia and syncope**.
- Implantation of permanent pacemaker can be performed safely, especially if the fetus is beyond 8 weeks gestations (with echo guidance).

VIII. HYPERTENSIVE DISORDERS

Hypertension is the most common medical problem in pregnancy, complicating up to 15% of pregnancies and accounting for about a quarter of all antenatal admission.

 Diagnosis and risk assessment
- Lab test: urine analysis, blood count, hematocrit, liver enzyme, serum creatinine and serum uric acid, 24hour proteinuria, urine metanephrine and normetanephrine
- Ultrasound of the adrenals
- Doppler ultrasound of uterine arteries (to detect uteroplacental hypoperfusion), which is associated with a higher risk of pre-eclampsia and intra uterine growth retardation.

 Definition and classification of hypertension in pregnancy
- *The definition of hypertension in pregnancy is based on absolute BP value (SBP ≥ 140mmHg or DBP ≥ 90mmHg).*
- Mildly hypertension: 140-159/90-109mmHg
- Severely hypertension: ≥ 160/110mmHg

Pre-existing hypertension: hypertension that either precedes pregnancy or develop before 20 weeks of gestation. This is usually persists > 42 days post-partum.

Gestation hypertension or **pregnancy induced hypertension**: develop after 20 weeks gestations and resolves in most cases within 42 days post-partum. It is characterized by poor organ perfusion.

Pre-existing hypertension plus superimposed gestational hypertension with proteinuria.

Antenatally unclassifiable hypertension: when BP is first recorded after 20 weeks gestations and hypertension is diagnosed.

Pre-eclampsia is a pregnancy specific syndrome that occurs after mid-gestation: de novo appearance of hypertension with new onset of significant proteinuria > 0.3g/24h.

Signs and symptoms of pre-eclampsia
- Right upper quadrant/epigastric pain due to liver oedema +/- hepatic hemorrhage
- Headache +/- visual disturbance (cerebral edema)
- Occipital lobe blindness
- Hyperreflexia +/- clonus
- Convulsion (cerebral edema)
- HELLP syndrome

 Pharmacological Management

- Low dose aspirin (100-150mg daily) is recommended in women at high or moderate risk of pre-eclampsia from week 12 to weeks 36-37.
- **Methylodopa, labetalol and calcium antagonists** are recommended for the treatment of hypertension in pregnancy.
- **IV Nitroglycerine** is recommended in case of *pre-eclampsia with pulmonary edema*, infusion of *5mcg/min and gradually increase every 3-5mins to a maximum dose of 100mcg/min*.
- **IV labetalol or oral methyldopa or nifedipine** is recommended in *severe hypertension.*
- ACE inhibitors, ARBs or direct renin inhibitor are not recommended.
- Diuretic should be avoided because they may decrease blood flow to the placenta.

In women with *gestational hypertension or pre-exiting hypertension superimposed by gestational hypertension, or with hypertension and sub clinical organ damage or symptoms*, **initiation of drugs treatment is recommended at SBP > 140mmHg or DBP > 90mmHg**. In all other cases, **initiation of drug treatment is recommended if SBP ≥ 150mmHg or DBP ≥ 95mmHg**.

SBP ≥ 170mmHg or DBP ≥ 110mmg in a pregnant woman is an emergency and hospitalization is recommended.

Delivery

- In women with gestational hypertension or mild pre-eclampsia, delivery is recommended at 37 weeks.
- Induction of delivery is recommended in gestational hypertension with proteinuria with adverse conditions such as visual disturbances, coagulation abnormalities, or fetal distress.

IX. VENOUS THROMBO-EMBOLISM

1. Prevention

- **Early mobilization and avoidance of dehydration.**
- **Using compression stoking**

In case of anticoagulation is needed:

- **Enoxaparin 0.5IU/KG body weight or**
- **Dalteparin 50IU/Kg body weight twice daily.**

Please see Table 7 and Table 8 to stratify venous thrombo-embolism and indication for anticoagulant prophylaxis.

