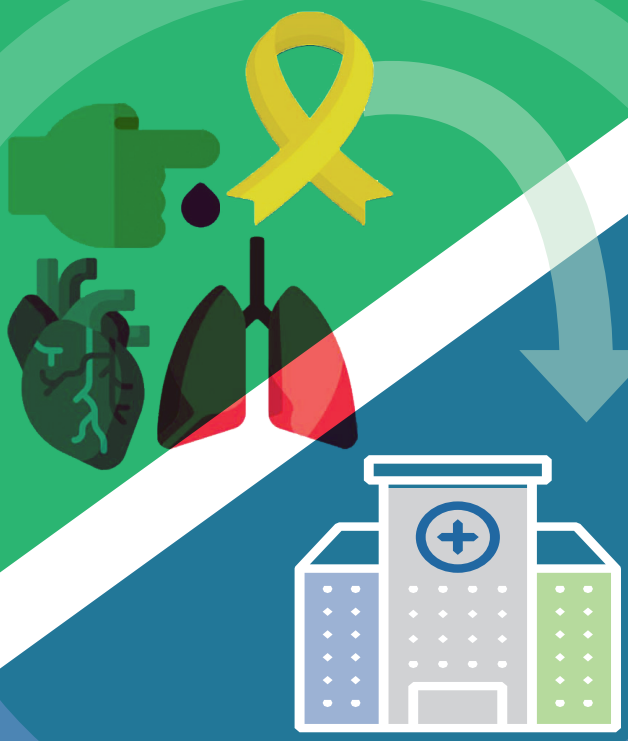
PEN-Plus Clinical Protocol

For Management of Severe & Chronic NCDs in the First Level Referral Hospitals of Nepal



Government of Nepal
Ministry of Health and Population
Department of Health Services
Epidemiology and Disease Control Division
Teku, Kathmandu, Nepal

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Preface

Non-communicable diseases (NCDs) are long-standing non-infectious chronic diseases and are the result of a combination of genetic, physiological, environmental and behavioral factors. It mainly consists of cardiovascular diseases (heart attack and stroke), cancer, chronic respiratory disease (COPD and bronchial asthma) and Diabetes. NCDs kill 41 million people each year, equivalent to 74% of deaths globally.

In the context of Nepal, NCDs are a major public health problem and is the leading cause of death with 2/3rd (66%) of death attributed to NCDs (WHO Nepal Country Profile 2018). Of the total death in the country, Ischemic Heart Disease contributes to nearly one in six death (16%) with one in ten deaths claimed by Chronic Obstructive Pulmonary Disease (COPD). The majority of these deaths are preventable with accessible, affordable, equitable, and quality NCD care delivery.

The Government of Nepal (GoN) has initiated several innovative and progressive structural policies and plans including the Package of Essential Non-Communicable Diseases (PEN) interventions nationwide. This action-oriented set of cost-effective interventions delivered to an acceptable quality of care, even in poor- resource settings was piloted in two districts in October 2016 and has now been extended to all 77 districts of the country. PEN provides basic NCD services for cardiovascular diseases (CVDs), Diabetes Mellitus, Chronic respiratory diseases, and cancer at the PH level in Nepal. However, there is still a lack of service for management of severe NCD at the first level referrals which compels individuals living in poor- resource settings to travel a long distance to the higher referral centers and spend out of pocket to avail of the services. Eventually, this has led to a huge disparity in service delivery when it comes to severe NCDs at the country's lower levels of health care. This calls for an urgent need for expansion of the services available in PEN to meet the prevailing health inequity.

The PEN-Plus is the model developed for integrated health service delivery for severe or advanced chronic NCDs at the firstlevel referral hospital built upon the PEN intervention. It incorporates integrated care teams to provide chronic care for severe NCDs such as Type 1 Diabetes, Rheumatic Heart Disease (RHD), and Sickle Cell Disease (SCD) at first-level referral hospitals. This approach will also expedite the process of decentralizing service delivery at the PHCC level in regards to the common NCDs, establish the referral chain from PHCC to the first level referrals and then to the higher center for NCD care, and ultimately protects the vulnerable population from financial hardship.

I would like to express my sincere gratitude to the Kathmandu Institute of Child Health (KIOCH) for initiating and implementing the PEN-Plus and also would like to thank NCDI Poverty Network Secretariat at the Center for integration science, Brigham and Women's Hospital, Boston, USA, and UNICEF for providing the initial funding. Similarly, I would like to thank NCD and Mental Health section, EDCD for leading the PEN-Plus initiation and implementation. I would also like to appreciate and thank all the contributors to the PEN-Plus, including DoHS, NHRC, NHTC, and WHO for their valuable support. Lastly, I would like to acknowledge the efforts of all consultants involved in the development of the PEN-Plus protocol.

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Secretary

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FOREWORD

Nepal is witnessing an epidemiological transition from communicable diseases like water borne and vector-borne disease to a state of long-standing chronic diseases called Non-communicable diseases. There are majorly four non-communicable diseases recognized as a public health challenge in the country's context, which includes cardiovascular disease (heart attack and stroke), Diabetes, Chronic Respiratory Disease (COPD and Bronchial Asthma) and cancer (Cervical, Oral and Breast). NCDs are responsible for 41 million people's death each year, equivalent to over 7 out of 10 deaths worldwide. The high burden of NCDs among productive age group has led to high healthcare costs, limited ability to work, and financial insecurity, immature death, catastrophic expenditure eventually leading to increased impoverishment.

In Nepal, NCD is a major public health problem and is the leading cause of death with more than 2/3rd of total deaths attributed to NCDs. Out of the total deaths in the country, Ischemic Heart Disease contributes to nearly one-sixth of total deaths (16%). Similarly, one-tenth of deaths are claimed by chronic obstructive pulmonary disease (COPD).

The Government of Nepal (GoN) has initiated several innovative and progressive structural policies and plans including the Package of Essential Non-Communicable Diseases (PEN) interventions nationwide. PEN is an action-oriented, cost-effective intervention delivered with an acceptable quality of care, even in resource-poor settings. It was piloted in two districts in October 2016 and has now been extended to several districts of the country. PEN provides basic NCD services for Cardiovascular diseases (CVDs), Diabetes Mellitus, Chronic respiratory diseases, and cancer at the PHCC level in Nepal. However, there is still a lack of management for severe NCDs at the first-level referral centers which compels people to get services from higher referral centers. In this context, it is a dire necessity to enhance and extend such services even at first referral health centers. PEN-Plus will fill up the gap, and the Department acknowledges this timely and effective initiative in Nepal

Finally, I would like to extend my sincere gratitude to EDCD for coordinating such an important initiative and to the Kathmandu Institute of Child Health (KIOCH) for partnering in the implementation of the PEN-Plus program. Similarly, I would like to acknowledge the efforts of all the consultants involved in the development of the PEN-Plus protocol. Lastly, I would like to appreciate and thank all the contributors to the PEN-Plus for their valuable support.

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Acknowledgement

I feel privileged to put down a few words of appreciation for the admirable work of developing this Clinical Protocol a milestone step in addressing and managing the Non-Communicable disease in Nepal.

Non-communicable disease (NCDs) are also known as long-standing chronic disease usually of noninfectious origin and is a result of a combination of genetic, behavioral, physiological, and environmental factor. The non-communicable disease mainly includes cardiovascular disease (CVDs like Heart attack, Stroke) Diabetes, Cancer, and chronic respiratory disease (COPD and Bronchial asthma). Behavior like Tobacco use, alcohol consumption, an unhealthy diet like less amount of fruits and vegetables and high consumption of increased trans-fat, high salt, and absence of physical activity are some of the modifiable risk factors and conditions like obesity. NCDs threaten progress toward the 2030 agenda for Sustainable Development, which includes a target of reducing the probability of death from any of the four main NCDs between the ages 30 and 70 years by one-third by 2030.

Non-communicable Diseases (NCDs) are leading public health challenges globally in the 21st century, resulting in ill health, economic loss, diminished quality of life, and poor social development equally in both high-resourced and low-resourced countries. These low-resourced countries like Nepal though have made a concerted effort to improve the health status of its citizens, particularly regarding preventing and treating infectious communicable diseases, such as HIV/AIDS, Tuberculosis. However, little attention is devoted to preventing and treating NCDs in these countries, resulting in an increased burden of such conditions on an individual, communities, and healthcare systems. Despite the growing evidence of NCD in these populations, we are only focused on the treatment of specific diseases on an individual patient basis. The worrying part is that our health care system is not well equipped to tackle this situation and address the disease as a whole on a preventive basis.

I would like to express my sincere gratitude to Kathmandu Institute of Child Health (KIOCH) for initiating and implementing the PEN-Plus and also would like to thank NCDI Poverty Network Secretariat at the Center for integration science, Brigham and Women's Hospital, Boston, USA, and UNICEF for providing the initial funding. Similarly, I would like to acknowledge the efforts of all consultants involved in the development of the PEN-Plus protocol. I would also like to appreciate and thank all the contributors to the PEN-Plus, including NCD and Mental Health section of EDCD, Dr. Phanindra Prasad Baral, Anil KC, Tekraj DC, Ramji Ghimire, Garima Bista, Tirthraj Acharya, Swastika Budhathoki and other staff of EDCD, and NHTC for their valuable support.

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Acknowledgement

I am writing to express my sincere gratitude to everyone involved in the development of the PEN Plus Clinical Protocol. The PEN-Plus Clinical Protocol is a comprehensive set of guidelines for the management of a wide range of non-communicable diseases (NCDs), including respiratory diseases, cardiovascular diseases, hemoglobinopathies, cancer, diabetes mellitus, and neurodevelopmental disorders. The protocol is based on the latest evidence and best practices, and it has been developed in collaboration with experts from Nepal and around the world.

The PEN-Plus Clinical Protocol will be used by healthcare providers at first-level referral hospitals in Nepal. The protocol will help these providers to provide high-quality care to patients with NCDs, and it will help to improve the health outcomes of these patients. PEN Program has been running all over the country for the management of the 4 X 4 NCD conditions in Nepal. However, we still have not fully met the demand for care for the mostly uncommon but severe non-communicable diseases (NCDs), which can place a significant financial burden on families if they are not detected and treated early. This protocol will be a valuable resource for healthcare providers in Nepal, and it will help to strengthen the chronic and severe NCDs care that is provided at district-level hospitals in Nepal. I hope this protocol will surely support in making a real difference in the lives of people in Nepal.

I would like to thank the members of the Epidemiology and Disease Control Division, for leading the PEN-Plus Program and for their implementation support. I would also like to express my sincere gratitude to all the members of the Steering Committee, Coordination Committee, and Technical working committee for their guidance and support in the PEN-Plus Program implementation. I am grateful for their patience, encouragement, and critical feedback. I appreciate the sincere efforts and contributions of all of the experts who were involved in the process of protocol development. I would like to thank the Kathmandu Institute of Child Health for implementing PEN-Plus Program in the selected district-level hospital in Nepal.

In addition, I would like to thank the funding agencies that supported this work, including the Brigham and Women's Hospital, USA and UNICEF. I am grateful for their financial and technical support, which made this program possible.

Sincerely,

.....

Dr. Phanindra Prasad Baral
Chief, Non-communicable Disease and Mental Health Section
Epidemiology and Disease Control Division
Department of Health and Services

ABBREVIATIONS

ABG	Arterial blood gas
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AFB	Acid-fast bacillus
AIDS	Acquired immuno deficiency syndrome
AR	Aortic regurgitation
ARB	Angiotensin receptor blocker
ARF	Acute rheumatic fever
AS	Aortic stenosis
ASO	Antistreptolysin 0 titre
BB	Beta blocker
BId	Twice a day
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAR	Central African Republic
CBC	Complete blood count
CBE	Clinical breast examination
CCB	Calcium channel blocker
CCTA	Cardiac CT angiography
CHD	Congenital heart disease
CK	Creatine kinase
CK-MB	Creatine kinase myocardial binding
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
CXR	Chest x-ray
DAPT	Dual anti-platelet therapy
DASH	Dietary approach to stop hypertension
DBP	Diastolic blood pressure
DEXA	Dual-energy x-ray absorptiometry
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DORV	Double outlet right ventricle
DPI	Dry powdered inhaler
DSM	Diabetic self-management
D-TGA	Dextro transposition of great arteries
ECG	Electrocardiogram
ECHO	Echocardiography
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESR	Erythrocyte sedimentation rate
FBS	Fasting blood sugar
FEV1	Forced expiratory volume in 1 second
FLACC	Face, Legs, Activity, Cry, Consolability

FRC	Functional Residual capacity
FVC	Forced vital capacity
G6PD	Glucose-6-phosphate dehydrogenase
GAS	Group A beta-hemolytic streptococcus
GLOBCAN	Global cancer observatory
GOLD	Global Initiative for lung disease
GRACE	Global registry of acute coronary events
HbA1c	Glycated hemoglobin
HBPM	Home blood pressure measurement
HCA	Heterocyclic amines
HDL	High density protein
HELLP	Hemolysis elevated liver enzyme low platelets
HFrEF	Heart failure with reduced ejection fraction
HHS	Hyperglycemic hyperosmolar state
HIV	Human immuno-deficiency virus
HPLC	High performance liquid chromatography
HPV	Human papilloma virus
HRCT	High resolution computed tomography
Hs-cTnT	High-sensitive cardiac troponin T
HTN	Hypertension
IARC	International Agency for Research on Cancer
ICS	Inhaled corticosteroid
IFG	Impaired fasting glucose
IGRA	Interferon-gamma release assay
IGT	Impaired glucose tolerance
INR	International normalized ratio
IV	Intravenous
JVP	Jugular venous pressure
LA	Left atrium
LABA	Long-acting beta-agonist
LADA	Latent autoimmune diabetes of adulthood
LAMA	Long-acting muscarinic agonist
LBBB	Left bundle branch block
LDL	Low-density lipoprotein
LFT	Liver function test
LMIC	Low- and middle-income countries
LMWH	Low molecular weight heparin
LTOT	Long-term oxygen therapy
LTRA	Leukotriene receptor antagonist
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MCV	Mean corpuscular volume
MDI	Metered dose inhaler
MI	Myocardial infarction
Mmrc	Modified medical research council
MODY	Maturity onset diabetes of young
MR	Mitral regurgitation
NABG	N-acetyl-β-d-glucosamine
NCD	Non-communicable disease
NDDs	Neurodevelopmental disorders
NHFTR	Febrile non-hemolytic transfusion reaction

NPO	Nil per oral
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drug
NSTEMI	Non-ST elevated myocardial infarction
NTDT	Non transfusion dependent thalassemia
NYHA	New york heart association
OD	Once daily
OHA	Oral hypoglycemic agent
OSA	Obstructive sleep apnoea
PAH	Polycyclic aromatic hydrocarbons
PBS	Peripheral blood smear
PCI	Percutaneous coronary intervention
PDA	Patent ductus arteriosus
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PEN	Package of essential non-communicable disease
Pmdi	Pressurized metered dose inhaler
PND	Paroxysmal nocturnal dyspnea
PO	Per oral
PPBS	Post-prandial blood sugar
PPD	Purified protein derivatives
PRP	Platelet-rich plasma
PTMC	Percutaneous transluminal mitral commissurotomy
QID	Four times a day
RAAS	Renin angiotensin aldosterone system
RBBB	Right bundle branch block
RF	Rheumatic fever
RFT	Renal function test
RHD	Rheumatic heart disease
RME	Routine microscopic examination
RR	Respiratory rate
SABA	short-acting bronchial agonist
SARS	Severe acute respiratory syndrome
SBP	Systolic blood pressure
SCD	Sickle cell disease
SIHD	Stable ischemic heart disease
SMART	Single maintenance and reliever therapy
STEMI	ST-elevation myocardial infarction
SVA	Single visit approach
TAPVC	Total anomalous pulmonary venous connection
Tdap	Tetanus diphtheria and acellular pertussis
TDT	Transfusion dependent thalassemia
TMT	Treadmill test
TOD	Target organ damage
TOF	Tetralogy of Fallot
URTI	Upper respiratory tract infection
UTI	Urinary tract infection
VIA	Visual inspection with acetic acid
VUR	Vesicoureteral reflux
WC	Waist circumference

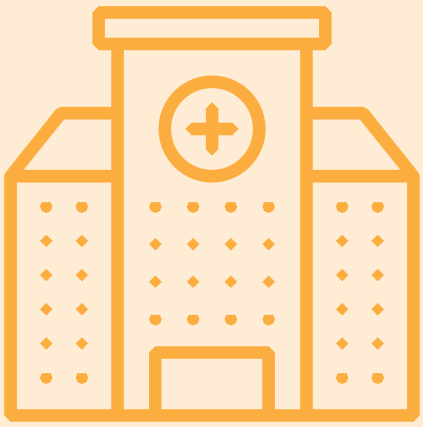
TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER-1

BACKGROUND AND INTRODUCTION



1.1 Introduction to PEN-Plus

PEN-Plus is a strategic approach designed to complement the Package of Essential Non-Communicable Diseases (PEN) in low and middle-income countries that are home to more than 90 percent. "PEN-Plus" approaches are built upon the World Health Organization's Package of Essential Non-communicable Disease Interventions (WHO PEN). PEN-Plus complements the WHO PEN, which provides basic NCDs service for common and less severe cardiovascular diseases (CVD), Diabetes Mellitus, Chronic respiratory disease and cancer at the health centers in Nepal.

PEN-Plus is an integrated care delivery model focused on alleviating the non-communicable diseases (NCDs) burden by increasing the accessibility and quality of severe and chronic NCD care at first-level referral hospitals. It incorporates integrated care teams to provide chronic care for below listed severe NCDs at first-level referral hospitals:

- Type I and Type II Diabetes Mellitus (DM)
- Rheumatic Heart Disease (RHD), Congenital Heart Disease (CHDs), Ischemic Heart Disease
- Chronic Respiratory Disease (CRDs)-asthma, COPD
- Hemoglobinopathies- Sickle Cell Disease (SCD),Thalassemia
- Cervical Cancer, Breast Cancer, Childhood Cancer.
- Neurodevelopmental disorders- Intellectual Disability, Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, and Epilepsy

In many low and middle-income countries, chronic care services for these severe conditions are only available at referral hospitals in major cities, making treatment both inaccessible and unaffordable for the poor. As a result, many poor children and young adults go without treatment for severe conditions that almost always lead to premature death if left untreated.

PEN-Plus addresses this service gap by bringing lifesaving chronic care for severe NCDs to first-level hospitals. PEN-Plus trains healthcare providers such as clinical officers and nurses in the skills needed to provide integrated chronic care services for a group of severe NCDs, including diagnosis, symptom management, psychosocial support, palliative care, and referral for surgical and other specialty care when necessary. PEN-Plus providers receive training and mentorship from specialists at referral hospitals.

An integrated health service delivery system with PEN-Plus at the first-level referral hospitals is also expected to reduce the caseload at referral hospitals in Nepal. This endeavor holds significant potential to transform the discourse on non-communicable disease (NCD) service delivery in Nepal, contributing towards the achievement of Universal Health Coverage (UHC) and Sustainable Development Goals (SDGs). Furthermore, it can serve as a pivotal cornerstone in establishing a decentralized NCD delivery system, with the potential for a national scale-up.

1.2 PEN-Plus Clinical Protocol

PEN-Plus Clinical protocol provides a guide to diagnose, manage and refer the identified severe and chronic NCDs at first-level referral/ district hospital of Nepal. As such the protocol is designed to represent therapeutically effective and economically efficient approaches for mid-level healthcare workers at district-level hospitals in Nepal. When implemented effectively, PEN-Plus clinical protocol offers the advantage to patients (e.g., it brings the health care services for severe and chronic NCDs closer to their home, provides more consistency, treatment and referral efficacy), providers(e.g. it gives expert consensus, quality of care standard and basis for monitoring), and health policy makers (e. g., it provides a focus for the therapeutic integration of special programs and promotes the efficient use of funds and addresses inequality in less common and more severe NCDs).

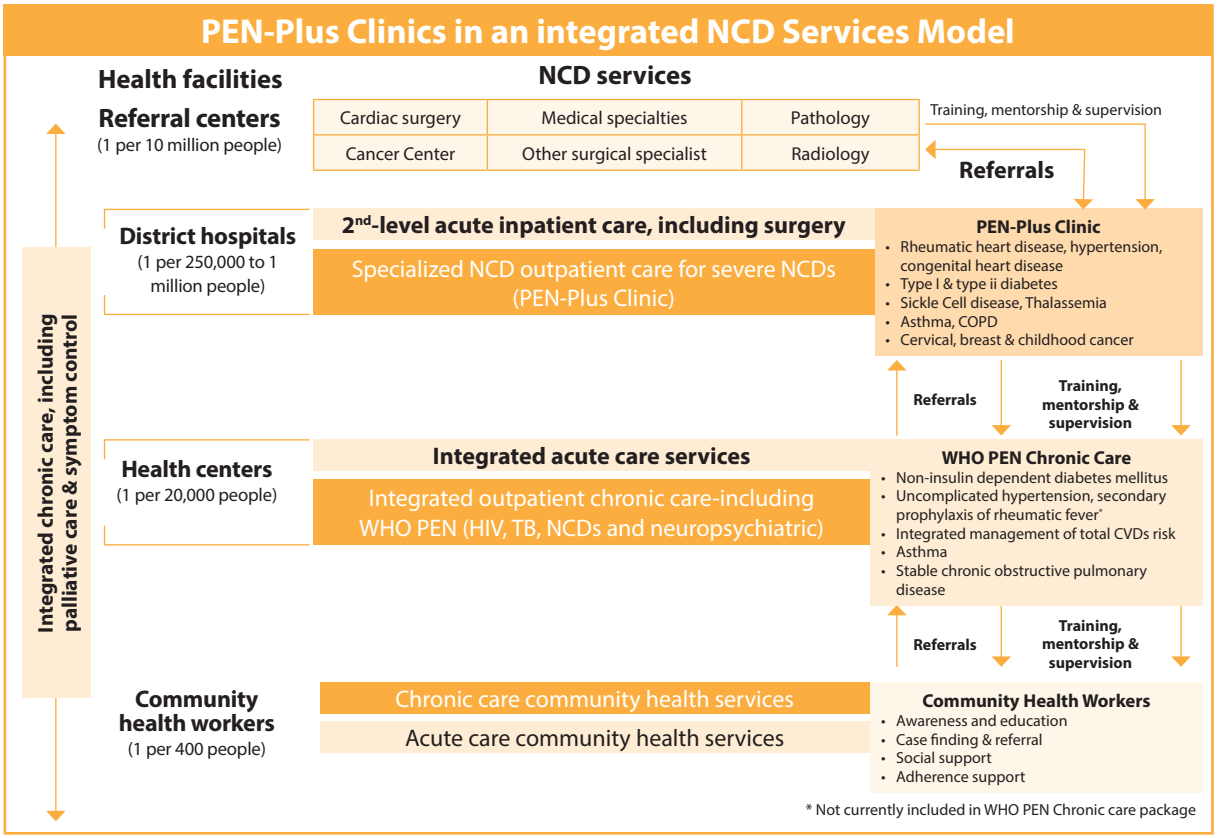


Figure 1: PEN-Plus Clinics in an integrated NCD Service Model

1.3 Development process of the PEN-Plus Clinical Protocol

The PEN-Plus Clinical Protocol is developed through a series of meetings and workshops, which were then improvised and completed through rigorous and extensive conversations with multiple stakeholders at various stages:

Step 1:	A meeting of the Steering Committee was conducted to identify experts in the field of the PEN-Plus prioritized diseases through the Steering Committee of the PEN-Plus Program, chaired by the Secretary of MoHP. These experts were hired as consultants according to their area of expertise and the first draft of the PEN-Plus protocol was developed by those consultants (Participants listed in Annex 1)
Step 2:	A Consultative workshop with experts of different PEN-Plus prioritized conditions and the identified consultants who developed the PEN-Plus protocol was conducted. In the workshop, discussion was carried out on the prepared first draft. Vital feedback and suggestions were provided by all the participants of the workshop. (Participants listed in Annex 7)
Step 3:	A Consultative review workshop with identified trainers from three the selected referral hospitals and identified consultants working on the protocol was conducted to review in the Protocol. The workshop also included other distinguished stakeholders for review and feedback. (Participants listed in Annex 6)
Step 4:	Series of meetings for approval of the PEN-Plus Clinical protocol was carried out with the Technical Working Committee, (Participants listed in Annex 3), Coordination Committee (Participants listed in Annex 2), and Steering Committee of PEN-Plus. (Participants listed in Annex 1)
Step 5:	A Consultative meeting was conducted to discuss the first draft of the PEN-Plus Clinical protocol with the Epidemiology and Disease Control Division, Curative Service Division, National Health Training Center and subject experts for feedback and endorsement.