Table 7. Risk factors for pregnancy related to venous thrombo-embolism

Pre-existing risk factors	Obstetric risk factors	Transient risk factors
- Previous recurrent VTE - Previous VTE-unprovoked or estrogen related - Previous VTE-provoked - Family history of VTE - Known thrombophilia - Medical co-morbidities: heart or lung disease, SLE,	- Pre-eclampsia - Dehydration / hyperemesis/ ovarian hyperstimulation syndrome - Multiple pregnancy or assisted reproductive therapy - Emergency cesarean	- Current systemic infection - Immobility - Surgical procedure in pregnancy < 6 weeks post-partum.

cancer, inflammatory conditions, nephritic syndrome, sickle cell disease - Ange ≥ 35 years - Obesity BMI > 30kg/m^2 - Parity ≥ 3 - Smoker - Gross various veins	section - Elective cesarean section - Mid cavity or rotational forceps - Peripartum hemorrhage (> 1L or transfusion)	

Table 8. Risk stratification and indication for anticoagulation prophylaxis

Risk group		
High risk	Patient with: - previous recurrent VTE (>1) or - VTE unprovoked / estrogen related or - single previous VTE + thrombophilia or family history	- should receive antenatal prophylaxis with LMWH as well as post-partum for the duration of 6 weeks - graduated compression stoking are also recommended during pregnancy and post-partum
Intermediate risk	Patients with: - 3 or more risk factors other than listed above as high risk or - 2 or more risk factors other than listed as high risk if patient is admitted to hospital	- antenatal prophylaxis with LMWH should be considered - prophylaxis is recommended postpartum for at least 7 days or longer if > 3 risk factors persist. - graduated compression stoking should be considered during pregnancy and post-partum
Low risk	Patient with: < 3 risk factors	- early mobilization and avoidance of dehydration is recommended.

2. Management of acute venous thrombo-embolism

 Pulmonary embolism

- **Clinical presentation (same as in non-pregnant state):** dyspnea, chest pain, tachycardia, haemoptiysis, and collapse.
- **Diagnosis:**
  - D-dimer levels increase physiologically in pregnant women with each trimester, thus a positive D-dimer test base on the conventional cut-off level is not necessarily indicated of VTE, but it helps **to rule out VTE in the case of negative D-dimer.**
  - **Bilateral compression ultrasonography** is indicated follow by measurement of D-dimer.
  - **MRI** may be used to rule out iliac vein thrombosis
  - CT pulmonary angiography should be performed with the diagnosis cannot be confirmed or excluded with the above-discussed tool.
- **Treatment:**
  - **LMWH:**
    - **Enoxaparin 1mg/kg body weight bid.**
    - **Dalteparin 100iu/kg body weight bid.**

- *Aiming for 4-6h peak anti Xa values of 0.6-1.2 IU/mL*

- **UFH (used in patients with renal failure and when urgent reversal of anticoagulation by protamine is needed**, as well as in the **acute treatment of massive pulmonary emboli:**
  - **Loading dose of 80U/Kg** followed by
  - **IV continuous fusion of 18U/Kg/h**
  - *Therapeutic target aPTT ratio 1.5-2.5 times the average laboratory control value*
  - *The aPTT has to be determine 4-6h after the loading dose, 6h after any dose change and then at least daily when in the therapeutic range.*

  When haemodynamics are improved and the patient is stabilized, UFH can be switched to LMWH in therapeutic dose and maintain during pregnancy.
- LMWH should be switched to i.v. UFH at least 36h before the induction of labour or caesarean delivery.
- UFH should be discontinued 4-6h before anticipated delivery and restarted 6h after a vaginal birth or 12h after caesarean delivery if there are no bleeding complications.
- UFH and LWMH are not contraindicated to breastfeeding.
- **VKA may be started on the second day after delivery** and **continued for at least 3 months or for 6 months if pulmonary embolism** occurred late in pregnancy.
- INR should be between 2 and 3 and needs regular monitoring, ideally once every 1-2 weeks.
- **Thrombolysis:** Relatively contraindicated during pregnancy and peripartum => should only be used in high-risk patients with severe hypotension or shock.
- Other anti-coagulants: Fondaparinux and Rivaroxaban are not recommended to use in pregnancy (due to transplacental passage of the drug)

Acute deep vein thrombosis

- **Clinical presentation:**
  - leg swelling (> 85% left sided due to compression of the left iliac vein by the right iliac artery and the gravid uterus),
  - isolated pain in the buttock, groin, flank or abdomen (in case of isolated iliac vein thrombosis)
- **Diagnosis:**
  - D-dimer (see diagnosis in pulmonary embolism)
  - Compression ultrasound leg vein imaging

In women with <u>high pre-test probability</u>, a positive D-dimer and a normal initial compression ultrasound => **magnetic resonance venography** may be considered to exclude isolated pelvic DVT.