1.4 Utilization of the PEN-Plus Protocol

The guidelines provided in this clinical protocol will be useful for all clinicians including doctors and nurses from the first-level referral hospital of Nepal. Here, the first-level hospital refers to the hospital comprising 25-50 beds and has sufficient resources to receive emergent as well non-emergent patient transfers and referrals from primary health care centers. The protocol would be resourceful to:

- Support the management of severe and chronic NCDs using enlisted standard treatment protocols for PEN-Plus prioritized diseases in the first-level referral hospitals in Nepal.
- Ensure that all the necessary equipment and resources are available at the implementation sites.

The protocol is proposed to be used at the following level of health service as endorsed in Public Health Service Regulation, 2020 by the Government of Nepal:

- General Hospitals (25-50 bedded hospitals)

Assumptions made for the implementation of the PEN-Plus

1. The minimum necessary infrastructure and human resources with adequate skill will be available to provide the service.
2. A dedicated PEN-Plus Clinic/OPD should be run by the first-level referral hospital for PEN-Plus prioritized NCD conditions and patients referred from PEN clinics.
3. Ensure the supply chain is functional and maintained at the hospitals.
4. Institutions with operational/ implementation plans will be developed to implement the PEN-Plus program.
5. The PEN-Plus training is provided to the healthcare workers.
6. Each PEN-Plus implementing hospital will provide timely health care for severe and chronic NCDs prioritized by PEN-Plus based on the PEN-Plus Protocol.

How to use the PEN-Plus Clinical Protocol

The management of severe and chronic NCDs has been elaborated in this protocol using tables, figures and flowcharts, and the diseases are grouped as follows:

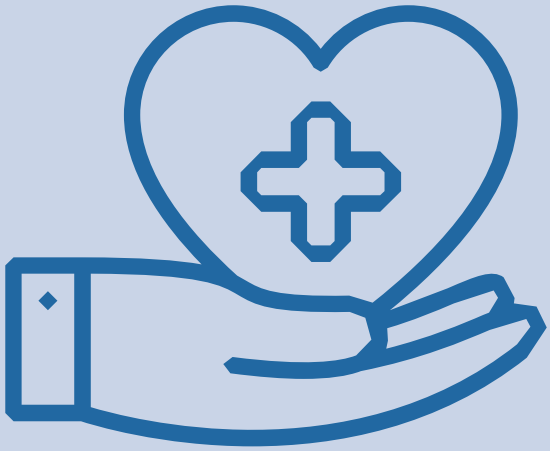
1. Respiratory diseases: Asthma and COPD
2. Cardiovascular diseases: Hypertension, Acute rheumatic fever, rheumatic heart disease, Ischemic Heart Diseases, Acute Coronary Syndrome (ACS), Congenital heart defect
3. Hemoglobinopathies: Sickle cell Disease, Thalassemia
4. Cancer: Childhood Cancer, Breast Cancer, Oral Cancer, Cervical Cancer
5. Diabetes: Type I and Type II Diabetes Mellitus
6. Neurodevelopmental disorders: Intellectual Disability, Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, and Epilepsy

The protocol includes an introduction, etiopathogenesis, signs and symptoms, diagnosis, treatment algorithm, management protocol for complications, and referral chain for the diseases mentioned above. Competencies of the healthcare providers, and availability of resources including appropriate human resources, diagnostics, medications, and equipment present in the healthcare facility are crucial for the effectiveness of the PEN-Plus training.

The bibliography and list of participants of the various consultative meetings are provided in the annexes.

CHAPTER-2

ESSENTIAL CARE & PRACTICES



2.1 ESSENTIAL CARE AND PRACTICES

This module outlines the principles of essential care for addressing all the PEN Plus conditions in the community, including those in Child and Adolescent (C&A), the healthcare professionals and nurses at healthcare facilities, and the carers of C&A.

The first part of this module covers the general principles of clinical care and aims to promote respect for the privacy of patients seeking care for various health conditions, foster good relationships between healthcare professionals, patients, and their carers; and ensure care is provided in a non-judgmental, non-stigmatizing, and supportive manner. The second part covers the essentials of clinical practice. The third part covers the Psychosocial interventions.

In this chapter, we will discuss the general principles and approaches relevant to the management of all health conditions included in PEN Plus, and those principles relevant specifically to mental health or neurodevelopmental disorders (NDDs) as well.

2.1.1 General Principles

I. **Use Effective Communication Skills:** Using effective communication skills allows healthcare professionals to deliver good quality care to patients with health conditions. Consider the following core communication skills and tips:

Ia) Communication Tip

Create an environment that facilitates open communication

- Meet the patients in a private space, if possible.
- While interviewing young children, consider play as a medium and focus on informal assessment methods.
- Be welcoming and conduct introductions in a culturally appropriate manner.
- Maintain eye contact and use body language and facial expressions that facilitate trust.
- Explain that information discussed during the visit will be kept confidential and will not be shared without prior permission.
- If carers are present, suggest speaking with the patient alone (except for young children), if the patient is a young female then arrange for a female staff during the interview and obtain consent to share clinical information.

Ib) Communication Tip

Involve the patient

- Include the patient (and with their assent, their carers, and family) in all aspects of assessment and management as much as possible.

Ic) Communication Tip

Start by listening

- Actively listen. Be empathic and sensitive.
- Allow the patient to speak without interruption.
- If the history is unclear, ask for clarification with the carer if available, or else schedule another appointment with the carer.
- For children, use language that they can understand. For example, ask about their interests

(toys, friends, school, etc.).
- For adolescents, convey that you understand their feelings and situation.

Id) Communication Tip

Be friendly, respectful, and non-judgmental at all times
- Always be respectful.
- Don't judge patients by their behaviors and appearance.
- Stay calm and patient.

Ie) Communication Tip

Use good verbal communication skills
- Use simple language. Be clear and concise.
- Use open-ended questions, summarizing, and clarifying statements.
- Summarize and repeat key points.
- Allow the patient to ask questions about the information provided.

If) Communication Tip

Respond with sensitivity when patients disclose difficult experiences (e.g. physical/ sexual abuse, violence, or self-harm)
- Show extra sensitivity to difficult topics.
- Remind the patients that what they tell you will remain confidential.
- Acknowledge that it may have been difficult for the patients to disclose the information.

II. **Promote Respect and Dignity:** Patients with health conditions should be treated with respect and dignity in a culturally appropriate manner. As a health professional, make every effort to respect and promote the will and preference of patients, and support and engage them and their carers most inclusively. C&A with health conditions are often more vulnerable to human rights violations. Therefore, it is essential that in the healthcare facility setting, providers promote the rights of C&A with health conditions in line with international human rights standards, including the UN Convention on the Rights of Persons with Disability (CRPD).

DOs
- Treat patients with respect and dignity.
- Protect the confidentiality of patients.
- Ensure privacy in the clinical setting.
- Always provide access to information and explain the management process and treatment options.
- Make sure the patient provides assent to treatment.
- Promote autonomy and independent living.
- Provide C&As with health conditions with access to supported decision-making options.

DON'Ts

- Do not discriminate against patients with health conditions.
- Do not ignore the priorities or wishes of patients.
- Do not make decisions for, on behalf of, or instead of the C&A with health conditions, without their informed assent.
- Do not use overly technical language in explaining the proposed treatment

2.1.2 Essentials of Clinical Practice

I. Assess Physical Health

Patient must always receive a physical health assessment as part of a comprehensive evaluation. Be sure to take a proper clinical history, followed by a physical health assessment to identify concurrent conditions. These actions must always be undertaken with the patient's informed consent and C&A's informed assent.

Assessment of Physical Health

- Take a detailed history and ask about risk factors.
  - Presenting complaint, Birth and Developmental history, School and academic history (more relevant for children and adolescent with neurodevelopmental disorders), family history, personal history (including sexual history and substance use history), social history, and details of emotional and behavioral problems if any. Inquire specifically about suicide and self-harm.
- Perform a general physical examination and systemic examination.
- Consider a differential diagnosis.
- Identify comorbidities.
  - Often, a patient may have more than one physical/ mental health condition at the same time. It is important to assess and manage this when it occurs.

II. Assess Mental Health

Perform a mental state examination where necessary

Mental Status Examination adapted for non-specialists may include:

- Behavior and Appearance: Symptoms and signs involving the way a patient looks or acts;
- Mood and Affect: Symptoms and signs involving the regulation and expression of emotions or feeling states;
- Content of Thought: Symptoms and signs involving the subject matter of thoughts including delusions, paranoia, suspiciousness, and suicidal ideation;
- Perceptual Disturbance: Sensory perceptions occurring in the absence of the appropriate (external) stimulus (e.g. auditory or visual hallucinations). The patient may or may not have insight into the unreal nature of the perception;
- Cognition: Symptoms, signs, and clinical findings are indicative of a disturbance in mental abilities and processes related to attention, memory, judgment, reasoning, problem-solving, decision-making, comprehension, and the integration of these functions.

III. Management of Physical Health

- Take a detailed clinical history, and perform a general physical and systemic examination. Send relevant investigations as per availability and need.
- Manage the physical health condition following respective sections in the manual.

- Refer to a higher center for treatment of existing comorbidities, whenever necessary.
- Provide education on modifiable risk factors to prevent disease and encourage a healthy lifestyle.
- To support the physical health of patient, the healthcare professional should- Provide advice about the importance of physical activity and a healthy diet.
- Educate patient about the harmful effects of substance use. Encourage cessation of substance use.
- Provide education about other risky behavior (e.g. unprotected sex).
- Conduct regular physical health checks and vaccinations.
- Prepare children for developmental life changes, such as puberty, and provide the necessary support.
- Discuss contraception methods with adolescents.

Management Planning

- Discuss and determine treatment goals that respect the will and preferences for care.
- Involve the carer, after obtaining the patient's consent and C&A's assent.
- Encourage self-monitoring of symptoms and explain when to seek help urgently.

2.1.3 Psychosocial Interventions

I. Psychoeducation

Provide information about the health condition to the patients, including:

- What the condition is and its expected course and outcome
- Available treatments for the condition and their expected benefits- possible intervention and need for medications.
- Importance of adhering to treatment, including what the patients can do (e.g. taking medication or other relevant measures), and what carers can do to help the C&A adhere to treatment.
- Potential involvement of social workers, community health workers, or other trusted members in the community/ family.
- Potential side-effects (short and long term) of any prescribed medication that the patient, C&A (and their caregivers) need to monitor.
- Refer to relevant sections of the manual for specific information on management of the various health conditions.

II. Reduce Stress and Strengthen Psychosocial Support

a) First-Level Response to Patients

The first Level Response means the response given to patients in the first interaction with the service provider. How well this response is given determines the establishment of rapport, and the formation of a base upon which further evaluation, intervention, and assistance can be built. Following the following steps can ensure that the patients receive a first-level response that puts them at ease and helps to engage them further in the assessment and management protocols.

b) Ventilation

Ventilation means the expression of thoughts, feelings, emotions, and concerns that the patients may have. Allow the patient to express their feelings, emotions, thoughts, and concerns. Encourage them to say more and do not interrupt them. Do not force them to say anything if they don't want to. Mention that this is a safe space where their concerns are respected and privacy will be maintained. Consider having a female attendant when interviewing a female patient, girl child, or adolescent, also a child may be interviewed in the presence of a parent or trusted adult so that they are more comfortable.

c) Acknowledge and validate their thoughts, feeling and concerns

- Acknowledge the thoughts, feelings, and concerns that have been mentioned. This can be done by paraphrasing or rephrasing their concerns verbatim, back to the patients. This ensures the patient that their concerns have been paid attention to and noted. E.g. if a child says "I feel scared because of COVID-19 and I also get frequent headaches", you could respond by saying, "Oh I see, you are saying that you feel afraid because of COVID-19 and I also have frequent headaches, can you tell me more?"
- Universalize by stating that "similar things have been felt by patients all over the world, and that it is okay to be feeling these things because it is a difficult time for them, they are not alone".
- Validate their thoughts, feelings, and concerns as being important and thank them for sharing. You can say, "All these things you have shared with me are very important, and I can understand that you are very concerned by these difficulties."
- Empathize with the patient; mention that anyone in this situation would be feeling similar things and that we understand their concerns. Try to see things by "being in their shoes". Praise the patients for sharing their thoughts and feelings. You could say "Anyone in this situation would be having similar difficulties just like you, in your situation, I could also be feeling that way. I could try to understand more about what you are going through."

Note that if the patient is being engaged in a group, some concerns expressed can be similar and some can be different. Emphasize the importance of identifying and respecting these similarities and differences among themselves. This can help them to be supportive of one another.

d) Address current psychosocial stressors:

- Identify and discuss relevant psychosocial issues that place stress on patient and/or impact their life including, but not limited to, family and relationship problems, school and academic issues (more relevant to C&A), socioeconomic status, access to basic security/ services, stigma, discrimination, etc.
- Assess and manage any situation of maltreatment, abuse, and neglect. Discuss with the patient possible referrals to a trusted protection agency or informal protection network. In the case of C& A, inform the carers to contact legal and community resources, as appropriate.
- Identify supportive family members and involve them as much as possible and appropriate.
- Strengthen social supports and try to reactivate the patient's social networks.
- Identify prior social activities that, if reinitiated, would have the potential for providing direct or indirect psycho-social support (e.g. play & sports, recreation, peer relationships, family gatherings, visiting neighbors, community activities, religious activities, etc.).
- Teach stress management such as relaxation techniques.

III. Promote Functioning in Daily Activities

- Provide the patient support to continue regular social, educational, and occupational activities as much as possible
- Facilitate inclusion in developmentally appropriate activities.
- Life skills training, and /or social skills training if needed.

IV. Guidance to promote C&A's well-being and functioning

Clinical Tip:

- Can be provided to all patients and carers even if no disorder is suspected.
- Guidance for improving behaviour can be provided to all carers who are having difficulty with their child/adolescent's behaviour even if a behavioural disorder is not suspected.

a) Encourage the Carer to:

- Spend time with the C&A in enjoyable activities. Play and communicate with their C&A
- Listen to the C&A and show understanding and respect.
- Protect them from any form of maltreatment, including bullying and exposure to violence in the home, at school, and in the community.
- Anticipate major life changes (such as puberty, starting school, or the birth of a sibling) and provide support

b) Encourage and help the C&A to:

- Get enough sleep. Promote regular bed routines and remove TV or other electronic devices with screens from the sleeping area/bedroom
- Eat regularly. All patients need three meals (breakfast, mid-day, and evening) and some snacks each day.
- Be physically active. If they are able, C&A aged 5–17 should do 60 minutes or more of physical activity each day through daily activities, play, or sports.
- Participate in school, community, and other social activities as much as possible.
- Spend time with trusted friends and family.
- Avoid the use of drugs, alcohol, and nicotine.

c) Encourage the Teachers, and school staff to:

- Provide a non-judgmental, non-critical, and supportive environment in school.
- Support the C&A with academic activities.
- Assist gradual reentry to school and continuation of school routine.
- Encourage regular communication and collaboration between teachers, the school system, C&A, and carers.

V. Psychoeducation to patients, carers, and parenting advice in case of C & A

- Explain the health condition to the carer and the patients as appropriate and help them identify strengths and resources.
- Praise the carer and the patients for their efforts.
- Explain to the carer that parenting a C&A with a health condition can be rewarding but also very challenging.
- Explain that patients should not be blamed for having the conditions.
- Encourage carers to be kind and supportive and show love and affection.
- Promote and protect the human rights of the patients and their families and be vigilant about maintaining human rights and dignity.
- Help carers to have realistic expectations and encourage them to contact other carers of patients with similar conditions for mutual support.

VI. Guidance for improving behavior

Encourage the Carer to:

- Give loving attention, including playing with the child every day.
- Provide opportunities for the adolescents to talk to you.
- Be consistent about what your C&A is allowed and not allowed to do. Give clear, simple, and short instructions on what the child should and should not do
- Give the C&A simple daily household tasks to do that match their ability level and praise them immediately after they do the task
- Praise or reward the C&A when you observe good behavior and give no reward when behavior is problematic.
- Find ways to avoid severe confrontations or foreseeable difficult situations.
- Respond only to the most important problem behaviors and make punishment mild (e.g. withholding rewards and fun activities) and infrequent compared to the amount of praise)
- Put off discussions with the C&A until you are calm. Avoid using criticism, yelling, and name-calling.
- DO NOT use threats or physical punishment, and never physically abuse the C&A. Physical punishment can harm the child-carer relationship; it does not work as well as other methods and can make behavior problems worse.
- Encourage age-appropriate play (e.g. sports, drawing, or other hobbies) for adolescents and offer age-appropriate support in practical ways (e.g. with homework or other life skills).

VII. Psychoeducation for Neurodevelopmental Disorders

Encourage the Carer to:

- Learn what the C&A's strengths and weaknesses are and how they learn best, what is stressful to the C&A and what makes him/her happy, and what causes problem behaviors and what prevents them.
- Learn how the C&A communicates and responds (using words, gestures, non-verbal expressions, and behaviors).
- Help the C&A develop by engaging with her/him in everyday activities and play.
- C&A learns best during activities that are fun and positive
- Involve them in everyday life, starting with simple tasks, one at a time. Break complex activities down into simple steps so that the C&A can learn and be rewarded one step at a time
- Make predictable daily routines by scheduling regular times for eating, playing, learning, and sleeping.
- Keep their environment stimulating: avoid leaving the C&A alone for hours without someone to talk to and limit time spent watching TV and playing electronic games.
- Keep them in the school setting for as long as possible, attending mainstream schools even if only part-time.
- Use balanced discipline. When the C&A does something good, offer a reward. Distract the C&A from things they should not do.
- DO NOT use threats or physical punishments when the behavior is problematic.
- C&A with developmental disorders may often have associated behavioral problems that are difficult for the carer to manage. See guidance for improving behaviors.
- Promote and protect the human rights of the person and family and be vigilant about maintaining human rights and dignity.
    - Educate carers to avoid institutionalization.
    - Promote access to health information and services.

- Promote access to schooling and other forms of education.
- Promote access to occupations.
- Promote participation in family and community life.

Carer Support

- Assess the psychosocial impact of the patient's health conditions on the carers, and offer support for their personal, social, and mental health needs
- Promote necessary support and resources for their family life, employment, social activities, and health.
- Arrange for respite care (trustworthy carers taking over care on a short-term basis) to give primary carers a break.
- Support the family to handle social and familial problems and help to problem solve.

VIII. Liaise With Teachers And Other School Staff

- After getting assent from C&A and consent from the carer, collaborate with school teachers and provide advice/ make a plan on how to support the C&A with learning and participation in school activities.
- Explain that the C&A's health condition is affecting their learning/behavior/ social functioning and that there are things the teacher can do to help
- Ask about any stressful situations that may hurt the C&A's emotional well-being and learning. If the child is being bullied, advise the teacher on the appropriate action to stop it.
- Explore strategies to help engage the C&A in school activities and facilitate learning, inclusion, and participation.
- It is important to emphasize that provision of a supportive, non-critical, and non-judgemental environment in the school is important to support any C&A with any health conditions, and ensuring this environment in school also ensures the promotion of the health of all C&A in school.

Practical tips that can be applied in Schools to support C&A with CAMH problems:

- Provide opportunities for the child/adolescent to use their skills and strengths.
- For C&A who get distracted easily,
  - Ask them to sit at the front of the class.
  - Give the student extra time to understand and complete assignments.
  - Divide long assignments into smaller pieces and assign one piece at a time.
  - Provide extra praise for effort and rewards for achievements.
- DO NOT use threats or physical punishments or excessive criticism.
- For students with significant difficulties in the classroom,
  - Recruit a volunteer to come to class to provide one-on-one attention or pair the student with a peer who can provide support or help with learning.
- If the child/adolescent has been out of school,
  - Help them return as soon as possible by creating a gradually increasing reintegration schedule.
  - During the reintegration period, the student should be excused from quizzes and exams.
  - For C&A with behavioral problems,
    - Refer to the guidance for improving behavior.
    - DO NOT use threats or physical punishments or excessive criticism.

IX. Pharmacological Treatment

- Follow the guidelines on psychopharmacology in each module.
- Use pharmacological interventions when available and when indicated in the management algorithm and table provided.
- In selecting an appropriate essential medication, consider the side effect profile of the medication (short and long term), the efficacy of past treatment, drug-drug interactions, or drug-disease interactions.
- Consult the National Formulary or the WHO Formulary as needed.
- Educate the patient and carers about the risks and benefits of treatment, potential side effects, duration of treatment, and importance of adherence.
- Exercise caution when providing medication to high-risk patients, C&A, and pregnant. Refer to the higher center or consult a specialist as needed.

X. Referral to Higher Centre

If any health condition is detected in the patient and improvement is not seen in the initial treatment and intervention, a referral should be made to a higher center for further evaluation and management. This also includes patients with significant physical or mental health-related comorbidities.

XI. Follow-up

- Arrange a follow-up visit after the initial assessment.
- After every visit, schedule a follow-up appointment and encourage attendance. Schedule the appointment at a mutually convenient time.
- Schedule initial follow-up visits more frequently until the symptoms begin to respond to treatment. Once symptoms start improving, schedule less frequent but regular appointments.
- At each follow-up meeting, assess for:
  - Response to treatment, medication side-effects, and adherence to medications and psychosocial interventions.
  - General health status (be sure to monitor physical health status regularly).
  - Self-care (e.g. diet, hygiene, clothing) and functioning in the patient's environment.
  - Psychosocial issues and/or changes in living conditions that can affect management.
  - The patient's and the carer's understanding and expectations of the treatment. Correct any misconceptions.
- During the entire follow-up period:
  - Acknowledge all progress towards the treatment goals and reinforce adherence.
  - Maintain regular contact with the patient and their carer. If available, assign a trusted person in the community to support the patient (such as a family member).
  - Explain that the patient, C&A and carer should return to the healthcare facilities at any time in between follow-up visits if needed (e.g. for side-effects of medications, etc).
  - Have a plan of action for when the patient does not show up for appointments.
  - In the case of C&A, ensure a supportive environment for regular school attendance. Use family and community resources to contact C&A who have been absent from school for long periods.
  - Document key aspects of interactions with the patient and the family in the case notes.
  - Refer to the management section of the relevant module(s) for health condition-specific follow-up information.

XII. Involving Carers

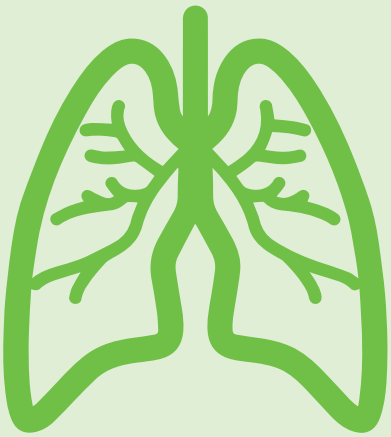
- When appropriate, and with the assent of the patient concerned, involve the carer or family member in the patient care.
- Acknowledge that it can be challenging to care for patients with various conditions.
- Explain to the carer the importance of respecting the dignity and rights of the patient with a health condition.
- Identify the psychosocial impact on carers.
- Assess the carer's needs to ensure necessary support and resources for family life, employment, social activities, and health.
- Encourage involvement in self-help and family support groups, where available.
- With the assent of the patient, keep carers informed about the patient's health status, including issues related to assessment, treatment, follow-up, and any potential side effects.

XIII. Link with Other Sectors

To ensure comprehensive care and based on the initial assessment, integrate the patient into health care services, social services, and other relevant sectors and C&A to school and education, peer relationships, play, and recreation.