Women with <u>low pre-test probability</u> and normal D-dimer should undergo **serial compression ultrasonography on day3 and after 1 week without anti-coagulation.**

- **Treatment**
  - **LMWH:**

- **Enoxaparin 1mg/kg body weight bid.**
- **Dalteparin 100iu/kg body weight bid.**
- *Aiming for 4-6h peak anti Xa values of 0.6-1.2 IU/Ml*

X. REFERRENCES

1. Mary M. Canobbio, RN, MN, FAHA, Chair Carole et al. Management of Pregnancy in patients with complex congenital heart disease. Circurlation, 2017;135:e50-e87. DOI: 10:1161/CIR0000000000000458
2. Lisa M. Hollier, MD, James N. Martin Jr., MD et al. Clinical management guidelines for obstetrician-gynecologists. ACOG practice bulletin, vol 133, NO.5, MAY 2019.
3. Vera Regitz-Zagrosek, Carina Blomstrom Lundqvist, Claudi Borhi et al. European heart journal (2011) 32, 3147-3197. DOI: 10.1093/eurheart/ehr-218
4. Robson SC , Hunter S , Boys RJ , et al.Serial study of factors influencing changes in cardiac output during human pregnancy. Am J Physiol 1989;256:H1060–5.doi:10.1152/ajpheart.1989.256.4.H1060
5. Balci A, Sollie-Szarynska KM, van der Bijl AGL, et al. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. Heart 2014; 100:1373–81.doi:10.1136/heartjnl-2014- 305597
6. van Hagen IM, Boersma E, Johnson MR, et al.Global cardiac risk assessment in the registry of pregnancy and cardiac disease: results of a registry from the European Society of Cardiology. Eur J Heart Fail 2016; 18:523–33.doi:10.1002/ejhf.501
7. van Hagen IM, Roos-Hesselink JW, Ruys TPE, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of cardiology registry of pregnancy and cardiac disease (ROPAC). Circulation 2015; 132:132-42.doi:10.1161/CIRCULATIONAHA.115.015242
8. Pijuan-Domenech A, Galian L, Goya M, Casellas M, Merced C, Ferreira-Gonzalez I, et al. Cardiac complications during pregnancy are better predicted with the modified who risk score. Int J Cardiol 2015;195:149–154.
9. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: A systematic review of safety and efficacy. Blood 2005;106:401–407.
10. Leffert L, Butwick A, Carvalho B, Arendt K, Bates SM, Friedman A, et al. The society for obstetric anesthesia and perinatology consensus statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants. Anesth Analg 2018;126:928–944.

CARDIOVASCULAR DRUGS AND PREGNANCY

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I. GENERAL PRINCIPLES

There are no uniform recommendations for the treatment of pregnant women yet. As drug treatment in pregnancy concerns the mother and the fetus, optimum treatment of both must be targeted. In case of emergency, drugs that are not recommended by the pharmaceutical industry during pregnancy and breastfeeding should not be withheld from the mother. The potential risk of a drug and the possible benefit of the therapy must be weighed against each other.

Before pharmacological treatment in pregnancy is started, it is recommended to check table below (Table 2) for clinical safety data.

In the absence of clinical safety data, it is recommended to check the electronic drug table (www.safefetus.com) for pre-clinical safety data.

In the absence of adequate human safety data, decision-making should be based on individual drug efficacy and safety profiles, and the available animal data, and the decision must be made together with the patient.

Decision making based on former US Food and Drug Administration (FAD) categories alone is no longer recommended.

Table 1. FDA Drug Classifications

Rating A	Controlled study in women fall to demonstrate a risk to the fetus in the first trimester; no evidence of a risk
Rating B	Either animal-reproduction studies have note demonstrate a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters)
Rating C	Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and there are no controlled studies in women or studies in women and animal are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.
Rating D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threating situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Rating X	Studies in animals or human beings have demonstrated fetal abnormalities, there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweigh any possible benefit. There drug is contraindicated in women who are or may become pregnant.

II. RECOMMENDATION FOR DRUGS USES

Angiotensin-converting enzyme (ACE) inhibitors and **angiotensin receptor blockers (ARB)** are pregnancy category D drugs because of the risk of reduced fetal renal function and increased fetal and neonatal morbidity and death, especially with use during the 2nd and 3rd trimester. Women taking ACE inhibitors or ARB who desire to become pregnant should be advised to stop taking these drugs before conception to minimize the risk of fetal abnormality.

ß-Blockers have a favorable safety profile, and no teratogenic risk have been reported with their use. They have been associated with an increase in small-for-gestational-age infants and neonatal bradycardia and hypoglycemia but in practical terms are considered safe to use. Atenolol has been associated with low birth weight and therefore is not the ß-blocker of choice during pregnancy.