CHAPTER-3

RESPIRATORY DISEASES



3.1. ASTHMA

Introduction

Bronchial asthma is a major non-communicable disease (NCD), affects both children and adults. Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and in intensity, together with variable expiratory airflow limitation. It is characterized by intermittent expiratory airflow obstruction. The estimated prevalence of asthma is 262 million people globally. The majority of the global burden of asthma lies in LMICs. In Nepal, the prevalence of asthma is 4.2-8.9%, and the majority of them are rural dwellers. Hence, identifying and managing patients with bronchial asthma at the primary and district healthcare levels is of utmost importance to reduce asthma-related morbidity and mortality.

Etiology

Table 1: Risk factors of bronchial asthma

Non-modifiable risk factor	Modifiable risk factor
Age: onset of asthma is more common in younger age group	Indoor allergens: house dust mites, animal proteins (mouse, cat and dog allergen, cockroaches and fungi
History of atopy	Tobacco smoke
Family history of asthma or atopy	Outdoor and indoor air pollution
Genetics	Respiratory viral infections
	Occupational dust (industrial) exposure
	Formula feed and cow milk in infancy
	Obesity

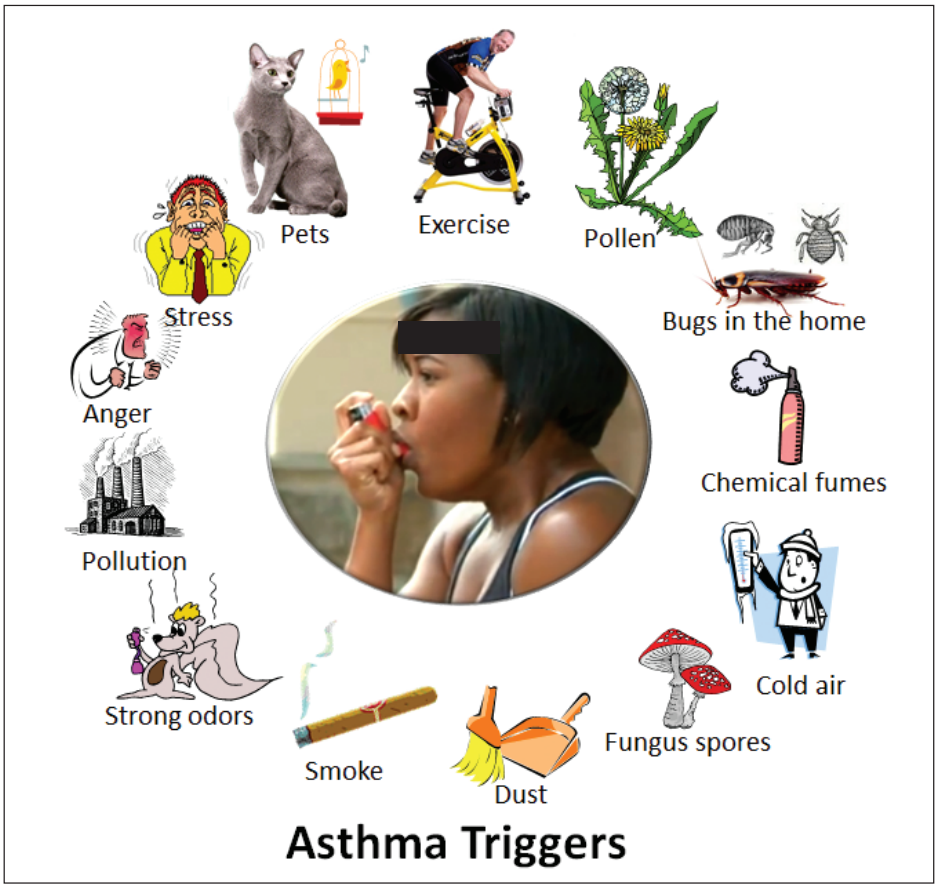


Figure 2: Triggers of bronchial asthma

Symptoms and signs

Symptoms:

- Intermittent shortness of breath
- Wheezing
- Cough
- Chest tightness

Patient may have combination of symptoms or individual symptoms like cough or wheezing. Symptoms aggravated on exposure to triggers as illustrated in Figure1.

Signs:

- May be normal
- Tachypnea
- Tachycardia
- Use of accessory respiratory muscle (Scalene, alae nasi, sternocleidomastoid)
- Bilateral polyphonic wheeze
- Cyanosis (severe case)
- Silent chest (severe case)
- Associated signs: atopy-urticaria, nasal polyp

Sign and Symptoms in severe bronchial asthma:

- Noisy breathing
- Chest tightness
- Breathlessness
- Cough
- Unable to complete sentences- speaks in words
- Stays hunched forward
- Agitated
- Respiratory rate >30/min (adult), >40/min (>1 year child), >50/min (2-12 months infant), > 60/min (<2 months infant)
- Use of accessory muscles
- Pulse rate >120 bpm
- Spo2 <90% on room air
- PEF < 50% of predicted or best
- Life-threatening: Drowsy, confused, or silent chest
- Alteration in sensorium

Diagnosis

Investigation

Pulmonary function test

Spirometry is a tool to evaluate the severity and reversibility of obstruction of the airway in a patient with suspected bronchial asthma. The results of spirometry are analyzed based on the FEV1/FVC ratio and the change in it after administration of a short-acting bronchodilator. FEV1/FVC less than 0.7 is suggestive of airway obstruction or lower limit of normal. Reversibility is checked by repeating spirometry after 10-15 minutes of administration of 2-4 puffs of MDI Salbutamol (100 ug/puff) via a spacer device. The bronchodilator response/ reversible airway obstruction is defined if improvement in FEV1 is >12% and >200 ml from the baseline.

Prerequisites for spirometry:

1. Patient should be stable
2. Withhold smoking for atleast 4 hrs prior to spirometry
3. Age >/= 5 yrs
4. Inhaler therapy should be withheld for 4 hrs
5. Patient should avoid exercise on the day of spirometry
6. No heavy meals prior to spirometry
7. Proper instructions to be given before procedure

Process of spirometry:

1. The patient sits up straight
2. Good seal around the mouthpiece
3. Rapidly inhale maximally
4. Blow out as hard and fast as possible
5. Continue exhaling till the patient can't blow
6. Expiration should continue for at least 6 seconds.
7. Repeat at least 3 technically acceptable times
8. Repeat the test after 10 to 15 minutes of administration of 2-4 puffs of salbutamol to check reversibility.

Peak expiratory flow meter

In low resource settings, the Peak expiratory flow meter is a useful tool to measure the airflow obstruction. It is portable and can be done easily. PEF measurements are also useful to monitor treatment response in patients with bronchial asthma.

Process of PEF measurement:

1. Connect a clean mouthpiece
2. Set the marker at ZERO
3. Stand up or sit upright
4. Take a deep breath and hold it.
5. Place the mouthpiece in your mouth and form a tight seal.
6. Breath as hard and as fast as possible
7. Observe and record recording
8. Repeat the process 3 times and record the highest
9. Interpret the result in the green zone (80-100%), Yellow zone (50-80%), and Red zone (less than 50%). When the patient measurement is in the green zone, it means the patient can do usual activities, yellow zones mean moderate symptoms and the red zone means a medical emergency.
10. PEFR value is not specific for asthma diagnoses, however,a change in PEFR by more than 20% after administration of salbutamol may suggest diagnosis of bronchial asthma.

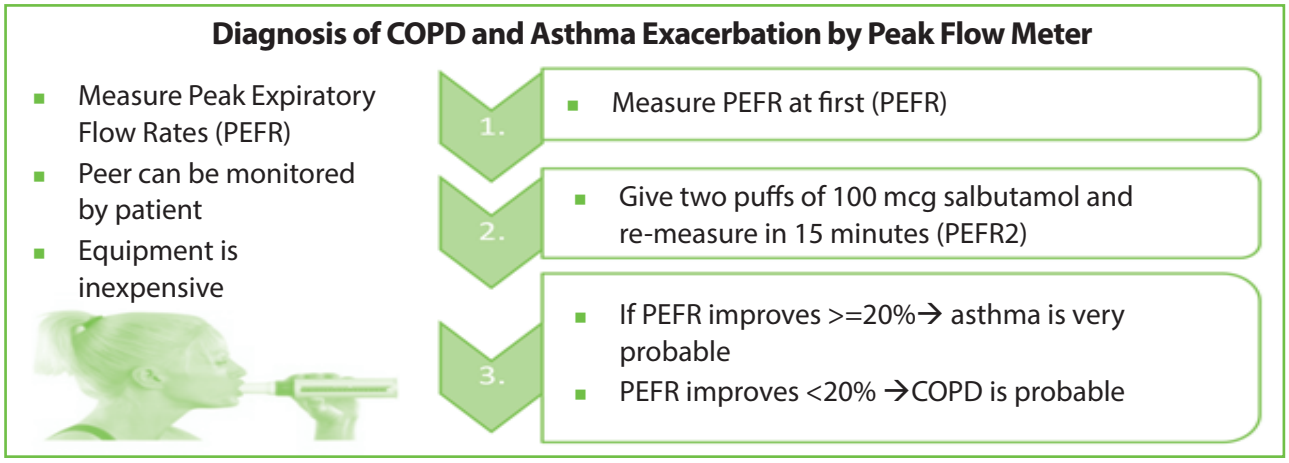


Figure 3: Using Peak Expiratory Flow meter to measure Peak Expiratory Flow Rate (PEFR) to diagnose bronchial asthma

Other tests

The presence of significant eosinophilia guides work-up further for eosinophilic pneumonia, parasitic infection, and allergic Broncho pulmonary aspergillosis. Chest X-ray in a patient with bronchial asthma are usually normal in the absence of other co-morbidities.

Diagnosis of bronchial asthma

1. Presence of cardinal symptoms of bronchial asthma (Shortness of breath, wheezing, cough, chest tightness). These symptoms are episodic or seasonal, variable over time, and usually worse during night and early morning.
2. Evidence of variable expiratory airflow limitation as demonstrated by spirometry and/or peak expiratory flow meter. Expiratory airflow can be normal when the patient is asymptomatic or present in between exacerbations. Thus, the diagnosis of bronchial asthma can be made solely on classical clinical findings after excluding asthma mimics as shown in Table 2. After the diagnosis of bronchial asthma, it should be classified according to its severity as shown in Table 3.

Table 2: Differential diagnoses of bronchial asthma (Asthma mimics)

ADULTS	CHILDREN	
	5-12 years	<5 years
COPD Heart failure Bronchiectasis Gastro-esophageal reflux disease Endo bronchial tuberculosis Major airway obstruction (tumor, infection, foreign body) Tropical eosinophilia	Tuberculosis Bronchiectasis Chronic rhino sinusitis Adenoidal hypertrophy Tropical eosinophilia Foreign body aspiration Cystic fibrosis Primary ciliary dyskinesia	Anatomic malformations e.g. tracheoesophageal fistula, tracheal compression, congenital heart diseases & tracheobronchomalacia Infections e.g. recurrent pneumonia, tuberculosis or pertussis Foreign body aspiration Gastro-esophageal reflux

Table 3: Classification of severity of bronchial asthma

Components	Classification of Asthma severity>12 years of age			
	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Symptoms	≤2days/week	>2 days/week but not daily	Daily	Continuous
Nighttime awakening	≤2 days/month	3-4/month	>1/Week but nightly	Nightly
Use of reliever medicine	≤2 days/week	> 2 days/week but not daily	Daily	Several times a day
Lung function	FEV1>80%	FEV1>80%	FEV1 60-80%	FEV1<60%

Management

The goals of asthma management are to control asthma symptoms, maintain normal daily activity, prevent asthma exacerbations, minimize the side effects of asthma medication, and avoid asthma-related death. The components of asthma management to achieve the targeted goals are

1. Patient Education
2. Monitoring the symptoms and changes in lung function of the patient
3. Controlling asthma triggers
4. Pharmacotherapy
5. Follow up visit

1. Patient Education

Educating patients and caregivers is a key component of asthma management. Healthcare providers should educate the patient regarding the disease, expected goals (asthma day symptoms ≤2 day/ week, night symptoms ≤1/month), ways to minimize the triggers (avoiding dust, smoke, fumes, cold weather), and methods of delivering medicine. Patient education is effective in minimizing emergency visits, asthma symptoms control, and hospital admission.

2. Monitoring the symptoms

Self-monitoring of asthma symptoms and lung function is a key aspect of asthma management. In this process, patients monitor asthma symptoms control, detect asthma exacerbation early and maintain PEFR records periodically. Physicians monitor the patient's symptoms control, review medication and further investigate the patient with poor asthma control. Proper monitoring of patient symptoms and lung function reduces the number of emergency visits, hospitalization, and lost time from school.

3. Controlling asthma triggers

The identification and avoidance of asthma triggers are important components of asthma management. Many triggers interact and influence the natural history of asthma. Doctors should meticulously ask patients about asthma triggers and advise them to avoid them. Controlling asthma triggers helps in asthma symptoms control and reduces the exacerbation of asthma.

4. Pharmacotherapy

The physician should be aware of the severity of the symptoms of the patient, frequency of use of reliever medications, lung function, and frequency of exacerbations while initiating pharmacotherapy in a patient with bronchial asthma. Stepwise treatment is recommended for a patient with bronchial asthma according to its severity (Table 3). Pharmacotherapy for asthma includes an inhaler steroid dose which depends upon the severity of the asthma. Table 4 illustrates the classification of strength of steroids the healthcare provider should teach the patient the proper technique of inhalation.

Single maintenance and reliever therapy (SMART therapy) as illustrated in Figure 3 is the mainstay of asthma treatment using a combination of formoterol and budesonide.

Step 1:	For intermittent asthma, low dose ICS + formoterol intermittently, as needed
Step 2:	For mild persistent asthma, low dose maintenance ICS + formoterol combination
Step 3:	For moderately persistent asthma, medium dose maintenance ICS + formoterol
Step 4:	For severely persistent asthma, High dose maintenance ICS + formoterol and long-acting muscarinic agonist (LAMA)

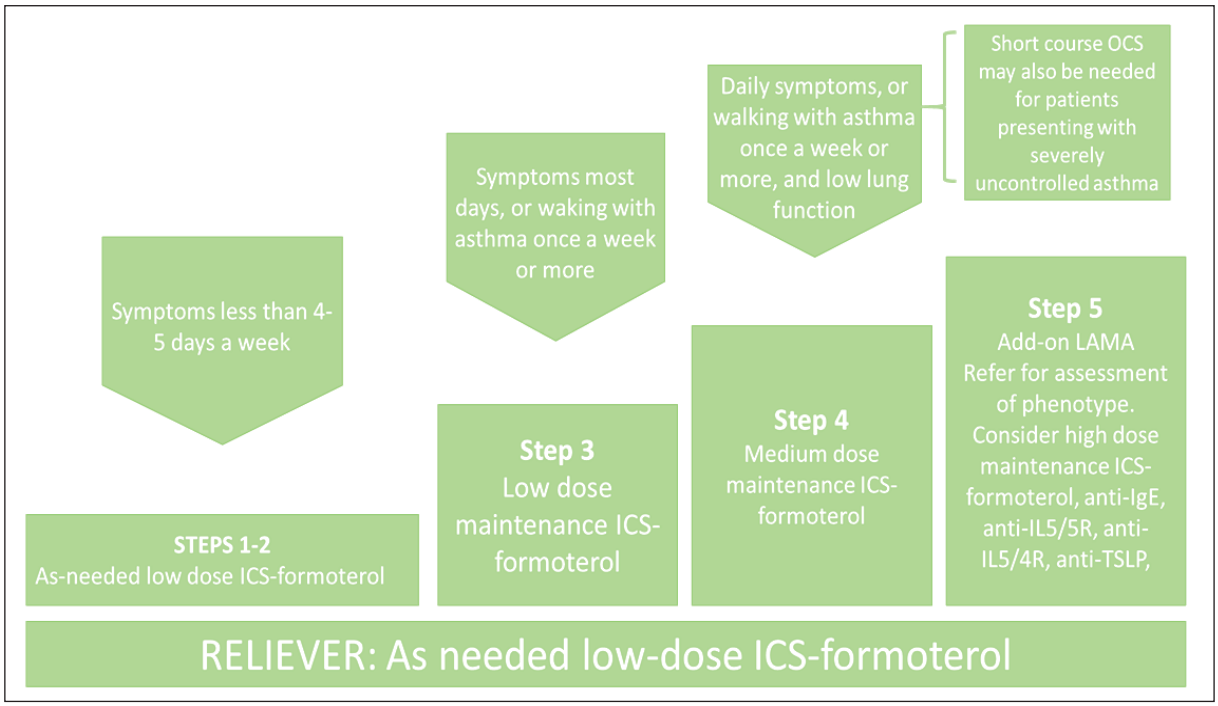


Figure 4: SMART therapy of bronchial asthma

Table 4: Classification of the strength of inhaler steroid

Inhaler steroid	Low daily dose(ug)	Medium daily dose(ug)	High daily dose(ug)
Beclomethasone	200-500	500-1000	1000-2000
Budesonide	200-400	400-800	800-1600
Fluticasone propionate	100-250	250-500	500-1000

5. Follow up visit

Follow-up visits of a patient with bronchial asthma should be kept at l-3 months after initiating treatment and 3-6 months thereafter. In each visit, the physician should inquire regarding the day symptoms, night symptoms, need for rescue medicine, limitation of daily activities, frequency of exacerbation, adherence to medication, and technique of inhalation. Accordingly, treatment should be stepped up or down.

Management of acute exacerbation of bronchial asthma

An asthma exacerbation is an acute or sub-acute episode of progressive worsening of symptoms of asthma, including shortness of breath, wheezing, cough, and chest tightness, i.e. they represent a change from the patient usual status that is sufficient to require a change in treatment. The physician should evaluate the severity of the exacerbation and rule out an alternative diagnosis.

Figure 5: Treatment of mild to moderate attack of asthma in children 5 years and younger

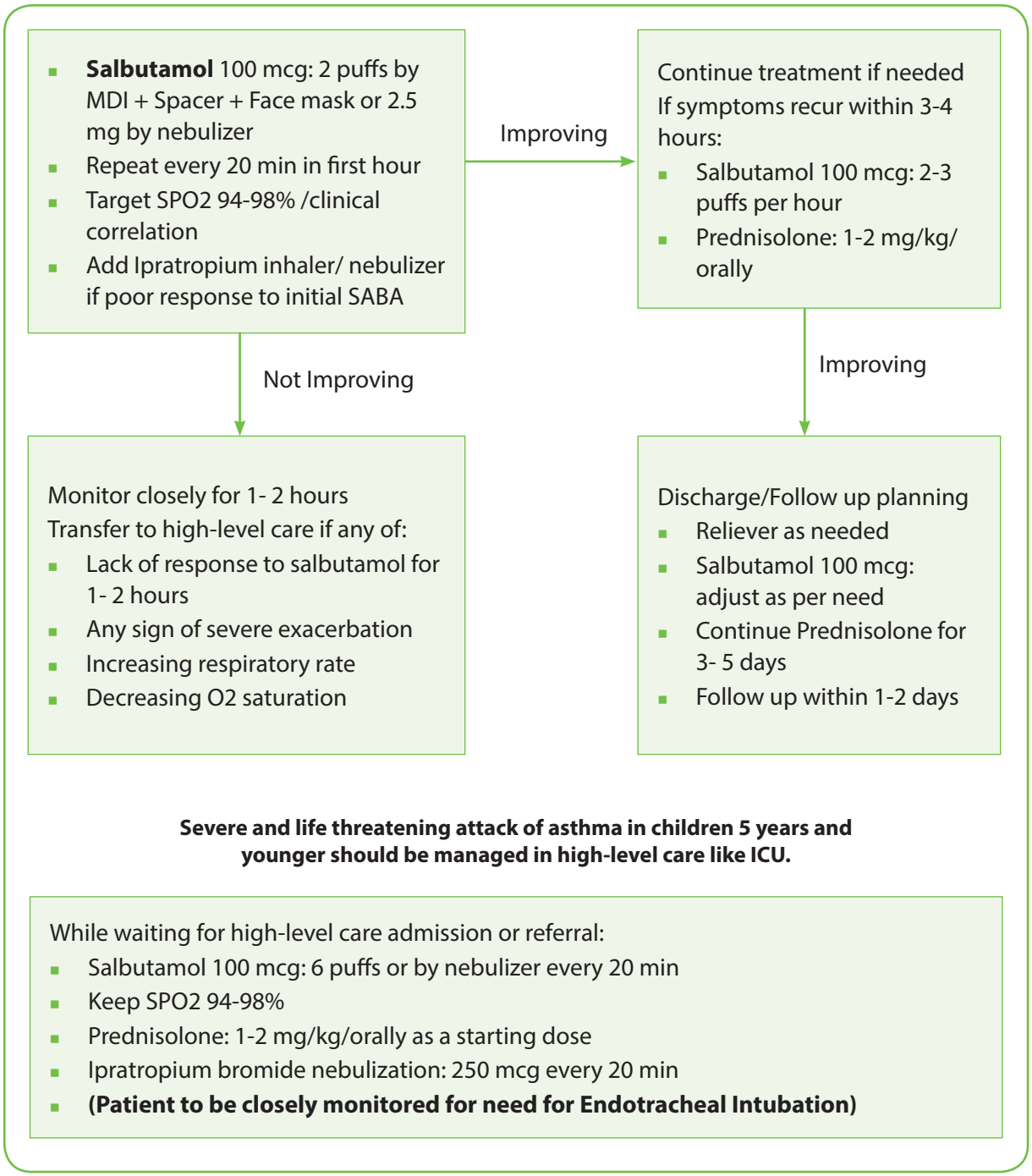
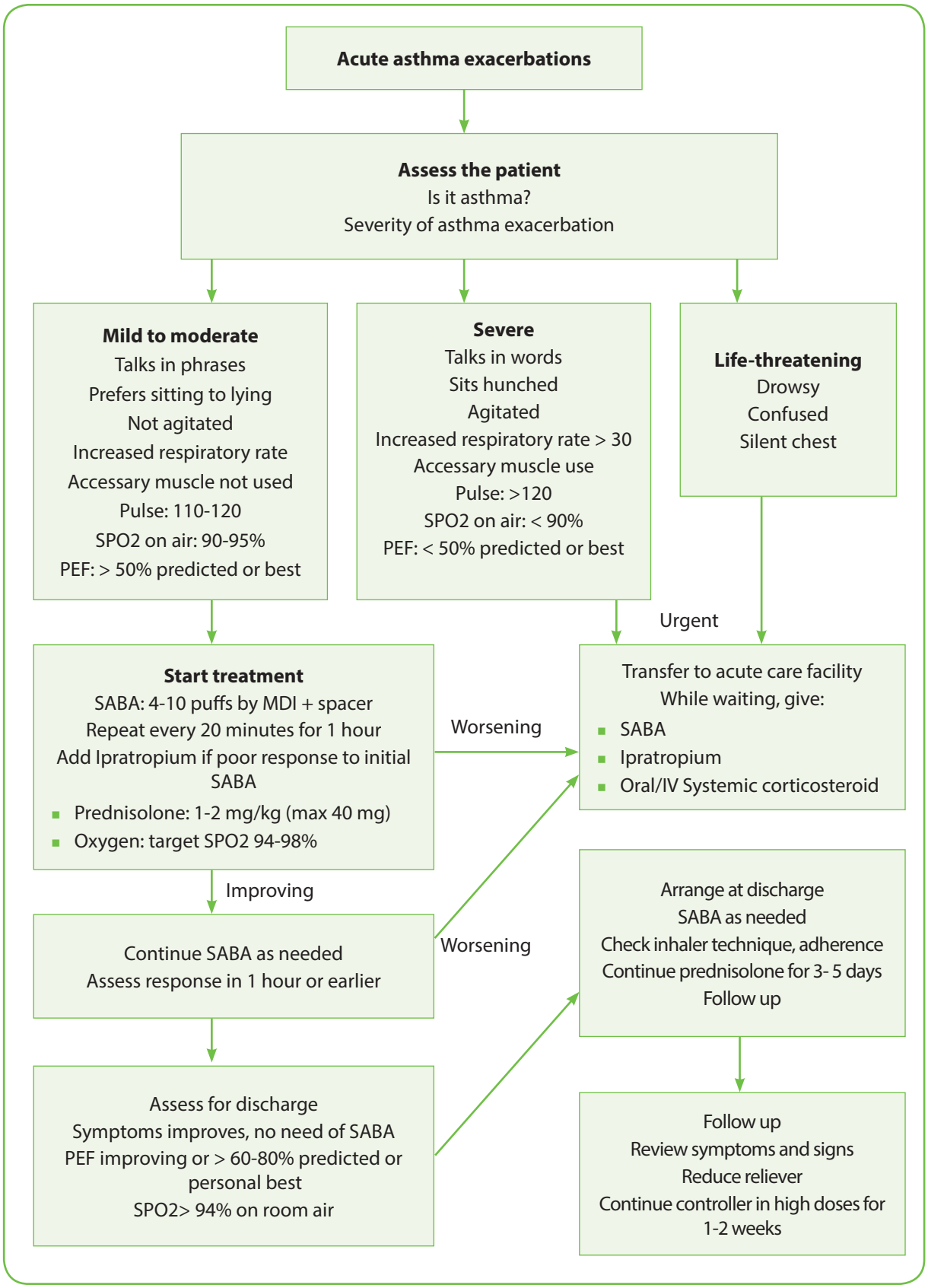