The routine use of **diuretics** is discouraged because of the potential reduction in maternal plasma volume early in gestation that is potentially harmful to the fetus. **They should be used judiciously**.

Amiodarone has been associated with a 9% incidence of fetal hypothyroidism and a 21% incidence of intrauterine growth retardation and should be reserved for cases of refractory ventricular arrythmia.

Drugs listed as category X include the following:

- Anticoagulants: Vitamin K antagonist cross the placenta and are potentially fetotoxic. They are commonly used in women with mechanical valves, and the risk and benefits associated with their use should be discussed with the patient before pregnancy is completed.
- Endothelin receptor antagonists (bosentan, ambrisentan, and macitentan)
- Statin: although inadvertent exposure to statin during early pregnancy appears unlikely to increase the risk of adverse pregnancy outcome, theoretical considerations concerning the role of cholesterol in embryo development and the lack of demonstration benefit of treating hyperlipidemia during gestation are reasons for not recommending statin during pregnancy.

Table 2. Medications during pregnancy

	Common examples	FDA Pregnancy Category	Teratogenic Risks (First trimester)	Other pregnancy concerns (second and Third Trimesters)	Suggested Evaluation	Lactation	Notes
Antihypertensives							
ß-Blockers	Metoprolol Propranolol Carvedilol Atenolol	C C C D	None reported	Possible association with fetal growth restriction in second and third trimesters (atenolol, propranolol), neonatal bradycardia (esmolol, nadolol)	Consider serial fetal sonography to assess interval fetal growth in second and third trimesters.	Except for atenolol, probably safe	
Combined α-/ß-blockers	Labetalol	C	None reported	No		Yes	
	Common examples	**FDA**	**Teratogenic Risks**	**Other pregnancy**	**Suggested**	**Lactation**	**Notes**

		Pregnancy Category	(First trimester)	concerns (second and Third Trimesters)	Evaluation		
Antihypertensives (continued)							
Calcium channel blockers	Nifedipine Verapamil Diltiazem	C	None reported	Caution if used in combination with magnesium sulfate		Yes	
ACE inhibitors	Captopril Enalapril Lisinopril	C (first trimester) D (second and third trimester)		Fetal renal dysplasia, oligohydramnios, growth restriction, and intrauterine demise reported in second and third trimesters.	Consider fetal echocardiography with first trimester exposure, serial sonography to assess interval fetal growth and amniotic fluid volume in second and third trimesters	Yes (captopril and enalapril) Unknown (lisinopril)	Avoid if possible during pregnancy
α2-Adrenergic agonists	Methyldopa Clonidine	B C	None reported	Induction of positive indirect Coombs testing (methyldopa), rare neonatal hypertension (clonidine)		Yes (methyldopa) Probably safe (clonidine)	
Vasodilators	Hydralazine Epoprostenol Nitroprusside Nitroglycerin Isosorbide dinitrate Sildenafil	C B B	None reported	Possible transient fetal bradycardia (nitroprusside)		Yes (hydralazine) Probably safe (nitroglycerin) Unknown (epoprosterol, nitroprusside, isosorbide dinitrate, sildenafil)	
Diuretics							
Thiazide diuretics	HTZ	B	None reported	Possible increase risk of neonatal hypoglycemia and thrombocytopenia	Consider neonatal blood count and electrolyte evaluation	Yes (AAP) No (WHO)	Maintenance therapy permissible, but therapy not usually stared during pregnancy
Loop of Henle diuretics	Furosemide	C	None reported	Possible association with neonatal PDA and sensorineural hearing loss	Maternal electrolyte monitoring	No	
Potassium sparing diuretics	Spironolactone (not recommended)	C	None reported			Yes (probably safe; not recommended)	
Anticoagulants							
Heparin (including LMWHs)	Heparin Enoxaparin Dalteparin	C	None reported	Possible maternal osteoporosis, heparin-induced thrombocytopenia and bleeding	Maternal platelet and coagulation status monitoring (as appropriate)	Yes	
	Common examples	**FDA**	**Teratogenic Risks**	**Other pregnancy**	**Suggested**	**Lactation**	**Notes**

		Pregnancy Category	(First trimester)	concerns (second and Third Trimesters)	Evaluation		
Anticoagulants (continued)							
Vitamin K antagonists	Warfarin	X	Fetal warfarin syndrome (craniofacial and skeletal anomalies) with exposure in weeks 6-9; fetal intracranial hemorrhage in second and third trimesters.		Comprehensive fetal sonography at 18-20 wk of gestation	Yes	Teratogenicity appears to be related to dose > 5mg daily
Antiplatelet agents	Aspirin (full dose) Clopidogrel	D (third trimester) B	None reported	Premature closure of fetal ductus arteriosus at ≥ 32 wk of gestation	Empirical recommendation to discontinue clopidogrel 7d in advance of anticipated delivery.	Unknown (AAP) No (WHO)	Low dose aspirin (≤ 100mg/d) does not appear to have deleterious effects
Direct thrombin inhibitors	Argatroban	B	None reported			Unknown	
Indirect factor Xa inhibitors	Fondaparinux	B	None reported	Possible neonatal factor Xa inhibition		Unknown	
Direct factor Xa inhibitors	Rivaroxaban	C	None reported	Theoretical risk of maternal hemorrhage		Unknown	
Fibrinolytics	Streptokinase	C	None reported			Unknown	
Inotropic / Vasopressors							
Cardiac glycosides	Digoxin Digitalis	C	None reported			Yes	
Adrenergic agents	Epinephrine Norepinephrine Phenylephrine Dopamine Isoproterenol	C	Possible association with gastroschisis or hemifacial microsomia (phenylephrine)			Probably safe (dopamine) Unknown (epinephrine, norepinephrine, phenylephrine, isoproterenol)	
Antiarrhythmics							
ß-Blockers	Metoprolol Propranolol Carvedilol Atenolol	C C C D	None reported	Association with fetal growth restriction in second and third trimesters (atenolol, propranolol), neonatal bradycardia (esmolol, nadolol)	Consider serial fetal sonography to assess interval fetal growth in second and third trimesters.	Except for atenolol, probably safe	
Class 1A	Quinidine Procainamide	C C	None reported			Yes	
Class 1C	Flecainide	C	None reported			Yes	
	Common examples	FDA	Teratogenic Risks	Other pregnancy	Suggested	Lactation	Notes

		Pregnancy Category	(First trimester)	concerns (second and Third Trimesters)	Evaluation		
Antiarrhythmics (Continued)							
Class III	Sotalol Amiodarone	B D	None reported	Thyroid dysfunction		No No WHO / (AAP Yes)	
Purine nucleosides	Adenosine	C	None reported			Unkown	

AAP: American Academy of Pediatrics; FDA: US Food and Drug administration; LMWH: low-molecular-weight heparin; PDA: Paten ductus arteriosus; and WHO: World Health Organization.

III. REFERECES

1. Mary M. Canobbio, RN, MN, FAHA, Chair Carole et al. Management of Pregnancy in patients with complex congenital heart disease. Circurlation, 2017;135:e50-e87. DOI: 10:1161/CIR0000000000000458
2. Lisa M. Hollier, MD, James N. Martin Jr., MD et al. Clinical management guidelines for obstetrician-gynecologists. ACOG practice bulletin, vol 133, NO.5, MAY 2019.
3. Vera Regitz-Zagrosek, Carina Blomstrom Lundqvist, Claudi Borhi et al. European heart journal (2011) 32, 3147-3197. DOI: 10.1093/eurheart/ehr-218

CARDIAC EVALUATION BEFORE NON-CARDIAC SURGERY (NCS)

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I. DEFINITIONS OF SRUGICAL TIMING AND RISK

TIMING	DEFINITION
Emergency	Immediate threat to life or limb without surgical intervention, where there is very limited or no time for preoperative clinical evaluation, typically <2 h.
Urgent	Threat to life or limb without surgical intervention, where there may be time for preoperative clinical evaluation to allow interventions that could reduce risk of MACE or other postoperative complications, typically ≥2 to <24 h.
Time-sensitive	Surgery may be delayed up to 3 months to allow for preoperative evaluation and management without negatively impacting outcomes.
Elective	The surgical procedure can be delayed permitting a complete preoperative evaluation and appropriate management.

RISK CATEGORY	DEFINITION
Low risk	Combined surgical and patient characteristics predict a low risk of MACE of <1%.
Elevated risk	Combined surgical and patient characteristics predict an elevated risk of MACE of ≥1%.