Figure 6: Management of asthma exacerbations in children ≥ 6 years



Non-severe exacerbation of Bronchial asthma

Management setting: outpatient

Criteria: All criteria should be fulfilled

- Patient not agitated
- Can talk in sentences
- Respiratory rate of less than 30 cycles/minute
- Pulse rate of 100 to 120 beats/minute
- Oxygen saturation of more than 92%

Management:

- SABA 4 to 10 puffs by MDI + spacer every 20 minutes for one hour
- Oral Prednisolone: Adult 0.5 mg/kg stat and once daily for 7 days (Pediatric age group-Prednisolone 1-2 mg/kg, the efficacy of oral and parenteral steroids is the same)
- Assess response after one hour, if improved and the patient does not require SABA with oxygen saturation of more than 94% can be discharged with controller therapy
- Arrange follow-up within 7 days
- In case of not responding to SABA therapy, the patient should be transferred to an acute care facility

Severe and life-threatening exacerbation

Criteria: Any two

- Agitation
- Inability to complete sentences in one breath or too breathless to talk or feed
- Respiratory rate ≥30/min
- Heart rate ≥110/min
- Saturation <92% or cyanosis

Management setting: Inpatient preferably high dependency /Intensive care unit

- Oxygen to maintain oxygen saturation within 93 to 95%
- Nebulized salbutamol (2.5mg) and Ipratropium (0.5mg) combination stat, and q20 minutes for one hour

  Alternatively, pMDI with spacer salbutamol 100 mcg 4-6 puffs every 20 minutes for one hour
- Inj. Hydrocortisone 200 mg IV stat dose and every 8 hourly (Children <5 yrs.: 5 mg/kg)
- Admit in high dependency /intensive care unit
- Refer to a higher center if the facility of high dependency /intensive care unit is not available

Referral of asthma patient to higher center

Few patients with bronchial asthma, especially severe bronchial asthma need a timely referral to a higher center. Optimizing proper referrals help the patients improve their severe symptoms. In the following situation, referral to a higher center is recommended

- Uncertainty of diagnosis
- Difficult to control asthma or frequent exacerbation (≥3 exacerbations per year)
- Evidence of side effects of medication
- Severe and life-threatening exacerbation of bronchial asthma requiring intensive care if facility is not available

3.2. CHILDHOOD ASTHMA

Introduction

Asthma is the most common chronic disease of childhood and the leading cause of childhood morbidity from chronic disease as measured by school absences, emergency department visits, and hospitalizations. Asthma often begins in early childhood; in up to half of the people with asthma, symptoms commence during childhood. The onset of asthma is earlier in males than in females.

Symptoms and Signs

It may be challenging to make a confident diagnosis of asthma in children 5 years and younger because episodic respiratory symptoms such as wheezing and cough are also common in children without asthma, particularly in those 0-2 years old. Additionally, it is not possible to routinely assess airflow limitation or bronchodilator responsiveness in this age group. Recurrent wheezing occurs in a large proportion of children 5 years and younger, typical with viral respiratory tract infection. Deciding when this is the initial presentation of asthma is difficult.

Diagnosis of asthma in young children with a history of wheezing is more likely if they have

- Wheezing or coughing that occurs with exercise, laughing, or crying, or in the absence of an apparent respiratory infection
- History of other allergic diseases (eczema or allergic rhinitis), allergen sensitization, or asthma in first-degree relatives
- Clinical improvement during 2-3 months of controller treatment, and worsening after cessation
- Exclusion of the alternative diagnoses

Table 5: Features suggestive of asthma in children 5 years and younger

Cough	▪ Recurrent or persistent non-productive cough that may be worse at night or accompanied by wheezing and breathing difficulties ▪ Cough occurring with exercise, laughing, crying, or exposure to tobacco particularly in the absence of an apparent respiratory infections
Wheezing	Recurrent wheezing including during sleep or with triggers such as activity laughing, crying, or exposure to tobacco smoke or air pollution
Difficulty breathing	Occurring with exercise, laughing or crying
Reduced activity	▪ Not running, playing, or laughing at the same intensity as other children ▪ Tires earlier during walks
Past or family history	Other allergic diseases (atopic dermatitis or allergic rhinitis, food allergy) Asthma in first-degree relatives
Therapeutic trial with low dose ICS and as needed SABA	Clinical improvement during 2-3 months of controller treatment and worsening when treatment is stopped

Management of bronchial asthma

Table 6: Choosing an inhaler device for children 5 years and younger

Age	Preferred device	Alternative device
0-3 years	Pressurized metered dose inhaler plus dedicated spacer with face mask	Nebulizer with face mask
4-5 years	Pressurized metered dose inhaler plus dedicated spacer with mouthpiece	Pressurized metered dose inhaler plus dedicated spacer with a face mask or a nebulizer with mouthpiece or face mask

Table 7: Management of bronchial asthma in children 5 years and younger

Category	Asthma symptoms	Therapy
Intermittent	Infrequent wheezing with viral infections and little to no symptoms between illness	Step 1 Short course of daily ICS at the start of respiratory infection
Mild persistent	▪ Daytime symptoms >2 days per week ▪ Night symptoms 1-2 per month ▪ Minor interference with activities	Step 2 Preferred: daily low-dose ICS Alternatives: Daily LTRA
Moderate persistent	▪ Daily Symptoms ▪ Night symptoms: 3-4 per month ▪ Daily use of SABA	Step 3 Preferred: double daily low-dose ICS Alternative: daily low-dose ICS plus LTRA
Severe persistent	▪ Symptoms throughout the day ▪ Nocturnal awakening >1 per week ▪ Need for SABA several times/day ▪ Extreme limitation of daily activities	Step 4 Preferred: continue doubled daily low-dose ICS and Refer to an asthma specialist for evaluation

Table 8: Stepwise asthma management in children 6-11 years old

Category	Asthma symptoms	Therapy
Intermittent	▪ Daytime symptoms ≤2 days per week ▪ Night symptoms ≤ 2 per month ▪ No interference with activities ▪ Exacerbation ≤1/ year	Step 1 Preferred: SABA as needed Alternatives: Low dose-ICS whenever SABA taken Or daily low-dose ICS
Mild persistent	▪ Daytime symptoms >2 days per week ▪ Night symptoms 1-2 per month ▪ Minor interference with activities	Step 2 Preferred: daily low-dose ICS Alternatives: Daily LTRA Or Low-dose-ICS whenever SABA taken
Moderate persistent	▪ Daily Symptoms ▪ Night symptoms: 3-4 per month ▪ Daily use of SABA	Step 3 Preferred: double daily low-dose ICS-LABA Or daily medium dose ICS Alternative: daily low-dose ICS plus LTRA
Severe persistent	▪ Symptoms throughout the day ▪ Nocturnal awakening >1 per week ▪ Need for SABA several times/day ▪ Extreme limitation of daily activities	Step 4 Preferred: continue doubled daily medium dose ICS- LABA Alternatives: Daily high-dose ICS Or Daily medium-dose ICS-LABA and add on tiotropium or LRTA
Poor controlled severe asthma	Poorly controlled severe asthma	Step 5 Preferred: Daily medium-dose ICS-LABA Refer to an asthma specialist

Key indications for referral of childhood asthma

- Failure to thrive
- Neonatal or very early onset of symptoms
- Vomiting associated with respiratory symptoms
- Continue wheezing
- Failure to respond to asthma medications
- No association of symptoms with typical triggers, such as viral URTI
- Focal lung cardiovascular signs or finger clubbing
- Hypoxemia outside the context of the viral illness

Table 9: Assessing asthma control and adjusting therapy in children

Symptoms	Well-controlled	Not well-controlled	Very poorly controlled
Day symptoms	≤ 2 days/week	>2 day/week	Throughout day
Night symptoms	≤1 time/ month	>1 time /month	>1 time/week
Use of SABA	≤2 days/week	>2 days/week	Several times in a day
Interference with normal activity	None	Some limitation	Severe limitation
Management	▪ Maintain current treatment ▪ Regular follow-up in 3-6 months ▪ Consider stepping down if well-controlled for at least 3 months	• Step up • Reevaluate in 2-6 weeks	• Consider a short course of oral steroid • Step up • Reevaluate in 2 weeks

Vaccination:

Annual seasonal influenza vaccination is recommended for patients with Bronchial Asthma.

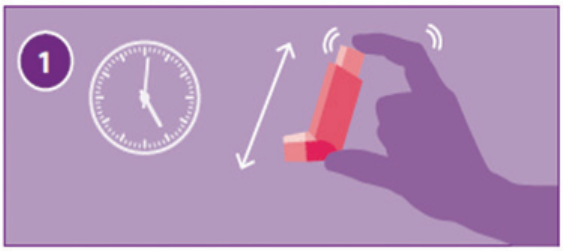
Management of exacerbation of bronchial asthma in children

Refer to the management of exacerbation of bronchial asthma in Figures 5 & 6.

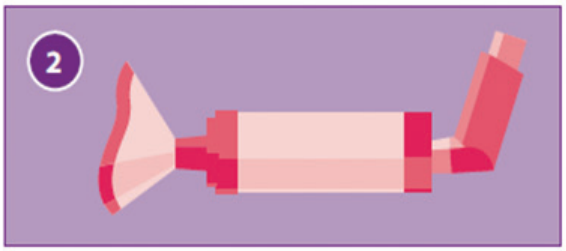
Steps of using MDI with mask

1. Remove the cap from MDI and spacer
2. Shake MDI 5 Sec before using
3. Insert MDI into the spacer
4. Attach mask to other end of spacer
5. Make a tight seal of mask over the nose and mouth of the child
6. Ask the child to breathe out
7. Press MDI
8. Ask the child to breathe in and out for 10 seconds
9. Ask the child to hold breath for 10 seconds
10. Repeat as necessary

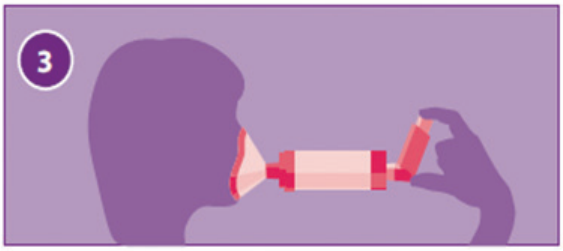
Holding chambers with masks are often recommended for children with asthma, but they are used by adults as well.



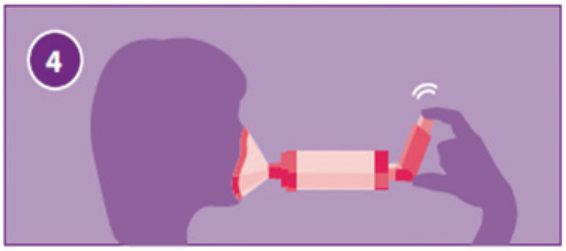
STEP 1: Take the cap off your MDI and shake the MDI well



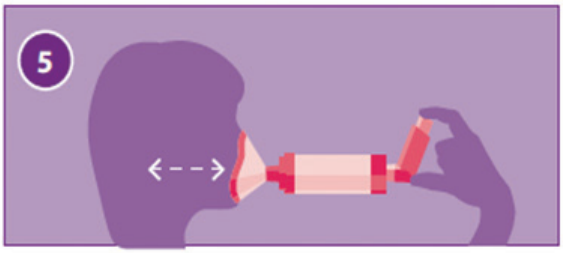
STEP 2: Attach the mask to the holding chamber (if it's not a single unit) and insert the MDI into the chamber.



STEP 3: The user should sit up straight or stand. Place the mask over the user's nose and mouth. The mask should fit firmly enough so none of the medicine can escape.

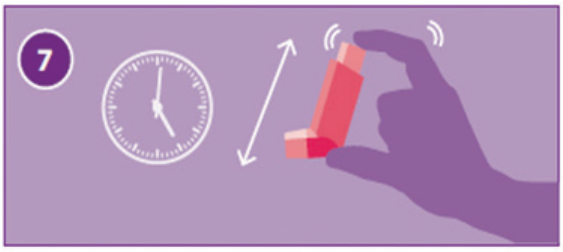


STEP 4: Press down on the MDI. This puts one dose of medicine into the chamber.

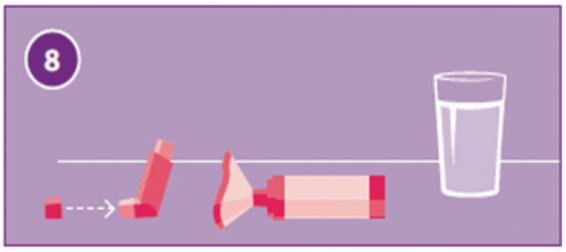


STEP 5: Have the user breathe in and out normally for six breaths to inhale the full dose of medicine. You can monitor the user's breathing by watching the valve open and close. Do not remove the mask until the sixth breath is completed

STEP 6: Remove the mask from the user's face



STEP 7: If you need to take another dose of medicine, wait 1 minute. After 1 minute, shake the inhaler again and repeat steps 3 through 6.



STEP 8: Remove the MDI from the chamber and recap both devices. If the medicine is a corticosteroid, the user should rinse their mouth out with water after the last puff of medicine. Make sure to spit the water out – DO NOT SWALLOW IT.

Figure 7: Meter dose inhalation

3.3. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Introduction

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. COPD is one of the major non-communicable diseases affecting people across the globe with serious socioeconomic consequences. It is the third leading cause of death in the world. The global prevalence of COPD is estimated to be around 10 %. COPD is the most common non-communicable disease in Nepal affecting about 11.7% of the population. COPD is the second leading cause of death in Nepal, with seven out of every 100 deaths ascribed to this disease. This protocol is meant for the management of COPD in District Hospitals.

Etiology

Table 10: Risk factors of chronic obstructive pulmonary disease

Established risk factors	Probable risk factors
Tobacco smoking	Outdoor air pollution (dust, fumes, etc.)
Environmental (second) tobacco smoke	Pulmonary tuberculosis
Exposure to indoor biomass fuel	Poor treated chronic bronchial asthma
Occupational exposure (dust, fumes)	Intrauterine growth retardation
Genetic predisposition (Alpha-1 antitrypsin deficiency)	Poor nutrition
	Recurrent lower respiratory tract infections
	Others (age, gender, low socioeconomic status)

Signs and symptoms

The common symptoms of COPD are chronic cough, sputum production, and progressive exacerbation of shortness of breath. The health care provider should suspect COPD in a patient with the aforementioned clinical features with a history of significant exposure to risk factors associated with the disease.

Examination findings of COPD:

- Tachypnea
- Tachycardia
- Barrel-shaped chest (in emphysema)
- Subcoastal recession and hyper resonance notes appreciated
- Diminished breath sound
- Wheeze

Clinical signs in advanced COPD

- Pursed lip breathing
- Use of accessory muscle of respiration
- Retraction of suprasternal, supraclavicular and intercoastal spaces during inspiration
- Cyanosis
- Hepatomegaly
- Pitting leg edema
- Altered mental status (confusion, delirium, somnolence) due to hypoxemia/hypercapnia

Diagnosis

Spirometry:

In a patient >40 years age, who has symptoms of chronic cough, sputum production and,or, progressive shortness of breath, with spirometry findings of:

The presence of post-bronchodilator FEV1/FVC <0.7 that suggests persistent airflow limitation along with symptoms of GOLD defining criteria for COPD (Table 11) confirms the diagnosis of COPD in a clinical setting.

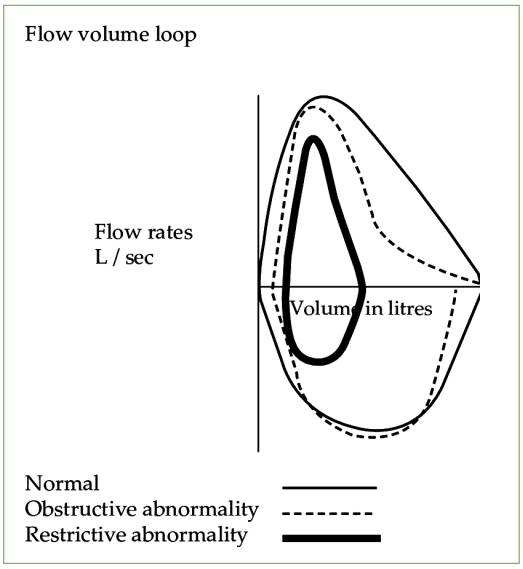


Figure 8: Flow- volume loop in spirometry showing obstructive pattern (dotted line)

Chest X-RAY

Chest X-RAY findings in early COPD may be normal, whereas in advanced COPD, hyperinflated lungs, flattened diaphragm, bullae, and hyperlucency can be appreciated. Chest X-RAY assists in ruling out alternative diagnoses like bronchiectasis, interstitial lung disease, and heart failure.

Other lab evaluation

The common findings are anemia (nutritional or chronic disease associated) or polycythemia, and normal leucocyte counts except in infective exacerbation. An electrocardiogram may demonstrate evidence for cor pulmonale (P wave ≥2.5 mv, R/S ration in V1> 1, right axis deviation), arrhythmias (atrial fibrillation, atrial flutter, multifocal atrial tachycardia). Electrolytes, renal function test, liver function test, and sputum analysis should be done at the time of exacerbation. Arterial blood gas analysis shows hypoxemia and hypercapnia. Pulmonary tuberculosis should be ruled out in all COPD suspects by doing two sputum samples for acid-fast bacilli. Transthoracic echocardiography to look for evidence of cor pulmonale and other cardiac co-morbidities.

The severity of COPD is given by GOLD classification (Table 11). COPD can be divided into chronic bronchitis or emphysema as shown in Table 12 and modified medical research council (mMRC) grading (Table 13). The differential diagnosis of COPD is illustrated in Table 14.

Table 11: GOLD criteria for diagnoses of COPD

In Patients with age>40 years, suspect COPD if they have the following features
Chronic progressive dyspnea
Chronic Cough
Sputum production
Risk factors: Smoking history(Pack year>10), exposure to household smoke
Family history of COPD
Recurrent childhood infection

Table 12: Difference between chronic bronchitis and emphysema

Clinical characteristics	Chronic bronchitis	Emphysema
Age of onset	4^{th} -5^{th} decade	5^{th}-6^{th} decade
Predominant symptoms	Cough	Shortness of breath
Barrel shaped chest	Rare	Common
Chest X-RAY	Prominent broncho-vascular marking	Hyper inflated lung with small heart shadow

Table 13: Modified medical research council grading of severity of dyspnea

Characteristic	Grading
Dyspnea only with strenuous exercise	0
Dyspnea on hurrying or walking slightly uphill	1
Walks slower than people of the same age due to dyspnea or have to stop to breathe while walking at their own pace	2
Stop to breathe on walking 100 yards (91 meters) or after a few minutes	3
Too dyspneic to leave the house or dyspnea when dressing	4

Table 14: Differential diagnoses of COPD

COPD	Asthma	Pulmonary TB	Congestive Heart Failure	Bronchiectasis	Central Airway Obstruction
- Onset in mid-life - Symptoms slowly progressive - Long smoking history - Exertional Dyspnea - Irreversible airflow Limitation	- Onset early in life - Symptoms vary from day to day - Symptoms at night/ early morning - Allergy, rhinitis, and eczema may be present - Family history of Asthma - Reversible airflow limitation	- Can be present in any age groups - Chest X-Ray may show infiltrates (upper zones commonly involved), scarring and/ or calcified granuloma, cavitation etc - Positive for PPD or Interferon-gamma release assay (IGRA) - Sputum for AFB will be positive	- Fine basilar crackles on auscultation - Chest X-Ray may show features of pulmonary edema and cardiomegaly	- Large volume of purulent sputum, - Hemoptysis - Recurrent respiratory infection - Coarse crepitation - Digital clubbing - HRCT chest findings could be diagnostic	- Monophonic wheeze or stridor - Chest X-ray may show mass lesions and/ or collapse/ consolidation

Management

Medical management of stable COPD

The determinants of medical management of COPD are the severity of symptoms, and risk of exacerbations that can be kept in the ABCD scheme as illustrated in Figure 9. Based on this assessment using simplified tools such as the modified Medical Research Council (mMRC) Dyspnoea Scale (see Table 13) for breathlessness and history of moderate to severe exacerbation in past COPD patients are broadly categorized into 4 groups i.e. A (low symptoms, low risk), B (more symptoms, low risk), C (fewer symptoms, high risk) and D (more symptoms, high risk).

Group A

They have low symptoms that do not bother their day-to-day activities and less than 2 moderate exacerbations in a year. Short-acting (MDI/DPI Salbutamol 200 ug) or long-acting bronchodilator is offered as per their breathlessness.

Group B

They have persisting symptoms hampering their day-to-day activities, however, less than two moderate exacerbations in a year. They should be offered a long-acting bronchodilator LAMA (MDI/DPI tiotropium 18 ug once daily).

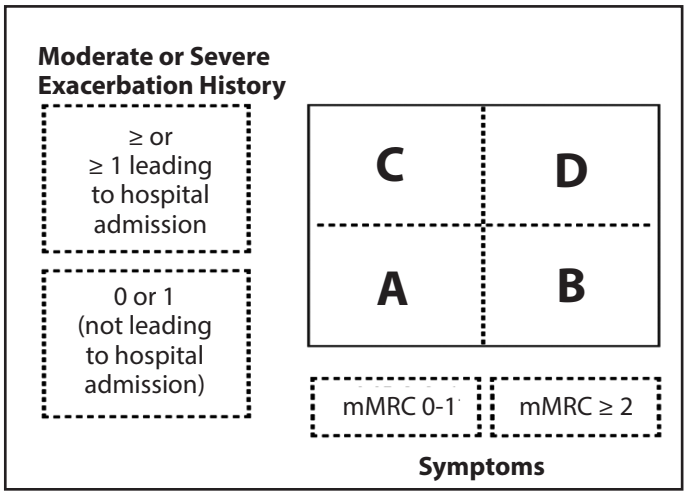


Figure 9: ABCD assessment tool for the severity of COPD

Group C

They have persistent mild symptoms and a history of more than 2 moderate exacerbations in a year. LAMA (MDI/DPI tiotropium 18 ug once daily) is recommended for initial therapy in this group of patients.

GROUP D

They have both persistent severe symptoms and more than 2 moderate exacerbations in a year. The initial choice of LAMA (MDI/DPI tiotropium 18 ug once daily). In those patients with more severe symptoms, combination of LAMA and LABA can be considered (MDI/DPI 12 ug formoterol plus 18 ug tiotropium). In the patient with concomitant bronchial asthma or COPD patient with severe symptoms with blood, eosinophil counts≥300 cell/ulLABA/ICS is initial therapy (MDI/DPI formoterol plus budesonide, salmeterol plus fluticasone).