* MACE: Major Adverse Cardiac Events (Death, Heart Attack, Heart failure, Arrhythmia, Stroke)

II. EPIDEMIOLOGY

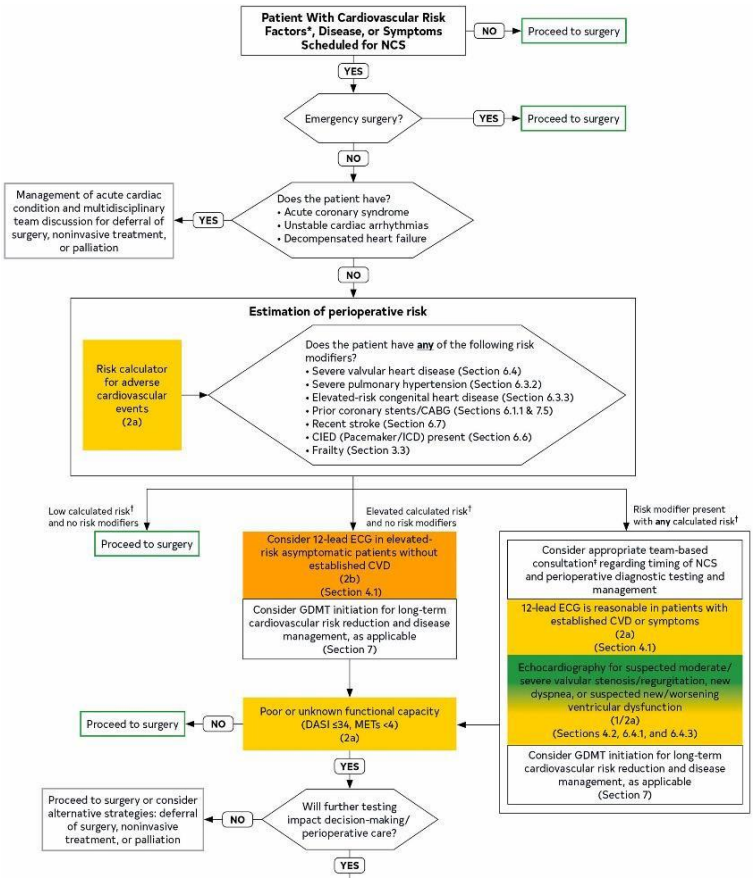
- Each year, approximately 14.4 million inpatient and 19.2 million ambulatory surgeries are performed in the United States, with an estimated 313 million surgeries performed worldwide. Cardiovascular risk factors and disease are prevalent among adults undergoing NCS, and perioperative cardiovascular complications are an important cause of morbidity and mortality.
- In a large retrospective analysis of adults ≥45 years undergoing in-hospital surgery, perioperative death, myocardial infarction (MI), or ischemic stroke occurred in 1 of every 33 surgical admissions, corresponding to >150,000 annual perioperative events in the United States. Although orthopedic

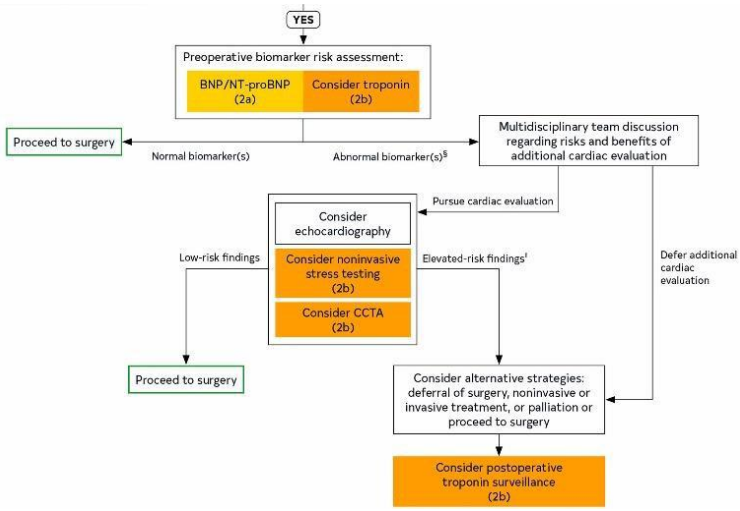
(40.0%), general (21.4%), and vascular (10.7%) surgeries were the most performed, patients undergoing vascular, thoracic, and solid organ transplantation surgeries had the highest incidence of cardiovascular events. Irrespective of the surgical subtype, perioperative cardiovascular complications are associated with prolonged inpatient hospitalizations, significantly higher medical costs, and increased mortality.