Table 15: Treatment of stable COPD based on the ABCD assessment tool

Group	Initial Therapy	Add on
A (Low symptoms, Low risk)	SABA or SAMA	LAMA
B (More symptoms, Low risk)	LAMA	ICS+LABA
C (Low symptoms, High risk)	LAMA	ICS+LABA
D (More symptoms, High risk)	LAMA	ICS +LABA

Inhaler technique

Education on inhaler technique is an important step in COPD management. Improper inhaler techniques lead to an increase in exacerbation rate, hospital admission rate, emergency visits, and increase in antimicrobial use and steroid use. Repeated face-to-face inhaler education by health care provider improves patients' inhaler satisfaction, technique, and adherence. Selecting the type of device (MDI/ Rotahaler/ Revoliser) is determined by cognitive function, hand musculoskeletal problem, and inspiratory flow rate. In each visit, the health care provider should inquire and look for the technique of inhalation.

MDI inhalation steps

1. Shake the canister (3-4 sec)
2. Hold the canister upright
3. Gently exhale to functional residual capacity(don't exhale to residual volume)
4. Place the mouthpiece in the mouth between the teeth and close the lips
5. With the initiation of inhalation, actuate the canister
6. Slowly inhale up to the maximum capacity (total lung capacity)
7. Hold the breath for 10 seconds or as long as possible
8. Wait for at least 60 seconds before the next puff

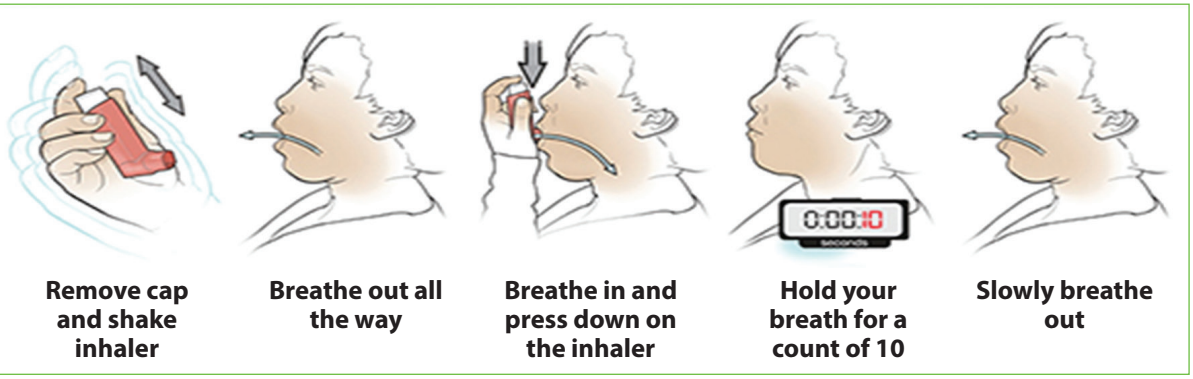


Figure 10: **Metered dose inhalation**

MDI with spacer inhalation technique

1. Shake to mix the ingredients
2. Attach the MDI to the holding chamber/spacer
3. Exhale to Functional residual capacity
4. Place the mouthpiece into the mouth
5. Press the MDI canister once and breathe in slowly through the mouth
6. Hold the breath for 10 seconds (as long as comfortable)
7. Allow 15-30 seconds between puffs

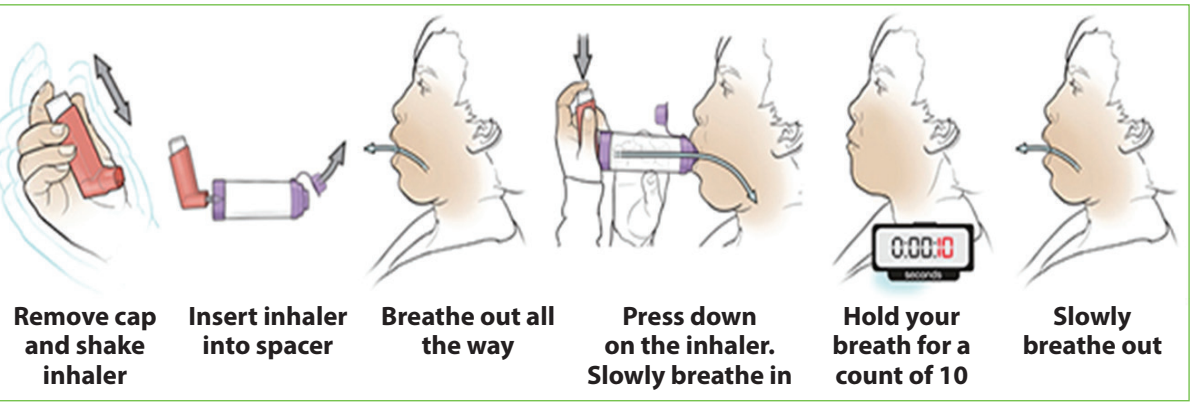


Figure 11: **Metered dose inhaler with spacer**

DPIs Inhaler technique

1. Remove cover (device-specific)
2. Load dose (device-specific)
3. Pierce/cut the capsule (single-dose devices)
4. Exhale to FRC
5. Place mouthpiece between lips
6. Inhale deeply and quickly
7. Hold breath (10s)

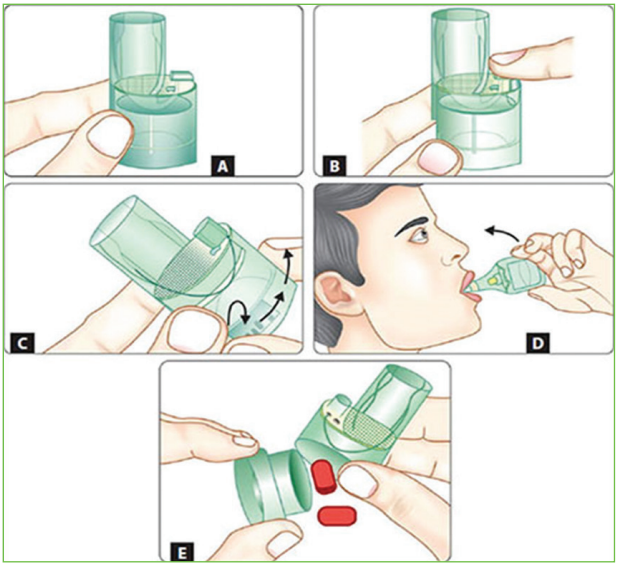


Figure 12: Steps for using dry powder inhaler

Follow-up assessment

- The severity of symptoms according to mMRC
- Understanding the treatment regimen
- Assessment of inhaler technique
- Determine the status of comorbidities
- Assessing the need for long-term oxygen.
- Status of smoking cessation
- Nutrition status of the patient

Non-pharmacological treatment of COPD

Smoking cessation

Continuing smoking has a serious impact on the progression of COPD. Hence, smoking cessation is the most effective tool to change the natural course of COPD. It decreases COPD-related mortality too. Even brief face-face counseling by healthcare providers has shown a significant quit rate. A five-step strategy (as illustrated in Table 16) helps in a smoking cessation program. Other strategies for smoking cessation are nicotine replacement therapy, bupropion, and varenicline therapy.

Table 16: The 5A's intervention for smoking cessation

Ask	Quantity of smoke, duration of smoke
Advise	Discuss harmful effects, advise to quit
Assess	The willingness of the patient to quit
Assist	Help create the best plan for quitting
Arrange	Follow up

Long term Oxygen therapy in COPD

Oxygen therapy for more than 15 hours a day in COPD with severe resting hypoxemia improves survival, exercise capacity, sleep quality, and decreases dyspnea.

Indication of Long term oxygen therapy for at least 15 hours/day for COPD **Prerequisite** ▪ Smoking cessation ▪ Two ABGs / Oxygen saturation monitoring 3 weeks apart
1. PaO2 ≤55 mm Hg,/SPO2≤ 88%
2. PaO2=56-59 mm Hg / Spo2=89% with one of the following - Edema, - Hematocrit ≥55% or - P pulmonale in ECG

Vaccination in COPD

Annual seasonal influenza vaccination is recommended for a patient with COPD. It decreases the number of exacerbations and hospitalization admission rates. The WHO and CDC recommend SARS-COV2 vaccination in patients with COPD. Other vaccinations needed to be considered in people with COPD are 23-valent pneumococcal polysaccharide (for age <65 years with FEV1< 40%), 13-valent conjugated pneumococcal vaccine (for age> 65 years), Tdap (for unvaccinated), and zoster vaccine (> 50 years).

Education and counseling

Health education should be an integral part of patient management regardless of the disease or condition. This is true for COPD as well. Health education may include informal outpatient discussions, didactic lectures, group sessions, and others. The role of multimedia, especially the role of the internet and online support groups should also be considered. However, modifying the habits of a lifetime is difficult. Various topics that may be covered in an educational program include:

1. Risks and benefits of stopping smoking and cessation strategies.
2. Risk factors for COPD and how to avoid them.
3. The concept of normal lung function.
4. Inhaler use: It is important to check that the patients are taking their medicine properly. The inhaler technique should be demonstrated to the patient and accompanying attendants and reinforced at every visit. The demonstration of the inhaler technique to the attendants is especially important in the case of the elderly.
5. Use of other medications, including oxygen.
6. Nutritional education.
7. Adequate physical exercise, especially if the patient is not enrolled in a pulmonary rehabilitation program.
8. Breathing strategies.
9. Advice related to travel and sexuality.
10. End-of-life planning.

Management of Acute exacerbation of COPD

Exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication. Change in cardinal symptoms of COPD like an increase in cough frequency, sputum production, or shortness of breath is a clue to acute exacerbation of COPD.

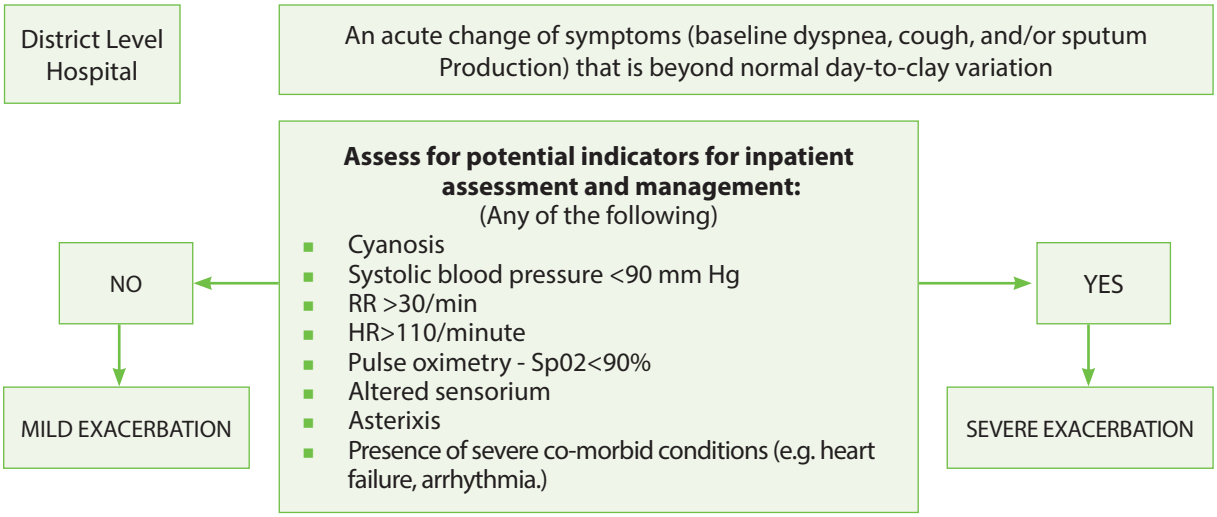


Figure 13: Algorithm to categorize the severity of exacerbations of COPD

Indications for hospitalization during exacerbation of COPD*

Symptoms:

- Marked reduction in the activity of daily living due to dyspnea
- Altered sensorium
- New onset cyanosis

Signs:

- Use of accessory respiratory muscles
- Paradoxical chest wall movements
- Central cyanosis
- Systolic blood pressure <90 mm Hg
- Respiratory rate 30/min
- Heart rate >110/min
- Asterixis
- Altered mental status

Others

- Presence of severe comorbid conditions
- Lack of social support
- Pulse oximetrySpO2<90%

* **(Presence of any of these qualifies a patient with a need for admission; The ultimate decision to admit depends on the overall clinical assessment of the physician. COPD: Chronic obstructive pulmonary disease)**

Treatment of Acute exacerbation of COPD

1. Oxygen:

All patients with severe exacerbations should be given low-flow oxygen (2-3 L/min). If SpO_2 monitoring is available, administer supplemental oxygen therapy only if hypoxia is present, with a target Spo_2 of 92%.

2. Bronchodilators:

The inhaled route is the preferred route for administering bronchodilators.

- Nebulized salbutamol – 2.5 mg every 20 min OR
- Salbutamol (MDI) 100 µg 2-4 puffs every 20 min for 1 h to be given initially.

Additional bronchodilation:

- Combination of ipratropium (500 µg nebulized or 20 µg 2-4 puffs with pMDI) and salbutamol (2.5 mg nebulized or salbutamol pMDI 100 µg 2-4 puffs) every 4-6 h can be used.

***Nebulizers or pMDIs with spacer are equally effective.**

3. Steroids:

- A short course of oral prednisolone 30 mg/day (or equivalent) for 5 days
- In patients who cannot tolerate oral medication – Intravenous steroids – Hydrocortisone 100 mg thrice daily

4. Antibiotics:

Antibiotics (Amoxy-clavulanic acid plus Azithromycin) should be prescribed for all exacerbations of COPD.

Algorithm for management of severe exacerbation of COPD

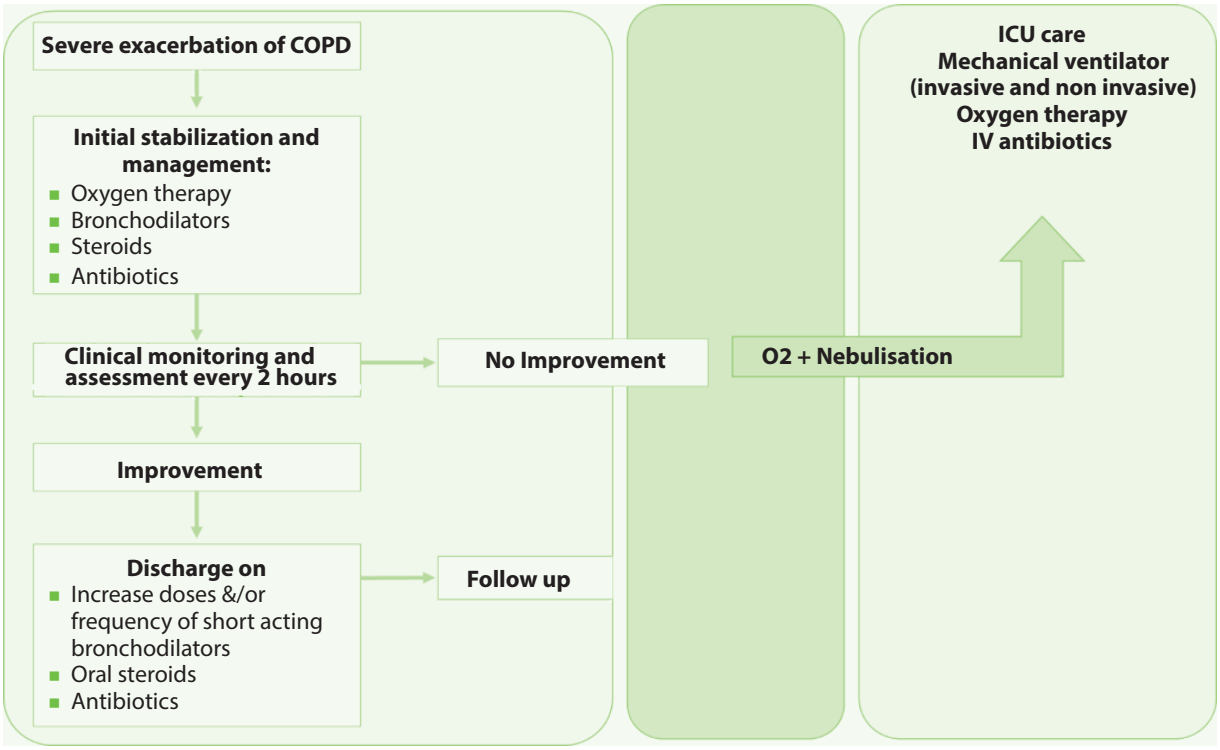


Figure 14: Approach to the management of severe exacerbation of COPD

Referral to the acute care facility if not available

- Change in mental status
- Hemodynamic instability
- Persistent hypoxemia despite supplemental oxygen therapy
- Signs of respiratory muscle fatigue
- Patient's inability to handle respiratory secretions

Discharge criteria from the hospital (All of the following)

- Partial or complete resolution of the symptoms
- No cyanosis
- Systolic blood pressure > 90 mm Hg
- RR <30/min
- HR <110/minute
- Pulse oximetry – SpO2 > 90%
- No altered sensorium or asterixis
- No use of accessory muscle for respiration

Assessment at the time of discharge

- Understanding of maintenance long-term therapy
- Reassess inhaler technique
- Asses need for oxygen therapy at home
- Ensuring follow-up early follow-up within 4 weeks and late follow-up within less than 12 weeks
- Addressing management plan for co-morbidities

Pulmonary rehabilitation

Pulmonary rehabilitation in COPD improves exercise capacity, 6-minute walking distance, and quality of life, it also decreases breathlessness and the rate of hospitalization. It should be offered to Group B to Group D patients with COPD, however, the benefit is seen more in Group B patients (Refer to the PEN trainee manual, pages 60, 75, and 130 for a healthy diet, physical exercise, and patient education respectively). Pulmonary rehabilitation includes

1. Exercise: Endurance training, resistance training, and breathing exercise
2. Education: Nutrition counseling, medication use, inhaler technique, oxygen utilization
3. Emotional support

CHAPTER-4

CARDIOVASCULAR DISEASES

4.1. HYPERTENSION

Introduction

Hypertension is defined as systolic blood pressure (SBP) of 140 mm Hg above and or diastolic blood pressure (DBP) of 90 mm Hg or more.

In general, hypertension is diagnosed if, on two to three visits of 1 to 4 weeks interval, systolic blood pressure is ≥140 mm Hg and or diastolic blood pressure on both days is ≥90 mm Hg.

Etiopathogenesis:

Essential hypertension or primary hypertension accounts for 95% cases of hypertension. The risk factors for primary hypertension are advancing age, obesity, family history, high sodium diet (sodium intake (>3 g/day), excessive alcohol intake, cigarette smoking, and physical inactivity. Secondary hypertension is hypertension due to an identifiable cause, which may be treatable with an intervention specific to the cause.

Table 17: Criteria for hypertension based on office, ambulatory blood pressure monitoring (ABPm) and home blood pressure measurement (HBPm)

Types of BP measurement	SBP/DBP, mm Hg
Office BP	140 and/or≥ 90
ABPm	
24 hours average	≥ 130 and/or≥ 80
Day time (or awake) average	≥135 and or ≥85
Night time (or asleep) average	≥120 and /or 70
HBPm	≥135 and or ≥85

Table 18: Classification of hypertension based on office blood pressure (BP) measurement

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Normal BP	<130	and / or	<85
High-normal BP	130–139	and / or	85–89
Grade 1 hypertension	140–159	and / or	90–99
Grade 2 hypertension	≥160	and / or	≥100

Optimal method of blood pressure measurement

Patient preparation:

- Patient should be relaxed, sitting in a chair (feet on the floor, back supported) for >5min.
- Patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement.
- Patient should have emptied his/her bladder.
- Neither the patient nor the observer should talk during rest period or during measurement.
- Thick clothing covering the location of cuff placement should be removed.

Technique of measurement:

- Patient's arm should be supported (e.g. Resting on a desk).
- Middle of the cuff is to be positioned on the patient's upper arm.
- Correct cuff size should be used such that the bladder encircles 80% of the arm.
- For auscultatory determinations, a palpated estimate of radial pulse obliteration pressure should

be used to estimate SBP and cuff inflated 20–30 mm Hg above this level for an auscultatory determination of the BP level.

- For auscultatory readings, cuff pressure should be deflated at 2 mm Hg per second, listening for Korotkoff sounds.
- SBP and DBP should be recorded as the onset of the first Korotkoff sound and the disappearance of all Korotkoff sounds.
- BP should be recorded in both arms. If the difference between the two arms is more than 15 mm Hg, the measurement should be repeated. If the difference persists, the blood pressure of the arm with high recording is considered.

If the blood pressure in the clinic is 140/90 mm Hg or higher, take a second measurement. If the two are substantially different, third measurement should be taken. The lower of the last 2 measurements is recorded as clinic blood pressure.

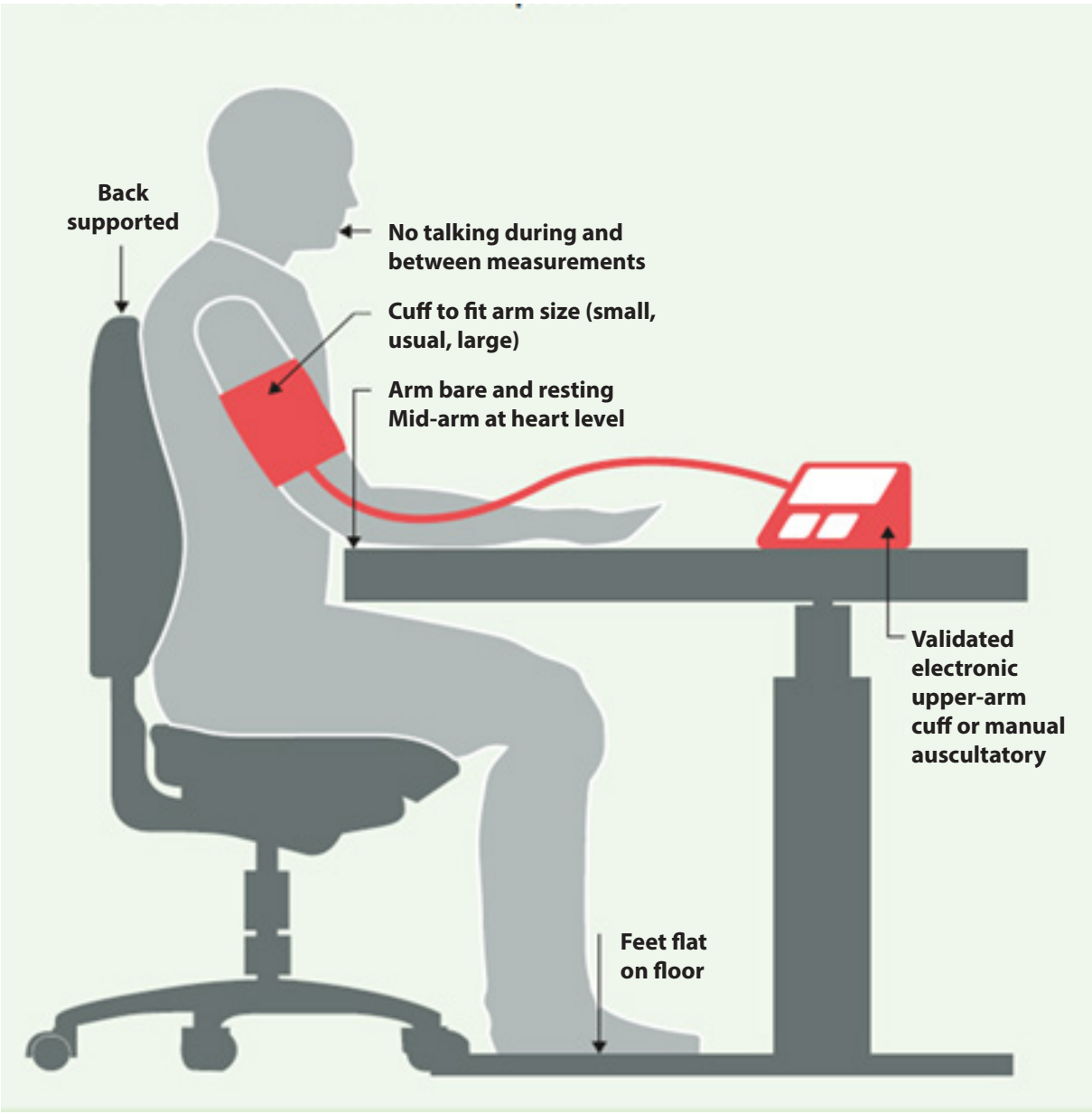


Figure 15: How to measure blood pressure (figure from 2020 ISH global hypertension practice guidelines)

Out-of-office BP and self-monitoring of BP:

Ambulatory blood pressure measurement: Hypertension is considered when day time BP is ≥ 135/85, night BP ≥ 120/80 and the mean BP ≥130/80.