III. PREOPERATIVE CARDIOVASCULAR DIAGNOSTIC TESTING

- ECG: For patients with known coronary heart disease, significant arrhythmia, peripheral arterial disease, cerebrovascular disease, other significant structural heart disease, or symptoms of CVD undergoing elevated risk surgery (COR:2a)
- ECHOCARDIOGRAPHY to assessment of ventricular function: In patients undergoing NCS with new dyspnea, physical examination findings of HF, or suspected new/worsening ventricular dysfunction (COR: 1)
- STRESS TESTING: Vasodilator pharmacological stress imaging, Exercise stress testing, Dobutamine stress echocardiography
- CARDIOPULMONARY EXERCISE TESTING: in whom objective functional capacity is reduced. Reduced cardiorespiratory fitness increases the risk of postoperative complications.
- CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY: In patients with acute chest pain and no known CAD, CCTA may be useful to exclude atherosclerotic plaque and obstructive CAD and is recommended as an alternative to invasive angiography.
- INVASIVE CORONARY ANGIOGRAPHY:

IV. APPROACH TO PERIOPERATIVE CARDIAC TESTING





V. CARDIOVASCULAR COMOBIDITIES AND PERIOPERATIVE MANAGEMENT

- **CORONARY ARTERY DISEASE**: In patients with ACS being considered for elective NCS, coronary revascularization as appropriate and deferral of surgery is recommended to reduce perioperative cardiovascular events. (COR:1C)

- **HYPERTENSION**:
  - **Pre-operative**: In most patients with hypertension planned for elective NCS, it is reasonable to continue medical therapy for hypertension throughout the perioperative period. Except, poorly controlled hypertension (systolic blood pressure [SBP] ≥180 mm Hg or diastolic blood pressure [DBP] ≥110 mm Hg before the day of surgery), deferring surgery may be considered to reduce the risk of perioperative complications.
  - **Intraoperative Blood Pressure Management**: In patients undergoing NCS, maintaining an intraoperative mean arterial pressure (MAP) ≥60 to 65 mm Hg or SBP ≥90 mm Hg is recommended to reduce the risk of myocardial injury.
  - **Postoperative Blood Pressure Management:**
    - In patients undergoing NCS, treatment of hypotension (MAP <60-65 or SBP <90 mm Hg) in the postoperative period is recommended to limit the risk of cardiovascular, cerebrovascular, renal events, and mortality.
    - In patients with hypertension undergoing NCS, it is recommended that preoperative antihypertensive medications be restarted as soon as clinically reasonable to avoid complications from postoperative hypertension.

- **HEART FAILURE:**
  - In patients with HF undergoing elective NCS, **sodium-glucose cotransporter-2 inhibitors (SGLT2i) should be withheld for 3 to 4 days** before surgery when feasible to reduce the risk of perioperative metabolic acidosis.

- it is reasonable to continue **GDMT** (Guideline Direct Medical Therapy) (excluding SGLT2i) in the perioperative period, unless contraindicated, to reduce the risk of worsening HF.

➢ **HYPERTROPHY CARDIOMYOPATHY:**
- For patients with hypertrophic cardiomyopathy (HCM) undergoing NCS, factors that aggravate or trigger dynamic outflow obstructions (Ex, positive inotropic agents, tachycardia, or reduced preload) are harmful and should be avoided to reduce the risk of hemodynamic instability.
- **If hypotension develops**:
  - Prioritize intravenous fluid administration to correct hypovolemia.
  - Use alpha-agonists, such as phenylephrine or vasopressin,[7] rather than beta-agonists, which can worsen LVOT obstruction.
  - Consider intraoperative echocardiography to evaluate LVOT obstruction in the setting of hypotension.
  - In selected cases, intravenous beta-blockade may be necessary to reduce LV myocardial contractility and relieve LVOT obstruction.

➢ **PULMONARY HYPERTENSION**:
- In patients receiving stable doses of targeted medical therapies, continue these agents.
- In patients with severe[†] PH undergoing elevated-risk NCS, Referral to or consultation with a specialized PH center and invasive hemodynamic monitoring.

➢ **ADULT CONGENITAL HEART DISEASE**
- Preoperative consultation with an adult congenital heart disease (ACHD) specialist is recommended before the surgery.

➢ **VALVULAR HEART DISEASE**
- Patients with severe valvular heart disease should be evaluated for the need for valve intervention before elective NCS.
- In asymptomatic patients with moderate or severe AS and normal LV systolic function as assessed by echocardiography within the past year, it is reasonable to proceed with elective low-risk NCS.

➢ **ATRIAL FIBRILLATION**
- Treat potential underlying triggers contributing to AF and rapid ventricular response (Ex, sepsis, anemia, pain).
- Initiation of postoperative anticoagulation therapy can be beneficial after considering the competing risks associated with thromboembolism and perioperative bleeding.