Home blood pressure measurement: Measuring blood pressure with calibrated semiautomatic digital machine twice (in one or two minutes interval) in the morning and evening of at least three consecutive days can provide home blood pressure which is considered high when the threshold is ≥135/85.

White-coat hypertension: BP that is consistently elevated by office readings but does not meet diagnostic criteria for HTN based upon out-of-office readings. The prevalence of white coat HTN is higher with increasing age, female sex, nonsmoking status, and routine office measurement of BP by clinicians. There is an identified minimal increase in the risk of CVD complications or all-cause mortality in patients who have white-coat HTN.

Masked hypertension: The patient has normal clinic blood pressure (less than 140/90 mm Hg) but higher outside clinic especially using average ambulatory or home blood pressure measurement).

Investigations

There are mainly 3 objectives of investigation in a case of hypertension.

- Detection of target organ damage (cause-specific).
- Detection of coexisting cardiovascular risk factors.
- To identify the reason for referral to a tertiary center for the detection of secondary causes of HTN.

Approach to hypertension

History taking

Most of the patients with hypertension are asymptomatic.

Patients can have chest pain, shortness of breath, palpitations, headaches, and blurred vision.

Make note of the history of hypertension, dyslipidemia, cardiovascular disease, diabetes, stroke or renal disease, smoking, dietary habit and salt intake, alcohol consumption, level of physical activity, sleep history including snoring habit, recreational drug uses and in female the oral contraceptive uses and hypertension in previous pregnancy and other relevant family history.

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Measure BP with Optimal Method

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Diagnosis of Hypertension

SBP of ≥ 140 mm Hg and/or DBP of ≥90 mm Hg measured on 2 to 3 visits on different days in 1 to 4 weeks interval

On single visit, if blood pressure is more than or equal to 180/110 mm Hg

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Clinical examination includes measurements of waist circumference, height and weight and general physical examination and examination of cardiovascular system

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Advice Basic Investigation:

- Blood Investigation: Renal function test, serum sodium, potassium, blood sugar and if available, lipid profile
- Urine RME
- ECG, chest x-ray, ambulatory blood pressure monitoring (if available)
- Ophthalmology evaluation for retinopathy
- Echocardiography for concentric LV hypertrophy

Additional investigations when indicated can be undertaken to assess and confirm the suspicion of target organ damage, coexistent diseases or/and secondary hypertension

Cardiovascular disease risk assessment should be done based on the WHO CVD risk prediction chart.

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Management of Hypertension

Non-Pharmacological:

- Dietary Sodium restriction
- Increase intake of fruits and vegetables
- Maintain healthy eating plan
- Regular physical activity
- Weight reduction and Maintain body mass index (BMI)
  18.5 to 23 kg/m^2
- Smoking cessation
- Abstinence or moderation of alcohol consumption
- Eat heart-healthy diet: DASH diet (dietary approaches to stop hypertension)

Pharmacological:

Initiation of pharmacological hypertension (HTN) treatment

- Should start no later than four weeks following diagnosis of HTN
- If systolic ≥160 mm Hg or diastolic ≥100 mm Hg) or there is accompanying evidence of end organ damage
- For individuals with existing cardiovascular disease, left ventricular systolic dysfunction, proteinuria, diabetes mellitus and systolic blood pressure of 130–139 mm Hg

- **Monotherapy:** First-line single-agent includes thiazide diuretics, CCB and ACE inhibitors or ARB. Use monotherapy for low-risk patients with stage 1 hypertension, very high-risk patients with high–normal BP, frail older patients. CCB or thiazide diuretics are preferred for age > 65 years
- **Combination therapy:** Initiation with 2 first-line agents of different classes either as separate agents or in fixed-dose combinations is recommended with stage 2 hypertension and an average BP more than 20/10 mm Hg above their target.

  Drug combinations can be selected depending on additional comorbidity. The combination can be done as enlisted below.
  - Step 1. Single pill dual low dose combination. A+C
  - Step 2. Single pill dual full dose combination. A+C
  - Step 3. Triple combination. A+C+D
  - Step 4. Add spironolactone or other antihypertensive groups for resistant hypertension

  A: ACE inhibitors/AR Blocker; C: Calcium Channel Blocker; D: Diuretics

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Referral to a tertiary center for detection of secondary causes of HTN in the following conditions:
- Onset of hypertension in young adults <30 years
- Onset of hypertension after age 55 years
- Disproportionate target organ damage (TOD) for degree of hypertension
- Abrupt onset of hypertension
- Exacerbation of previously controlled hypertension
- Accelerated /malignant hypertension
- Drug induced/resistant hypertension
- Unprovoked or excessive hypokalemia

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Follow up:

Monthly follow-up until BP is controlled then once in 3 to 6 months.

Table 19: Commonly Used Anti-hypertensive Medications and Their Common Adverse Effects

Class of drugs	Medications	Doses	Common adverse effects	Definite indications	Contraindications
CCB	Amlodipine Nifedipine Cilnidipine	2.5-10 mg OD 5-20 mg OD 5-20 mg OD	Pedal edema	Elderly, angina, systolic HTN, DM	
ARB	Losartan Telmisartan Olmesartan Irbesartan	25-100 mg OD/BD 20-80 mg OD 20-40 mg OD 150-300 mg OD	Hyperkalemia	DM, proteinuria, lv dysfunction, ACEI-induced cough	Bilateral renal artery stenosis, pregnancy
ACEI	Enalapril Ramipril	5-40 mg BD 2.5-10 mg BD	Hyperkalemia, dry cough	DM, proteinuria, HF, LV dysfunction, post-MI	Bilateral renal artery stenosis, pregnancy
BB	Atenolol Metoprolol Bisoprolol Nebivolol	25-100 mg 50-200 mg 2.5-10 mg 5-30 mg	Fatigue, depression	Angina, post mi, tachyarrhythmia, HF	Asthma, chronic obstructive pulmonary disease (COPD), peripheral vascular diseases, and diabetes mellitus
Diuretics	Chlorthalidone Hydrochlorothiazide Furosemide Torsemide Spironolactone	12.5-25 mg 25-50 mg 20-80 mg BD 2.5-5 mg OD 25-100 mg OD	Increase urination, low sodium, gout	HF, elderly patients, systolic HTN	Gout, dyslipidemia
AB	Prazosin sustained release	2.5-20 mg OD	Orthostatic hypotension		
AA	Clonidine Methyldopa	0.1-0.8 mg BD 250-500 mg 2-4 times/day maximum 3gm/day	Rebound HTN if the dose is missed, dry mouth, drowsiness	CKD Pregnancy	

Table 20: Selection of antihypertensive drugs for patients with co-morbid conditions

Left ventricular hypertrophy	RAAS blocker + CCB
Albuminuria	RAAS blocker + other drugs
Renal dysfunction	RAAS blocker + other drugs
Heart failure	RAAS blocker + diuretics ± CCB ± mineralocorticoids
Diabetes/metabolic syndrome	RAAS blocker + CCB ± diuretics
Peripheral arterial disease	CCB or diuretic or both
Coronary artery disease	Beta blocker+ RAAS blockers ± CCB
Cerebrovascular disease	CCB + other drugs
Pregnancy	Methyldopa, Labetalol, Nifedipine
Atrial fibrillation	ARB, Beta Blocker
Aortic disease	Beta Blocker

Resistant hypertension:

Resistant hypertension is defined as SBP/DBP ≥140/90 mm Hg with ≥ 3 antihypertensive medications at optimal doses, including diuretics after excluding pseudo resistance (ensuring accuracy of office BP measurement, white coat effect and compliance of medications). It is recommended to identify and reverse contributing life style factors, discontinue or minimize interfering substances like NSAID, oral contraceptives and screening for other secondary causes of hypertension.

Management is done by increasing diuretics, adding mineralocorticoids or other agents with different mechanism of action.

Hypertensive Urgency and Emergency:

Systolic BP > 180 mm Hg and/or DBP >120 mm Hg is severe hypertension. Severe hypertension without acute target organ damage is Hypertensive Urgency. Blood pressure can be lowered with oral medications over days to weeks on an outpatient basis.

If acute target organ damage manifests in the form of encephalopathy, stroke, aortic dissection, pulmonary oedema, myocardial infarction, renal failure, retinal hemorrhages and eclampsia, it is called Hypertensive Emergency. In hypertensive emergencies systolic BP should be reduced by no more than 25% within the first hour and then if stable to 160/100 within 2 to 6 hours and then cautiously to normal during the following first 24 to 48 hours.

Common Medications used in Hypertensive Urgency and Hypertensive Emergency :

- Nitroglycerine (5 ugm/min increased to 20/ugm/min)
- Labetalol (20 mg IV over 2 minutes initially, then 40-80 mg IV every 10 minutes; total dose not to exceed 300 mg)
- Esmolol (loading dose of 500-1000 ugm/kg/min over 1 minute followed by a 25-50 ugm/kg/min infusion) or Enalaprilat (initial 1.25mg over 5 minutes increase up to 5mg every 6 hours)

Table 21: Timeline and Target BP Control in Hypertensive Emergencies

Clinical presentation	Timeline and target BP
Malignant hypertension with or without acute renal failure	Several hours, MAP –20% to –25
Hypertensive encephalopathy	Immediate, MAP –20% to –25%
Acute ischaemic stroke and SBP >220 mm Hg or DBP >120 mm Hg	1 h, MAP –15%
Acute ischaemic stroke with an indication for thrombolytic therapy and SBP >185 mm Hg or DBP >110 mm Hg	1 h, MAP –15%
Acute hemorrhagic stroke and SBP >180 mm Hg	Immediate, 130 < SBP <180 mm Hg
Acute coronary event	Immediate, SBP <140 mm Hg
Acute cardiogenic pulmonary edema	Immediate, SBP <140 mm Hg
Acute aortic disease	Immediate, SBP <120 mm Hg and heart rate <60 bpm
Eclampsia and severe preeclampsia/HELLP	Immediate, SBP <160 mm Hg and DBP <105 mm Hg

Table 22: Recommended Treatment For Lowering BP in Hypertensive Emergencies

Clinical presentation	First line treatment	Alternative treatment
Malignant hypertension with or without acute renal failure	Labetalol	Nitroprusside
Hypertensive encephalopathy	Labetalol	Nitroprusside
Acute ischemic stroke and SBP >220 mm Hg or DBP >120 mm Hg	Labetalol	Nitroprusside
Acute ischemic stroke with an indication for thrombolytic therapy and SBP >185 mm Hg or DBP >110 mm Hg	Labetalol	Nitroprusside
Acute hemorrhagic stroke and SBP >180 mm Hg	Labetalol	
Acute coronary event	Nitroglycerine, Labetalol	
Acute cardiogenic pulmonary edema	Nitroprusside or Nitroglycerine (with loop diuretic)	Loop diuretic
Acute aortic disease	Esmolol and Nitroprusside or nitroglycerine	Labetalol, Metoprolol
Eclampsia and severe preeclampsia/HELLP	Labetalol and Magnesium sulfate	

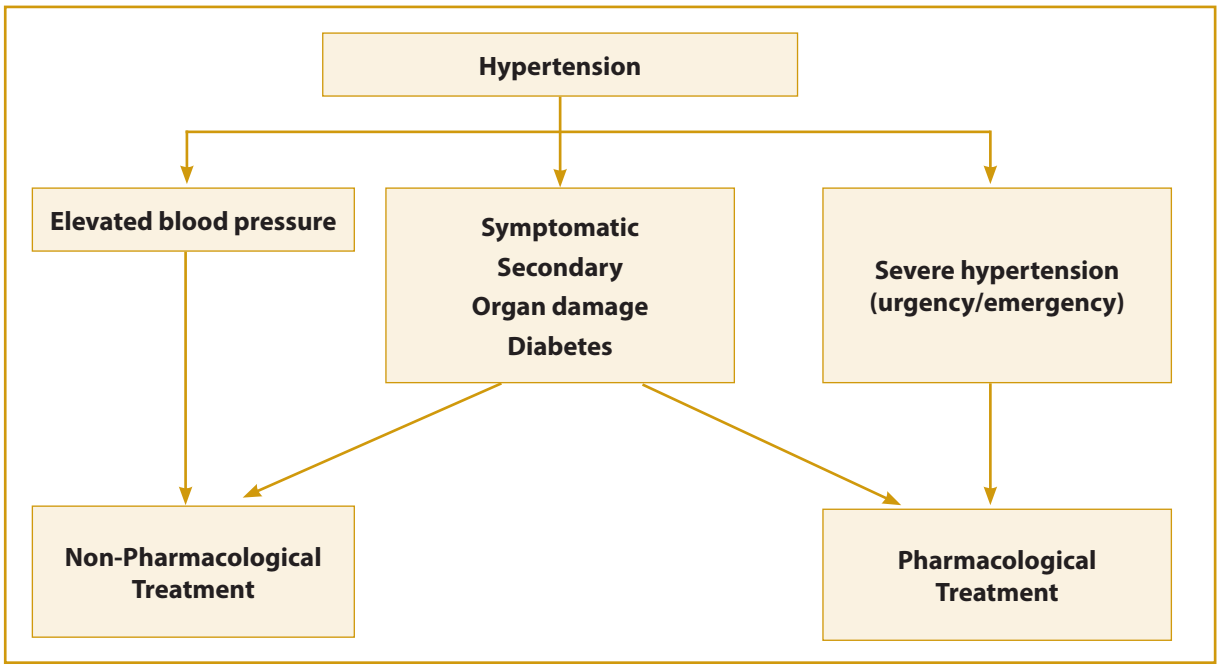


Figure 16: When to initiate antihypertensive treatment

4.2. HYPERTENSION IN CHILDREN

Hypertension in children is defined as having three elevated systolic or diastolic blood pressure (BP) readings for the subject's age, height, and sex. Specific charts are available for interpreting the values of recordings obtained.

Table 23: Classification of hypertension in children

Types	Children (ages 1 to 13 years)	Children (aged ≥13 years)
Normal BP	<90th percentile	<120/<80 mm Hg
Elevated BP	≥90th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower)	120/<80 to 129/<80 mm Hg
Stage 1 hypertension	≥95th percentile to <95th percentile + 12 mm Hg, or 130/80 to 139/89 mm Hg (whichever is lower)	130/80 to 139/89 mm Hg
Stage 2 hypertension	≥95th percentile + 12 mm Hg, or ≥140/90 mm Hg (whichever is lower)	≥140/90 mm Hg
Severe Hypertension		
Hypertensive urgency	>95th percentile + ≥30 mm Hg	>180/120 mm Hg
Hypertensive emergency	>95th percentile + ≥ 30 mm Hg associated with symptoms of target end-organ dysfunction such as headache vomiting, vision changes, and neurological symptoms (facial nerve palsy, lethargy, seizures, coma) with/without target-end organ damage	>180/120 mm Hg associated with symptoms of target end-organ dysfunction such as headache vomiting, vision changes, and neurological symptoms (facial nerve palsy, lethargy, seizures, coma) with/without target-end organ damage

Hypertension in children can also be classified based on etiology as follows:

1. **Essential or Primary HTN:** Where an underlying cause cannot be identified and is more likely if:
   - Older age (≥6 years)
   - Positive family history (in a parent and/or grandparent) of HTN
   - Overweight and/or obesity.
2. **Secondary HTN:** More common in younger children (<6 years old) with the renal disease being the most prevalent cause. This population is at greater risk of hypertensive emergencies.

Table 24: Common physical examination findings and history suggestive of secondary HTN

Body system	Finding (history/physical sign)	Possible etiology
Vital signs	Tachycardia	Hyperthyroidism, pheochromocytoma, neuroblastoma
	Decreased lower extremity pulses; drop in bp from upper to lower extremities	Coarctation of aorta
Eyes	Proptosis	Hyperthyroidism
	Retinal changes	Severe HTN
Ear, nose, throat	Adenotonsillar hypertrophy	Sleep-disordered breathing
	History of snoring	Sleep apnea
Height, Weight	Growth retardation	Chronic renal failure
	Obesity	Cushing syndrome
Facial appearance	Moon facies	Cushing syndrome
Neck	Webbed neck	Turner syndrome
	Goiter	Hyperthyroidism

Body system	Finding (history/physical sign)	Possible etiology
Skin	Pallor, flushing, sweating	Pheochromocytoma
	Acne, hirsutism, striae	Cushing syndrome, anabolic steroid abuse
	Café-au-lait spots	Neurofibromatosis
	Malar rash	Sle
	Acanthosis nigricans	T2 diabetes mellitus
Hematologic	Pallor	Renal disease, sickle cell anemia
Chest/cardiac	Chest pain, palpitations, exertional dyspnea	Cardiac disease
	Murmur	Coarctation of aorta
Abdomen	Abdominal mass	Wilm's tumor, neuroblastoma, pheochromocytoma
	Bruit (epigastrium, flank)	Renal artery stenosis
	Palpable kidneys	Polycystic kidney disease, hydronephrosis, multicystic dysplastic kidney
Genitourinary	Hematuria, edema, UTI, VUR	Renal disease
	Ambiguous or virilized genitalia	Congenital adrenal hyperplasia

Guidelines For Measurement of Blood Pressure In Children

- The child should be seated in a quiet room for 3–5 min before measurement, with the back supported and feet uncrossed on the floor.
- BP should be measured in the right arm for consistency, for comparison with standard tables, and to avoid a falsely low reading from the left arm in the case of coarctation of the aorta. The arm should be at heart level, supported, and uncovered above the cuff.
- The patient and observer should not speak while the measurement is being taken. The correct cuff size should be used. The bladder length should be 80%–100% of the circumference of the arm, and the width should be at least 40%. Blood pressure measurements are overestimated to a greater degree with a cuff that is too small than they are underestimated by a cuff that is too large. If a cuff is too small, the next largest cuff should be used, even if it appears large.
- For an auscultatory BP, the bell of the stethoscope should be placed over the brachial artery in the antecubital fossa, and the lower end of the cuff should be 2–3 cm above the antecubital fossa. The cuff should be inflated to 20–30 mm Hg above the point at which the radial pulse disappears. Overinflation should be avoided. The cuff should be deflated at a rate of 2–3 mm Hg per second. The first (phase i Korotkoff) and last (phase v Korotkoff) audible sounds should be taken as SBP and DBP. If the Korotkoff sounds are heard to 0 mm Hg, the point at which the sound is muffled (phase iv Korotkoff) should be taken as the DBP, or the measurement repeated with less pressure applied over the brachial artery. The measurement should be read to the nearest 2 mm Hg.
- To measure BP in the legs, the child should be in a prone position, if possible. An appropriately sized cuff should be placed midthigh and the stethoscope placed over the popliteal artery. The SBP in the legs is usually 10%–20% higher than the brachial artery pressure.

Interpretation of measured blood pressure using standard charts:

- Measure the height of the child
- Determine the height percentile of the child using the CDC growth charts by age and gender
- Plot the systolic and diastolic blood pressure against the height percentile of the child for his/her age and gender in the blood pressure percentile chart (in an appendix of the trainee manual) and document in notes

Table 25: Diagnostic testing recommendations for HTN in children

S.N.	Patient population	Tests
1.	All patients	• Urinalysis • Chemistry panel (electrolytes, blood urea nitrogen, and creatinine) • Lipid profile (fasting or non-fasting to include high-density lipoprotein and total cholesterol)
2.	Children < 6 years	Renal ultrasonography
3.	Children with abnormal urinalysis or renal function	Renal ultrasonography
4.	In the obese (BMI >95th Percentile) child or Adolescent	• Hemoglobin HbA1c • Aspartate transaminase and alanine transaminase • Fasting lipid panel • Urinalysis • Chemistry panel (electrolytes, blood urea nitrogen, and creatinine)

Other tests to be obtained based on history and physical examination can be done after referral to and consultation with the pediatrician/relevant subspecialty.

Management of Hypertension in Children

The overall goal for both primary and secondary HTN includes achieving BP target levels <90th percentile or <130/80 mm Hg, whichever is lower.

- Lifestyle and non-pharmacologic interventions
  - DASH (dietary approaches to stop hypertension) diet - high in fruits, vegetables, low-fat milk products, whole grains, fish, poultry, nuts, and lean red meats with a limited intake of sugar and sweets along with lower sodium intake
  - Physical activity - moderate to vigorous physical activity at least 3 to 5 days per week (30–60 minutes per session)
- Pharmacologic treatment with a single medication at the lowest possible dose in children with:
  - Hypertension despite a trial of 3–6 months of lifestyle modifications and weight loss
  - Symptomatic hypertension
  - Stage 2 HTN without a modifiable risk factor such as obesity
  - Any stage of HTN with CKD or diabetes mellitus
- Recommended initial drug for the treatment of HTN in children and adolescents should be provided based on etiology:
  - Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for children with diabetes mellitus (as long as GFR is > 30ml/min/1.73m^2)
  - Diuretics with/without calcium channel blockers in acute postinfectious glomerulonephritis-induced hypertension

A summary of commonly used drugs with dosing, safety profile, and side effects is listed in the table below:

Drug	Mechanism	Dose	Comments
Enalapril	ACE inhibitor	Initial: 0.08 mg/kg/day can be used once daily or BID.	Contraindicated during pregnancy and not advised in severe Renal disease. Monitor serum potassium and creatinine periodically.
Losartan	ARB	Initial: 0.7 mg/kg/day Max: 1.4 mg/kg/day up to 100 mg/day	FDA-approved for children older than 6 years
Amlodipine	Calcium Channel Blocker	Initial: 0.1 mg/kg/day used once daily or BID. Adolescents: 2.5 mg/day Max: 10 mg/day	May cause gingival hyperplasia, tachycardia, and/or edema
Frusemide	Diuretic	Initial: 0.5 - 2 mg/kg/day Max: 6 mg/kg/day	Monitor electrolytes periodically
Hydrochlorothiazide	Diuretic	1 mg/kg/day Max: 3 mg/kg/day up to 50 mg/day	Monitor electrolytes periodically

Follow-up and monitoring

- The child should be seen every 4–6 weeks for dose adjustment and/or the addition of a second/third drug until the target BP has been achieved
- Then every 3–4 months to assess adherence to treatment and laboratory testing (e.g., monitoring electrolytes for those on diuretics)

  If only lifestyle changes have been advised, the child can be followed up every 3–6 months to reinforce adherence and assess the need for initiation of medication

Acute Severe Hypertension

This is characterized by a BP of ≥ 30mm Hg above the 95th percentile based on age, sex, and height in children, and for older adolescents, the concerning BP is > 180/120, usually because of a rapid rise in BP.

Causes vary by age:

- Infancy: Congenital renal disease, renal vein thrombosis, coarctation of the aorta, bronchopulmonary dysplasia
- Childhood: Renal parenchymal disease. Renal vascular disease, endocrine, and drug – or toxin-induced disorders
- Adolescence: Renal parenchymal disease, primary HTN with nonadherence to treatment, use of drugs such as stimulants, anabolic steroids or corticosteroids, certain oral contraceptives, or certain illicit drugs like cocaine, marijuana, and amphetamines

Symptoms and signs

- Features of hypertensive encephalopathy: Headache, altered mental status (eg, lethargy, confusion, coma), seizures, and, in infants, irritability
- Heart failure with tachypnea, pulmonary edema, gallop rhythm, or a new or changed heart murmur.
- Renal insufficiency is usually asymptomatic, but peripheral edema may be present
- Hypertensive retinopathy, with papilledema, hemorrhages, and/or exudates

Diagnosis

- Blood pressure measurement
- Testing for target organ involvement in addition to history and physical examination findings:
  - Echocardiography (ECG) and chest x-ray to evaluate for heart failure and ventricular hypertrophy
  - Urinalysis to screen for renal parenchymal disease
  - Serum electrolytes, blood urea nitrogen (BUN), and creatinine to screen for kidney dysfunction (elevated creatinine) and adrenal abnormalities (low potassium)
  - Complete blood count to screen for hemolytic-uremic syndrome
  - CT or MRI of the head if significant neurologic findings
  - Drug and pregnancy tests (if eclampsia is suspected) in adolescents

Treatment:

- For hypertensive emergencies, admission to an intensive care unit (ICU) and initiation of IV antihypertensive drugs. The preferred IV drugs are labetalol and nitroprusside to be given as continuous IV infusions rather than bolus doses. A safe rate of lowering BP is to have the systolic BP decrease by 25% every 6 hours until the symptoms resolve. Then treatment can proceed more slowly until BP is ≤ the 95th percentile (or <140/90 in children >13 years).

  Important: Previously normotensive children with acute hypertension can be treated more aggressively than children with long-standing hypertension. Children with long-standing hypertension are less likely to have symptoms but are more likely to develop hypoperfusion and thus should have their BP lowered more slowly.

- For hypertensive urgencies, hospital admission and expeditious initiation of antihypertensive therapy is indicated. Intravenous therapy is not required, and oral antihypertensive agents can be given. As renal parenchymal (especially post-infectious glomerulonephritis and nephrotic syndrome) and renovascular disease are among the leading causes of hypertensive crises, preferred drugs are ACE inhibitors, beta blockers and loop diuretics, specially in patients with manifestation of fluid overload.

4.3. ACUTE RHEUMATIC FEVER

Introduction

Acute rheumatic fever (ARF) is a non-suppurative inflammatory sequel of group A Streptococcus (GAS) pharyngitis. ARF presents as fever, polyarthritis, pancarditis, chorea, and skin manifestations, occurring after a 2 to 3-week latent period. ARF is more common in children aged 5–15 years.

Rheumatic fever (RF) and Rheumatic Heart Disease represent a huge public health burden in developing countries with significant morbidity and mortality. Various study done in Nepal shows the prevalence of RHD to be around 1-7 per 1000 school children of age 5-16 years. Subclinical RHD exists in larger number in the community than the clinically evident one.

Signs and symptoms

The typical attack of ARF follows an episode of streptococcal pharyngitis after a latent period of 2 to 3 weeks. However, 1/3rd of the ARF develop after asymptomatic GAS infection. The major manifestations are carditis, arthritis, chorea, subcutaneous nodules, and erythema marginatum, independent of their severity. The minor manifestations are frequent and mostly related to the underlying systemic inflammation.

1. **Carditis:** Presents as sub-clinical to severe presentation with symptoms of heart failure such as shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, palpitation and has fulminating evolution and is usually diagnosed within the first 3 weeks of the acute episode. Endocarditis is the diagnostic hallmark of rheumatic carditis, being expressed by valvitis and mitral regurgitation is the dominant valvular lesion in over 90% of patients. It may be associated with aortic regurgitation. Isolated aortic regurgitation is seen in less than 5% of cases. Rheumatic carditis is characterized by pancarditis. However, pericarditis may rarely occur as a part of pancarditis which can present as chest pain and can produce mild pericardial effusion and myocarditis rarely.

   Subclinical carditis: Silent carditis, diagnosed by doppler echocardiography has been accepted as part of the spectrum of rheumatic carditis. The echocardiographic findings for subclinical RHD are mentioned in the annexure.
2. **Arthritis:** Polyarthritis is the most frequent major manifestation seen in older children, adolescents and adults. Polyarthritis is non-suppurative, asymmetric, migratory, and self- limited, which usually involves small joints of the hands and feet, but the shoulders, and hips are less commonly affected and the spine is rarely involved. Tenderness and severe pain, out of proportion to the findings of the physical examination, are the most prominent features. Redness, swelling and heat are usually less marked. Salicylates and nonsteroidal anti-inflammatory agents produce a marked and prompt relief of the symptoms and signs. Monoarthritis and polyarthralgia (after excluding other cause) has been also included as major criterion in revised Jones criteria for moderate-and high-risk populations.
3. **Sydenham's Chorea:** Usually affects children and adolescents, more commonly in pre-pubertal females. The latent period, after the streptococcal infection, is longer varying from1 to 7 months. Chorea may occur as an isolated manifestation, the so called pure chorea, or less frequently in association with carditis or arthritis which is usually a self- limited disorder, characterized by muscular weakness, hypotonia, and emotional instability, besides involuntary and purposeless but conscious movements of the skeletal muscles. One-fifth of patients have hemichorea, with the manifestations limited to one side of the body.
4. **Subcutaneous Nodules:** Subcutaneous nodules are seen over the extensor surface of joints and bony prominences, and are small, firm, painless, and freely movable under the skin.

5. **Erythema Marginatum:** Erythema marginatum is a very uncommon manifestation which is seen as a macular rash over the trunk, blanches on pressure, has a serpiginous or circular form, is painless and non-pruritic.

Diagnosis

Diagnosis of ARF is based on revised Jones criteria 2015, which includes major manifestations, minor manifestations, and evidence of preceding gas infection. Nepal falls into the moderate to high-risk population category (RHD prevalence of ≥2 per 100,000 school-aged children (usually 5–14 years old) per year or small-age RHD prevalence of >1 per 1,000 people per year).

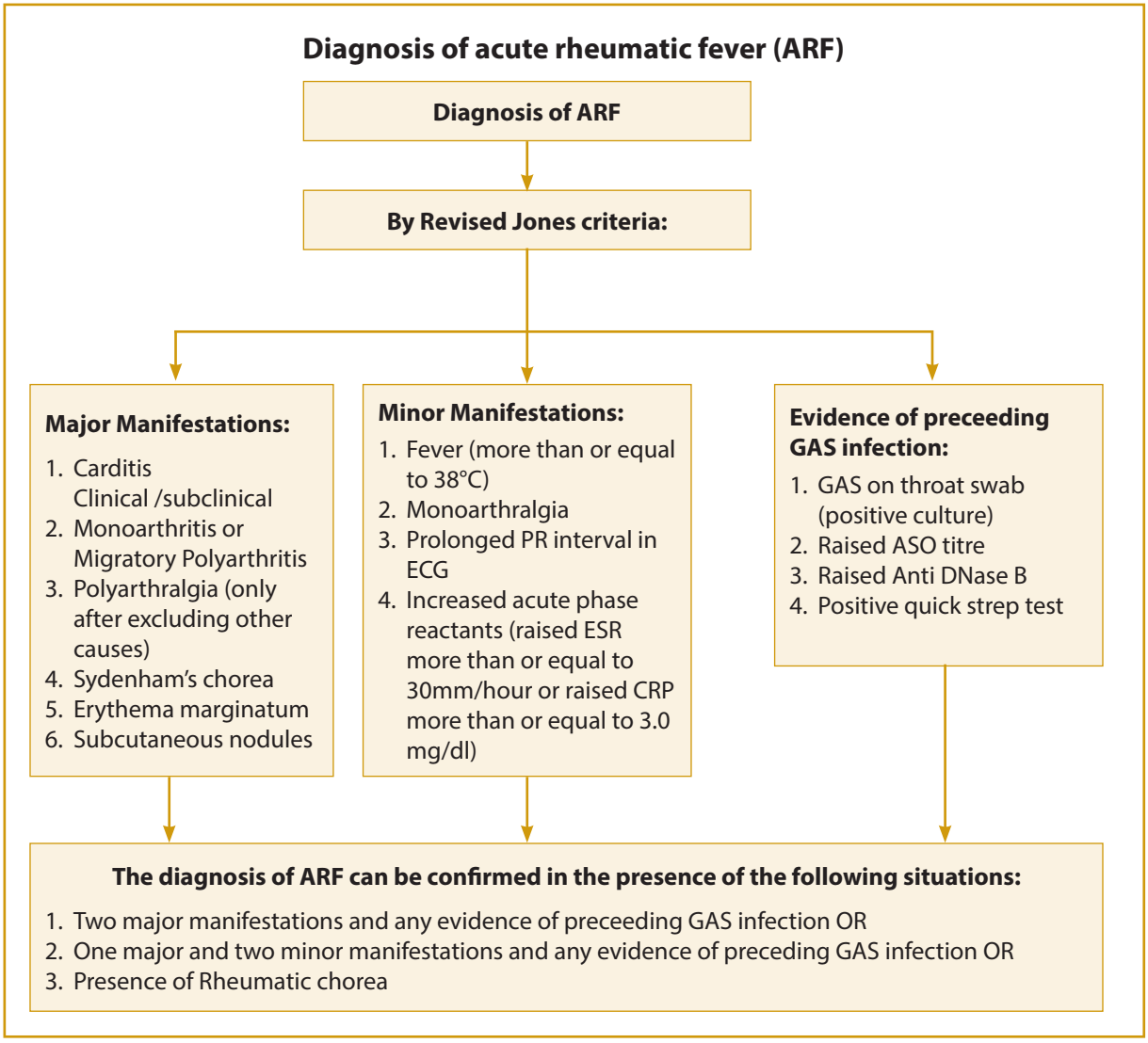
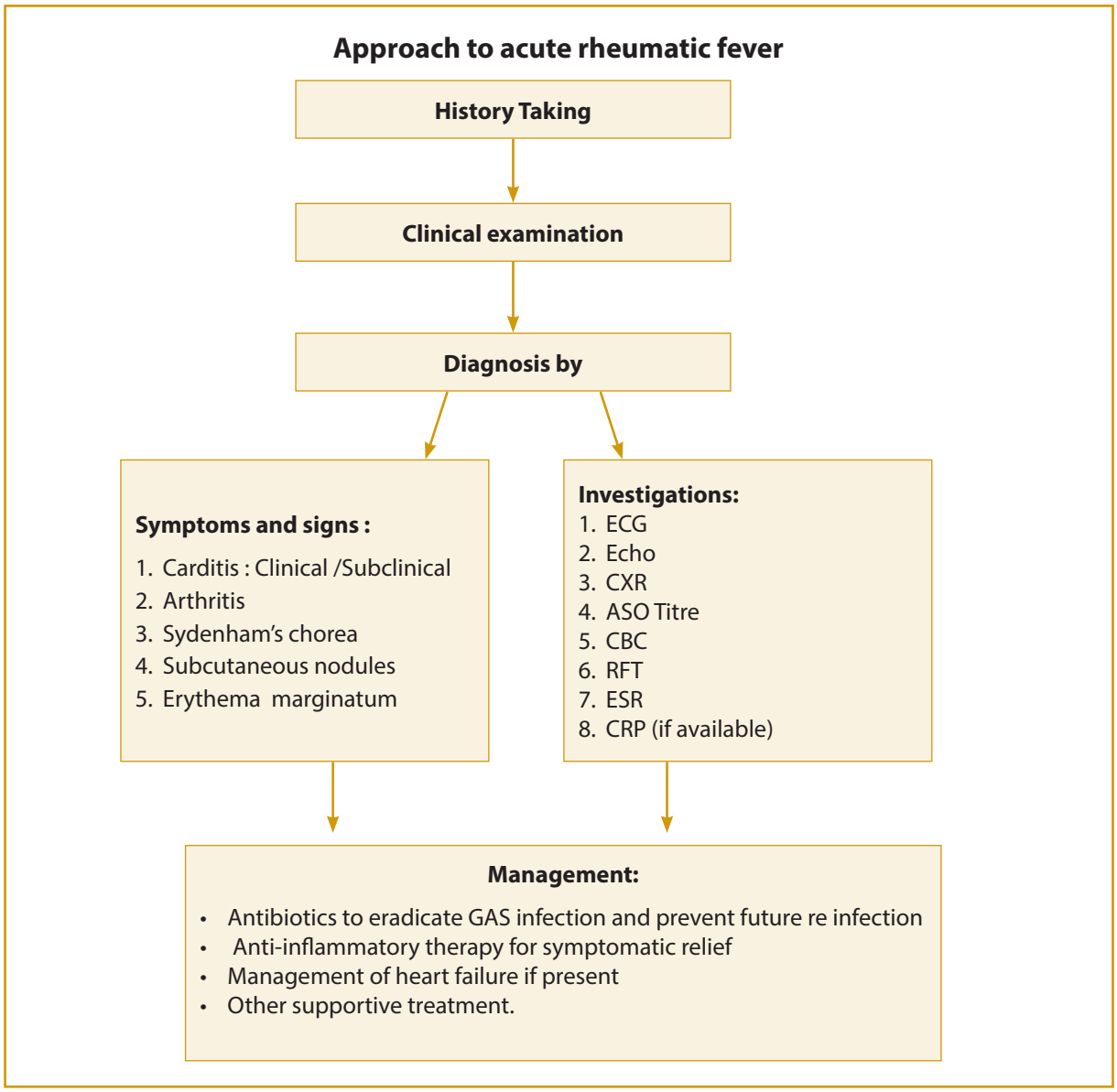


Figure 17: Diagnosis of Acute Rheumatic Fever (ARF)



Management

Treatment of ARF includes antibiotics to eradicate GAS infection and prevent future reinfection, anti-inflammatory therapy for symptomatic relief, management of heart failure if present, and other supportive treatment.

Antibiotics

All cases of ARF should receive a single injection of Benzathine penicillin g (BPG), 1.2 million units for >30kg and 0.6million units if <30 kg bodyweight), or

Oral penicillin V (children: 250mg QID, adults: 500 mg TDS) for10 days or Erythromycin if allergic to penicillin

Aspirin: (aspirin may mask symptoms of polyarthritis and fever. Paracetamol can be used until the diagnosis is confirmed). The usual dose of aspirin is 80-100mg/kg/day for children and 6-8 gm/day for adults in 4 divided doses (QID) for 4 weeks. Taper the dose once symptoms are resolved and the acute phase reactants (ESR, CRP) decrease. The total duration of treatment is 12 weeks but should be individualized depending on the severity of the illness.

Naproxen: If aspirin intolerance is detected: 10-20mg/kg/day

Prednisolone is indicated in the following situations:

1. Patients who do not tolerate aspirin
2. Patients who do not improve with aspirin
3. Patients with moderate to severe carditis

Dose of Prednisolone: 1-2mg/kg/day for 2-3 weeks then taper by 5 mg every 2-3 days and the total duration should be 8 to12 weeks. While tapering steroids, overlap with aspirin (initial dose 60mg/kg/day)

Heart failure should be treated according to the standard guidelines with anti-failure medications (e.g. Diuretics, ACEI, B-Blocker, and others). Limitation of physical activity and rest is recommended until symptoms get better. Fluid and salt restriction is advised. Anti-coagulant is indicated if atrial fibrillation is present.

Mild-moderate cases of chorea do not need medication. For severe cases, haloperidol, carbamazepine or valproic acid can be given (carbamazepine 4–10 mg/kg/day or valproic acid 20–30 mg/kg/day or haloperidol 2–6 mg/day).

When to refer a patient of ARF to a tertiary center for cardiac consultation:

Severe mitral stenosis and/ or regurgitation with heart failure after stabilization or those with refractory heart failure.

Prevention of RHD:

Rheumatic heart disease (RHD) is a preventable disease. The first episode of ARF can be prevented by treating a gas throat infection with an antibiotic. In patients who already have ARF, recurrent episodes of ARF can be prevented with long-term penicillin prophylaxis at regular intervals. This can prevent the progression of ARF to RHD.

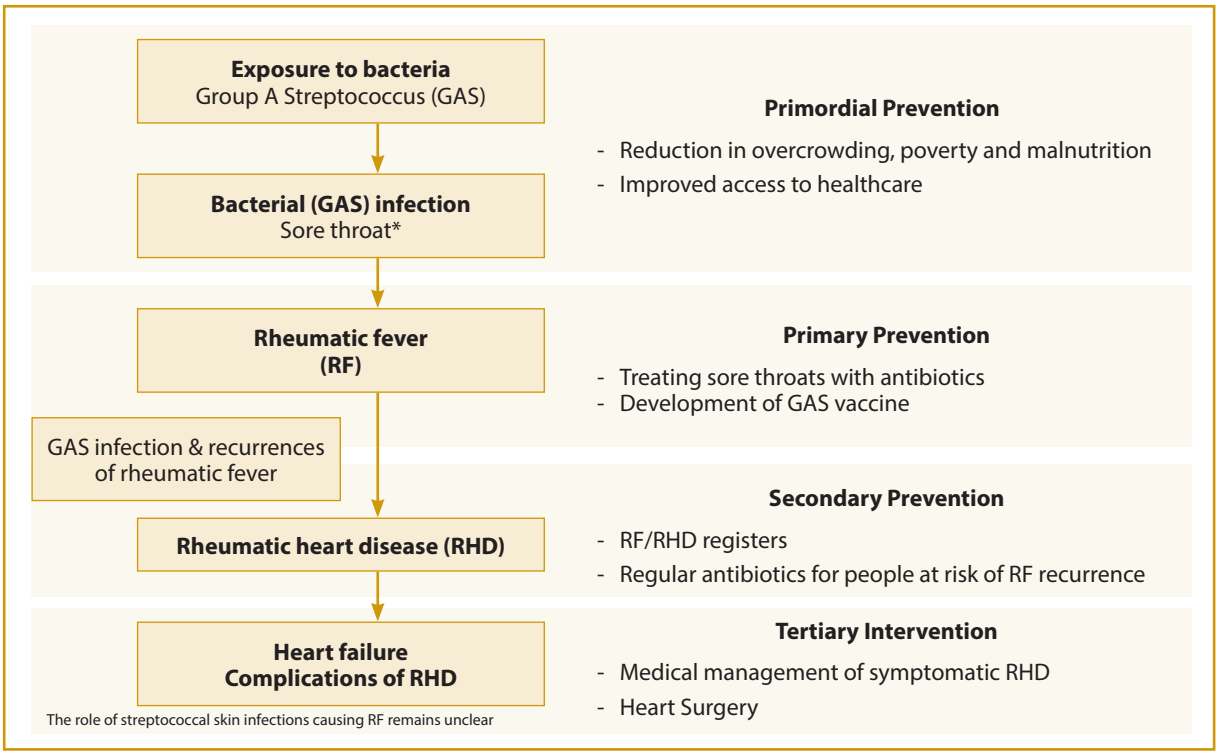


Figure 18: Prevention of RHD

Table 26: Differentiating signs and symptoms for tonsillopharyngitis: bacterial or viral

Type	Signs and symptoms
GAS	Throat pain, difficulty swallowing, enlarged tonsils, enlarged lymph nodes of the neck, enlarged tonsils with white or yellow spots, fever, absence of cough, headache
Viral	Cough, sneezing, runny nose, fever

Table 27: Primary prevention of rheumatic fever (treatment of streptococcal tonsillopharyngitis)

Agent	Dose	Mode	duration
Penicillin V	Children <27 kg: 250 mg three times daily; adolescents and adults: 500 mg two to three times daily	Oral	10 days
Amoxicillin	50mg/kg (maximum 1 g) once daily	Oral	10 days
Injection benzathine penicillin G	600,000 IU for patients <27 kg 1,200,000 IU for patients >27 kg	IM	Single dose
Cephalexin	Adult: 500mg twice daily Child: 25-50mg/kg twice daily	Oral	10 days
Cefuroxime	Adult: 250mg twice daily Child: 20mg/kg/day divided into 2 doses	Oral	10 days
Cefpodoxime	>12years: 100mg twice daily	Oral	5 to 10 days
	<12years: 5mg/kg twice daily		
Those Allergic to Penicillin			
Clindamycin	20mg/kg/day divided into 3 doses (maximum 1.8g/day)	Oral	10 days
Azithromycin	12 mg/kg once daily (maximum 500 mg)	Oral	5 days
Clarithromycin	15 mg/kg/day divided into 2 doses (max. 250 mg BID)	Oral	10 days

Secondary prevention of ARF:

Administration of specific antibiotics to patients with a previous attack of ARF, or well- documented RHD. The specific antibiotic with the mode of administration and their doses are mentioned in Table 28.

Table 28: Antibiotics for secondary prevention of acute rheumatic fever

Antibiotic	Mode of administration	Dose
Benzathine Penicillin G	Intramuscular injection	For adults and children >27kg : 1200000 units. For children <27kg: 600000 Iu.
Penicillin V.	Oral	<27 kg: 125 mg twice daily. >27 kg: 250 mg twice daily >27 kg: 250 mg twice daily.
Erythromycin (for individuals allergic to penicillin)	Oral	<27 kg: 125 mg twice daily. >27 kg: 250 mg twice daily.
Azithromycin	Oral	6mg/kg once daily

Table 29: Duration of therapy for secondary prevention of acute rheumatic fever

Category	Duration after the last attack
Rheumatic fever without carditis	5 years or until 21 years of age (whichever is longer)
No residual heart disease (Valvular Disease)	10 years or until 21years of age (whichever is longer)
Rheumatic fever with severe carditis and residual heart disease (persistent valvular disease) and post Intervention patients	Secondary prophylaxis until the age of 40 years Lifelong in severe disease or post-intervention patients

Continuation of care after return from tertiary care, if referred:

- Continue secondary prophylaxis
- Monitoring and evaluation of cardiovascular symptoms for progression of RHD as mentioned in RHD protocol

4.4. RHEUMATIC HEART DISEASE

Introduction

Rheumatic Heart Disease (RHD) is a sequelae of Acute Rheumatic Fever (ARF). The interval between the initial episode of RF and clinical evidence of valvular involvement is variable, ranging from a few years to more than 20 years. About 25% of all patients with RHD have isolated mitral stenosis (MS), and about 40% have combined MS and mitral regurgitation (MR). Multivalvular involvement is seen in 38% of patients, with the aortic valve affected in about 35% and the tricuspid valve in about 6%. Isolated MR accounts for 10–15% of chronic RHD patients. The pulmonic valve is rarely affected.

Symptoms

Gradually progressive dyspnea on exertion is the most common symptom of Rheumatic MS. Other symptoms are paroxysmal nocturnal dyspnoea, orthopnea, hemoptysis, palpitation, and swelling of limbs. Symptoms of chronic MR include exertional palpitation, dyspnea, fatigue, and pedal edema whereas acute MR presents symptoms of pulmonary edema. Rheumatic aortic stenosis (AS) patients are often asymptomatic and most patients are diagnosed incidentally. These patients can present with angina pectoris, syncope, and dyspnea. Chronic rheumatic aortic regurgitation (AR) patients are usually asymptomatic or can present with palpitation, shortness of breath, and angina.

Signs of RHD

a. Mitral Stenosis:

Mitral facies may be observed, i.e. a patchy, pinkish-purple appearance of the cheeks resulting from dilated venules. The arterial pulse has a normal or decreased pulse volume and a normal contour. Jugular venous pressure is normal in MS unless there is associated atrial fibrillation, pulmonary arterial hypertension, or right ventricular failure. Loud 1st heart sound (S1), opening snap, and mid-diastolic rumbling murmur are the typical auscultatory features in MS. The murmur is best heard with the bell of a stethoscope applied to the apical area with the patient lying supine on the left lateral decubitus position.

b. Mitral Regurgitation:

Cardiomegaly with displaced apical impulse, soft S1, loud S2 if pulmonary artery hypertension, presence of S3, pan systolic murmur in mitral area, mid-diastolic flow murmur at the mitral area.

c. Aortic Stenosis:

Small volume and slow upstroke arterial pulse with Pulsus Parvus Tardus. On auscultation, there is an aortic ejection systolic murmur at the right 2nd intercoastal space radiating to carotids and expiratory splitting of S2.

d. Aortic Regurgitation:

The left ventricular apical impulse is displaced and hyperdynamic with early diastolic murmur at the aortic and neo-aortic area or diastolic murmur at the mitral area (Austin Flint murmur). Patient with significant AR has peripheral signs of aortic regurgitation.

Diagnosis

a. Chest x-ray:

Mitral stenosis: Straightening of the left heart border, double right heart border, splaying of the carina. Features of pulmonary venous congestion (such as redistribution or cephalization of the

blood flow or interstitial edema with the presence of Kerley lines, peribronchial cuffing, background haze, septal and interstitial edema, pleural effusion or alveolar edema (bat wings appearance).

Mitral regurgitation: Shows enlarged left atrium (LA) and left ventricle(LV) and pulmonary venous congestion

Aortic regurgitation: LV-type cardiomegaly with features of pulmonary venous hypertension

Aortic stenosis: possible aortic calcification.

b. ECG:

Mitral stenosis: Classical P Mitrale, where the p wave is notched and broad in lead II and is biphasic. However, this finding is infrequently detected. Atrial fibrillation (AF) is common.