- **PREVIOUS STROKE OR TRANSIENT ISCHEMIC STROKE**
  - it is reasonable to delay elective NCS for ≥3 months after the most recent cerebrovascular event to reduce the incidence of recurrent stroke, MACE, or both.

VI. PERIOPERATIVE MEDCIAL THERAPY

- **STATTINE**: Continuation of statin therapy is recommended to reduce the risk of MACE.
- **RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS**: Omission 24 hours before surgery may be beneficial to limit intraoperative hypotension.
- **ANTIPLATELET THERAPY AND TIMING OF NCS IN PATIENT WITH CAD**
  - Timing of NCS after PCI:
    - In patients with recent coronary artery balloon angioplasty without stent placement, elective NCS should be delayed for a minimum of 14 days to minimize perioperative MACE.
    - In patients with DES-PCI placed for ACS who require elective NCS with interruption of ≥1 antiplatelet agents, surgery should ideally be delayed ≥12 months to minimize perioperative MACE.
    - In patients with DES-PCI placed for CCD who require elective NCS with interruption of ≥1 antiplatelet agents, it is reasonable to delay surgery for ≥6 months after PCI to minimize perioperative MACE.
  - Perioperative Antiplatelet Management Post PCI
    - In patients with prior PCI undergoing NCS, it is recommended to continue aspirin* (75-100 mg), if possible, to reduce the risk of cardiac events.
    - In patients with CAD who require time sensitive NCS within 30 days of PCI with BMS or <3 months of PCI with DES, DAPT should be continued unless the risk of bleeding outweighs the benefit of the prevention of stent thrombosis.
    - In patients with prior PCI in whom OAC monotherapy must be discontinued before NCS, aspirin should be substituted when feasible in the perioperative period until OAC can be safely reinitiated.
  - Perioperative Antiplatelet Management in Patients Without Prior PCI
    - In patients with CCD without prior PCI undergoing elective NCS, it may be reasonable to continue aspirin in selected patients when the risk of cardiac events outweighs the risk of bleeding.
- **ORAL ANTICOAGULANT**: multidisciplinary team-based approach to time-based interruption is recommended to balance the competing risks of thromboembolism and perioperative bleeding.

- **BETA BLOCKER**: beta blockers should be continued through the perioperative period as appropriate based on the clinical circumstances.

VII. MANAGEMENT OF POSTOPERATIVE STEMI/NSTEMI

- Patients who develop STEMI after NCS should be considered for GDMT, including consideration of ICA, balancing bleeding, and thrombotic risks with the severity of the clinical presentation.
- Patients who develop NSTEMI after NCS should receive medical therapy as recommended for patients with spontaneous MI but after consideration of postoperative bleeding risks and hemodynamic status.

VIII. SPECIAL CASES

- Preoperative evaluation before liver and kidney transplantation: Data from the
  U.S. Renal Data System and Medicare claims reported that more frequent invasive or noninvasive CAD testing in the year before kidney transplantation was not associated with lower rates of 30-day posttransplant death or acute MI.
- Obesity and bariatric surgery: careful attention to history and risk factors during preoperative assessments is essential, because:
  - patients who underwent Roux-en-Y gastric bypass or sleeve gastrectomy, prior cardiac history was associated with greater risks of perioperative cardiac arrest and 30-day mortality.
  - patients with obesity undergoing bariatric surgery reported that a history of ACS or HF was associated with increased risks of perioperative cardiovascular complications.

IX. REFERENCES:

1. Journal of the American College of Cardiology. (2024). AHA/ACC/ACS/ASNC/HRS/SCA/SCCT/SCMR/SVM Guideline for Perioperative Cardiovascular Management for Noncardiac Surgery; Retrieved January 19, 2025, from https://www.jacc.org/doi/10.1016/j.jacc.2024.06.013#sectitle0435
2. Smilowitz N.R., Berger J.S. Perioperative Cardiovascular Risk Assessment and Management for Noncardiac Surgery. JAMA. 2020;324:279. doi: 10.1001/jama.2020.7840.
3. Zipes D.P., Libby P. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 2-Volume Set. 11th ed. Elsevier; Philadelphia, PA, USA: 2019.
4. Perioperative management of antiplatelet therapy in patients with coronary stents undergoing cardiac and non-cardiac surgery: A consensus document from Italian cardiological, surgical and anesthesiologic societies. Euro Intervention. 2014;10:38–46. doi: 10.4244/EIJV10I1A8.
5. https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/ESC-Guidelines-on-non-cardiac-surgery-cardiovascular-assessment-and-management