Mitral regurgitation: Features of enlarged LA and LV and may show atrial fibrillation.

Aortic stenosis: left ventricular hypertrophy (LVH) with or without t-wave inversion in v6.

Aortic regurgitation: Features of LV enlargement.

c. Echocardiogram:

Echocardiogram is done to confirm the diagnosis and evaluation of chamber size, valve morphology, valve stenosis or regurgitation, and ventricular function and detail will be mentioned in the echocardiographic manual.

Management

a. **Heart failure (HF):** Diuretics relieve pulmonary congestion, peripheral edema, and symptoms of dyspnea. Digitalis, beta-blocker, and diltiazem are useful to control ventricular rate in patients with AF. Vasodilators such as ACE-I and ARBs help to control hypertension and help alleviate symptoms in patients with AR.

b. **Anticoagulation (monitoring and dose adjustment):** Anticoagulation with warfarin is indicated in patients with atrial fibrillation or left atrial /left atrial appendage clot, and previous history of thromboembolism. Warfarin is usually started with 2 to 5 mg per day and the dose is adjusted to target INR of 2-3. Anticoagulation with warfarin should be continued for lifelong after metallic valve replacement and for the initial first 3 months after biological valve replacement.

c. **Referral for intervention (PTMC/Repair /Replacement):** All asymptomatic or symptomatic severe valvular heart disease should be referred for further evaluation and intervention in a tertiary center.

d. **Referral back and continuation of care at the First Level Hospitals:** Continue secondary prophylaxis of RHD and other drugs as per guidelines. Monitor and follow up for the progression of valvular heart disease and possible adjustment of medical management. Patients with RHD should be followed up on a regular basis. Asymptomatic patients with severe mitral regurgitation and LVEF >60% and severe aortic stenosis should be followed every 6 months by clinical and echocardiography examinations. Asymptomatic patients with clinically significant mitral stenosis and severe AR with normal LVEF should be followed up yearly. Asymptomatic patients with mild to moderate valvular heart disease and preserved LV function can be followed every year.

Table 30: Strategies for treatment of AF

Strategies	Drugs
Rate control – for hemodynamically stable patients with chronic AF and fast AV conduction	Digoxin, calcium channel blockers, beta-blockers
Rhythm control – for hemodynamically unstable patients with AF of recent onset	Electrical cardioversion Pharmacological cardioversion – amiodarone
Anticoagulation – for all patients	Warfarin to achieve INR of 2-3

Drugs Used In Management of Heart Failure:

Table 31: Diuretics dosage in heart failure

Drug	Starting dose	Target dose	Maximum dose
Furosemide	Adult : 20mg once daily Pediatric : 1 mg/kg/dose PO or IV	As required May increase to QID	240mg twice daily
Torsemide	Adult : 10mg once daily Pediatric : safety and efficacy not established	As required	200mg once daily
Metolazone	Adult :2.5mg once daily Pediatric: 0.2 mg/kg/dose PO	As required	10mg once daily
Hydrochlorothiazide	Adult dose: 25mg once daily Pediatric dose: 2 mg/kg/day PO divided BID	As required	50mg once daily

Table 32: ACEI/ARBS dosage in heart failure

Drug	Starting dose	Target dose
Enalapril	Adult dose :2.5 mg twice daily Pediatric dose: 0.1 mg/kg/d PO divided OD/BID, not to exceed 0.5 mg/kg/d	10mg twice daily
Ramipril	1.25mg once daily Pediatric doses not established	10mg once daily
Losartan	Adult dose: 25mg daily Pediatric doses not established	150mg daily

Contraindications to the use of ACEI and ARB are bilateral renal stenosis, history of angioedema, pregnancy, and known allergy to the drugs. Seek specialist advice when serum potassium of >5mmol/l and serum creatinine >2.25mg/dl and symptomatic hypotension. Half the ACEI/ARB dose if creatinine increases more than 50% compared to baseline. Stop ACEI/ARB if the increase is more than 100% and serum potassium is more than 5.5 mmol/l.

Table 33: Beta-blockers dosage in heart failure

Drug	Starting dose	Target dose
Carvedilol	Adult dose: 3.125 mg twice daily Pediatric dose: therapeutic dosage range of 0.2-0.4 mg/kg/dose PO BID; initiate with a lower dose and gradually increase dose QID 2-3 weeks to a therapeutic range	25 mg twice daily
Metoprolol Succinate	Adult dose :25mg once daily Pediatric dose not established	200mg once daily

Table 34: Aldosterone Antagonists dosage in heart failure

Drug	Starting dose	Target dose
Spironolactone	12.5 to 25mg once daily Pediatric dose: 1-3.3 mg/kg/day PO in single or divided doses	25mg once daily

Recommend an aldosterone antagonist (Spironolactone) in selected patients with decreased EF and NYHA class II to IV. These patients should be monitored carefully for renal function and potassium concentration. Patients should have a serum creatinine of 2.5mg/dl or lower in men and 2.0mg/dl or lower in women and the serum potassium should be <5.0meq/l.

Digoxin in Atrial Fibrillation and Heart Failure:

Digoxin in Atrial fibrillation

Rapid digitalizing (loading-dose) regimen

- IV: 8-12 mcg/kg (0.008-0.012 mg/kg) total loading dose; administer 50% initially; then may cautiously give 1/4 the loading dose q 6-8 hr twice; perform a careful assessment of clinical response and toxicity before each dose
- PO: 10-15 mcg/kg total loading dose; administer 50% initially; then may cautiously give 1/4 the loading dose q 6-8 hr twice; perform a careful assessment of clinical response and toxicity before each dose

Maintenance

- PO: 3.4-5.1 mcg/kg/day or 0.125-0.5 mg/day PO; may increase the dose every 2 weeks based on clinical response, serum drug levels, and toxicity
- IV: 0.1-0.4 mg OD; IM route not preferred due to severe injection site reaction

Digoxin in Heart failure

- Preterm infants: 0.005 mg/kg/d PO divided into two doses or 75% of this dose IV.
- For children above the age of 10 years: 0.005 mg/kg/d PO daily or 75% of this dose IV.
- For adults: 0.125-0.25 mg PO q day;
- A loading dose to initiate digoxin therapy in patients with heart failure is not necessary.

Table 35: Inotropic Agents and Vasodilators for Acute Decompensated Heart Failure

Inotrope	Dose	Comments
Dobutamine	5-10 mcg/kg/min iv	Gradually titrate upward to desired effect
Dopamine	5-10 mcg/kg/min IV (usual dosage; maximal dosage may be up to 28 mcg/kg/min)	Gradually titrate upward to desired effect
Epinephrine	0.01-0.03 mcg/kg/min IV	Not to exceed 0.1-0.3 mcg/kg/min
Nitroglycerin	Pediatric dose : 0.1-0.5 mcg/kg/min IV Adult dose: 20 mcg/min to an effective dose of 40 to 400 mcg/min	Watch for hypotension, headache and tolerance with continuous use after 24 hours

4.5. ISCHEMIC HEART DISEASE

Introduction

Ischemic heart disease can present as stable ischemic heart disease (chronic stable angina) or as an acute coronary syndrome (ST elevation MI, non-ST elevation MI, unstable angina).

Etiopathogenesis

Stable ischemic heart disease (SIHD) is most commonly caused by atheromatous plaque that obstructs or gradually narrows the epicardial coronary arteries. Myocardial ischemia and myocardial infarction (mi) can result from various coronary disease processes, including vasospasm, increased myocardial demand in the setting of a fixed coronary lesion, and erosion or rupture of vulnerable atherosclerotic plaque leading to acute thrombus formation and subsequent ischemia. The atherothrombotic lesion is the hallmark pathobiological event of an acute coronary syndrome and the reduction in flow may be caused by a completely occlusive thrombus or by a sub-totally occlusive thrombus. All result in myocardial oxygen supply-demand mismatch and can precipitate ischemic symptoms, and all processes, when severe or prolonged, will lead to myocardial necrosis or infarction and present as an acute coronary syndrome.

Stable ischemic heart disease (SIHD)

The SIHD is a broad term and includes individuals with chronic stable angina, asymptomatic ischemia, prior myocardial infarction, and prior coronary revascularization, as well as individuals with non-obstructive coronary atherosclerosis, including micro vascular disease. The common clinical presentation of SIHD is chronic stable angina. A stabilized, frequently asymptomatic phase following an acute coronary syndrome (ACS) is also classified as SIHD.

Diagnosis

Clinical history of angina:

A detailed clinical history of angina includes assessing the magnitude, location, severity, duration, and precipitating factors of angina. The presence of a typical nature of the discomfort, precipitating factors and relieving factors should be suggestive of angina. Retrosternal chest pain, heaviness, pressure type with radiation to neck, jaw, epigastrium, shoulder, and left arm. Patients are usually asymptomatic at rest and chest pain is precipitated by exercise, cold weather, or emotional stress with a duration of 2 to 10 min and relieved by rest or taking sublingual nitrates. In addition to chest discomfort, dyspnea, palpitations, syncope or fatigue may also be present and sometimes may be the only symptom. Physical examination is required to corroborate and strengthen the diagnosis.

Investigation:

1. ECG to look for ischemic changes
2. X-ray Chest to rule out other causes of chest pain
3. Echocardiography to look for regional wall motion abnormalities and evaluation of ventricular function
4. Basic laboratory investigations: complete blood count, kidney function test, lipid profile, blood glucose
5. Stress testing in low to intermediate pretest probability of CAD (refer to tertiary center):
   Tread mill exercise testing: for those who can exercise
   Pharmacological stress testing: who cannot exercise to an adequate workload
6. Referral for CT coronary angiogram: in low to intermediate pretest probability of CAD
7. Referral for an invasive coronary angiogram is indicated in patients with frequent, significant symptoms, patients with high-risk features on non-invasive testing

Management:

The treatment of stable angina includes anti-anginal medication, medication to modify atherosclerosis and aggressive treatment of causative risk factors.

A. Lifestyle management and risk factor modifications:

1. Stop smoking.
2. Patients with previous acute MI, coronary artery bypass graft (CABG), percutaneous coronary interventions (PCI), stable angina pectoris, or stable chronic heart failure should be enrolled in exercise programs. Exercise should be gradually instituted and exercise prescription should be individualized with a goal of at least moderate-intensity aerobic exercise training, >3 times a week and 30 min per session.
3. Weight reduction in overweight and obese people is recommended to have favourable effects on blood pressure and dyslipidemia. More precisely, it is recommended to attain a BMI of <22.9 kg/ m2 and a waist circumference of 90 cm in men and 80 cm in women to minimize cardiovascular risk.
4. All the SIHD patients should be treated with statins (atorvastatin 20 to 80mg/d or rosuvastatin 10 to 40 mg/ day) to achieve optimal LDL-c goal <70 mg/dl.
5. All the SIHD patients with hypertension should be recommended to attain the SBP/DBP goal of 130/80 mm Hg with medical management.
6. HbA1c of < 7.0% should be the objective while treating SIHD patients with diabetes.
7. Patients should be counselled regarding proper diet.

B. Pharmacological management

A. Relief of angina symptoms

1. Short-acting nitrates are indicated for the immediate relief of anginal symptoms.
2. Beta-blockers and/or CCBs are the initial agents for long-term symptoms management and heart rate control based on co-morbidities, contraindications and patient preference.
3. The combination of non-DHP CCB with beta-blocker should be avoided in patients with an anticipated risk of atrioventricular block or severe bradycardia.
4. The addition of long-acting nitrates, trimetazidine or nicorandil is indicated in case of intolerance or contraindications or failure in achieving pain control by beta-blockers and calcium channel blockers. Consider referral to a cardiologist at this stage.
5. Ivabradine may be considered in symptomatic patients who do not tolerate beta-blockers or in whom the resting heart rate remains above 70 bpm, despite administration of the full tolerable dose of beta-blockers. Consider referral to a cardiologist at this stage.

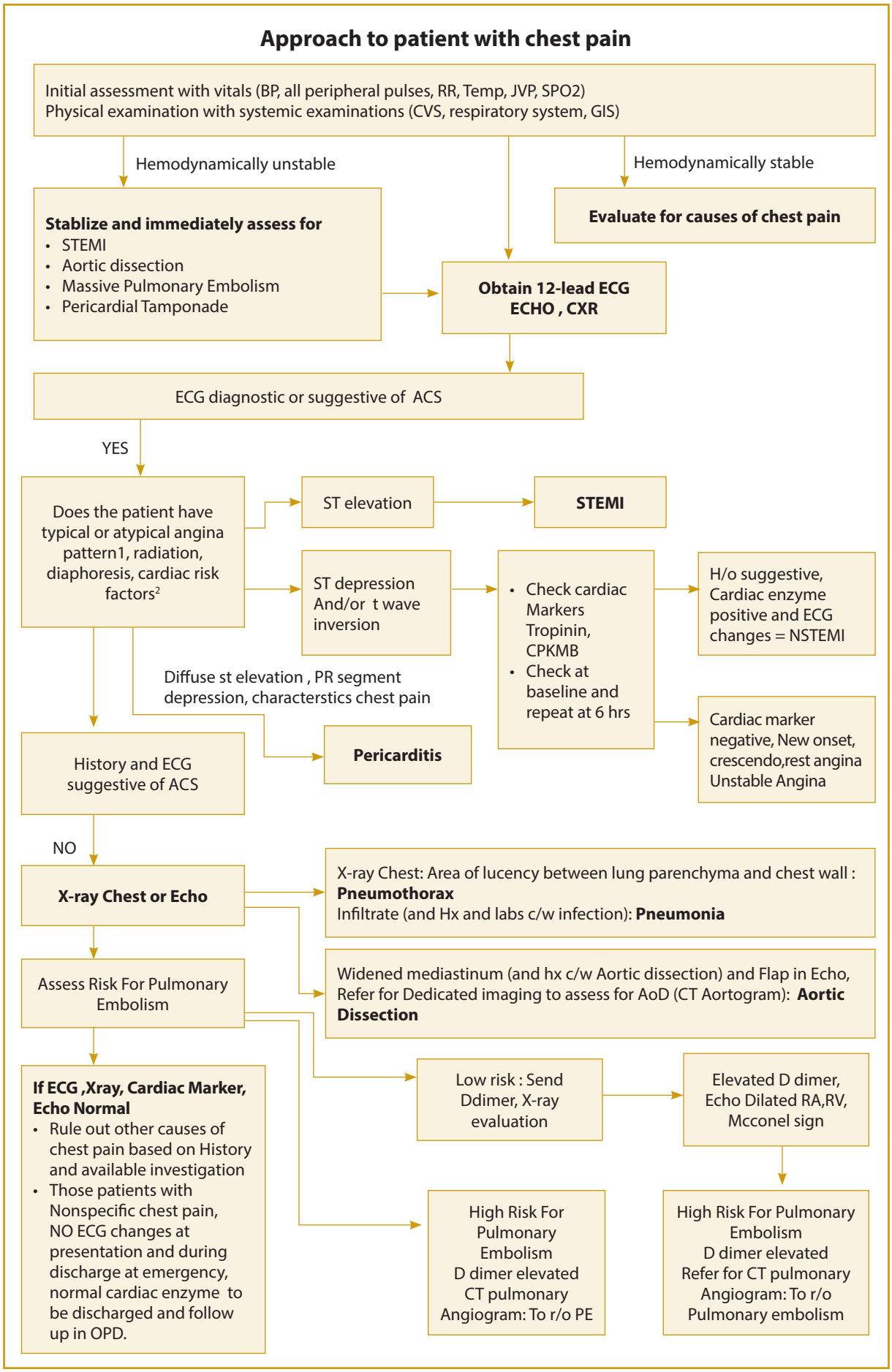
C. Recommendations on event prevention:

1. Daily low-dose aspirin 75 mg OD is recommended in all SIHD patients if not contraindicated.
2. Clopidogrel 75 mg PO OD is recommended in patients with aspirin intolerance.
3. High-intensity statins should be prescribed in all patients with SIHD irrespective of lipid levels.
4. All stable angina patients with diabetes, hypertension, heart failure or chronic kidney disease should be recommended to receive ACEIS/ARBS if no contraindications.

D. Referral:

Consider referral of patients for definite diagnosis and possible revascularization when symptoms are uncontrolled by optimal medical therapy alone and/or have high-risk features in non-invasive testing.

Approach to patient with chest pain



4.6. ACUTE CORONARY SYNDROME (ACS)

Introduction

ACS represents broad ranging disease conditions, that includes ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA).

Diagnosis

1. Unstable Angina: Chest pain (rest angina, crescendo angina, new onset), ECG changes and normal cardiac marker elevated.
2. NSTEMI: Chest pain (typical and atypical angina), ECG changes and elevated biomarkers.
3. STEMI: Chest pain (typical and atypical angina), typical ST elevation or Q waves in ECG and elevated biomarkers.

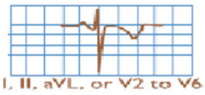
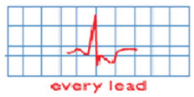
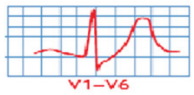
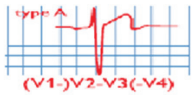
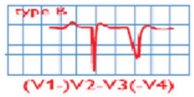
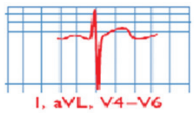
	ECG pattern	Criteria	Signifying	Figure
a	Normal ECG		No clue	
b	Isolated T-wave inversion	T-wave inversion >1 mm in ≥5 leads considering I, II, aVL, and V2-V6	Only mildly impaired prognosis	
c	ST-segment depression	J point depressed by ≥0.05mm in leads V2 and V3 or ≥1 mm in all other leads followed by a horizontal or downsloping ST-segment for ≥0.08 s in ≥1 leads (except aVR)	More severe ischaemia	 
d	Transient ST-segment elevation	ST-segment elevation in ≥2 continuous leads of ≥0.25 mV in men <40 years, ≥2 mm in men ≥40 years, or ≥0.15 mV in women in leads V2 through V3 and/or ≥0.1 mV in other leads lasting <20 min	Only mildly impaired prognosis	
e	De Winter ST-T	1-3 mm upsloping ST-segment depression at the J point in leads V1-V6 that continue into tall, positive, and symmetrical T waves	Proximal LAD occlusion/severe stenosis	
f **g**	Wellens sign	isoelectric or minimally elevated J point (<1mm) + biphasic T wave in leads V2 and V3 (type A) or symmetric and deeply inverted T waves in leads V2 and V3, occasionally in leads V1, V4, V5 and V6 (type B)	Proximal LAD occlusion/severe stenosis	 
h	Resting U wave inversion	Discrete negative deflection in the T-P segment (negative in comparison to the following P-R segment) no initial positive U wave deflection not obscured by fusion with terminal T wave or following P wave in I, aVL, and V4 through V6	Occlusion or severe stenosis of the left main artery or LAD	
i	Low QRS voltage	Peak to peak QRS complex voltage <0.5 mV in all limb leads and <1.0 mV in all precordial leads	High risk for in-hospital mortality	

Figure 19: 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: supplementary data

Unstable Angina/NSTEMI

The pain of myocardial ischemia is usually located in the retrosternal area but it may be felt in the epigastrium, upper back, arms or jaw; the description may be expressed as burning squeezing heaviness. Patients can present with prolonged (>20 min) chest discomfort at rest. New-onset (de novo) less than 3 months, severe angina (class III or IV), recent destabilization of previously stable angina with CCS class III angina characteristics (crescendo angina) post-myocardial infarction (MI) angina. Additional symptoms such as sweating, nausea, epigastric pain, dyspnoea, and syncope may be present.

Atypical complaints (e.g. isolated epigastric pain, indigestion-like symptoms, and isolated dyspnea or fatigue) are more often observed in the older patient, in women, and in patients with diabetes, chronic renal disease, or dementia.

Note: older age, male sex, family history of coronary artery disease (CAD), diabetes, hyperlipidemia, smoking, hypertension, renal dysfunction, a previous manifestation of CAD, and peripheral or carotid artery disease increase the likelihood of NSTE-ACS.

Physical examination:

Frequently unremarkable in patients with suspected NSTE-ACS. Physical examinations are done to look for signs of heart failure or hemodynamic or electrical instability.

Electrocardiogram (ECG): The resting 12-lead ECG is recommended to be performed within 10 minutes of the patient's arrival in the emergency room and to obtain an additional 12-lead ECG in case of recurrent symptoms or diagnostic uncertainty.

The ECG in the setting of NSTE-ACS may be normal in more than 30% of patients, characteristic abnormalities include st-segment depression, transient st-segment elevation, and t-wave changes. If the standard leads are inconclusive and the patient has signs or symptoms suggestive of ongoing myocardial ischemia, additional leads should be recorded; v7 to v9 or v3r and v4r. In patients with right bundle branch block (RBBB), ST-segment depression in lead 1, AVl, and V5,6 is indicative of ACS. In patients with paced ventricular beats, the ECG is often of no help for the diagnosis of ACS.

All patients diagnosed with ACS need to be risk stratified as below:

Very high-risk criteria:

- Hemodynamic instability or cardiogenic shock
- Recurrent or refractory chest pain despite medical treatment
- Life-threatening arrhythmias
- Mechanical complications of MI
- Heart failure related to NSTE-ACS
- Presence of ST-segment depression >1 mm in ≥6 leads additional to ST-segment elevation in AVR and /or V1

High-risk criteria:

- Diagnosis of NSTEMI
- Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischemia
- Transient ST-segment elevation
- Grace risk score >140

Medical therapy

1. Aspirin loading dose of 300 mg orally or, followed by 75 mg PO OD.
2. Clopidogrel loading dose of 600 mg orally, followed by 75 mg OD.
3. High-doses statin therapy: Atorvastatin 20 to 80 mg or rosuvastatin 20 to 40 mg daily.
4. Sublingual or IV Nitrates and early initiation of beta-blocker treatment to be started in patients with ongoing ischemic symptoms and without contraindications. IV nitrates are recommended in patients with uncontrolled hypertension or signs of heart failure.
5. Low molecular weight heparin (Enoxaparin) 1mg/kg bd; if creatinine clearance <30ml/min: 1mg/kg OD for 5 to 7 days.
6. ACE inhibitors (or ARBs in cases of intolerance to ace inhibitors) in patients with heart failure with reduced LVEF (<40%), diabetes, or CKD unless contraindicated.
7. Beta-blockers in patients with systolic LV dysfunction or heart failure with reduced LVEF (<40%).
8. Mineralocorticoid receptor antagonist (Aldactone) in patients with heart failure with reduced LVEF (<40%).

Refer all patients with very high and high-risk criteria to a tertiary care center after initial stabilization.

ST Elevation Myocardial Infarction (STEMI):

Signs and symptoms

Acute onset, precordial retrosternal discomfort, commonly described as a pressure, crushing, aching, or burning sensation. Pain is prolonged and lasts for more than 30 minutes duration and may radiate to the neck, back and arms which is associated with nausea and vomiting, sweating, breathlessness, extreme distress and a fear of impending death.

Approximately 20% of AMI patients are asymptomatic or have atypical symptoms, especially in elderly women and diabetics

Physical examination:

- Patients are often anxious and in considerable distress.
- Heart rate varies from normal to marked bradycardia, rapid regular or irregular tachycardia, depending on the underlying rhythm and degree of LV failure.
- Blood pressure is usually normal, but the hypertensive response may be a consequence of adrenergic discharge secondary to pain, anxiety, and agitation.
- Left ventricular (LV) dysfunction at presentation may have tachypnea, tachycardia, pulmonary rates, and a third heart sound (s3)
- In patients with right ventricular (RV) infarction, increased jugular venous pressure, Kussmaul sign (rise in jugular venous pressure with inspiration), and an RV third sound may be present

Electrocardiogram:

- New ST elevation of >0.1mv at the j point in two contiguous leads in all leads other than leads v2-v3.
- For leads v2-v3 the following cut points apply:
  ≥0.2 mV in men≥40 years,
  ≥0.25 mV in men <40 years, or
  ≥0.15 mV in women

STEMI with LBBB or paced rhythm:

A Sgarbossa criterion is well-validated for STEMI.

- concordant st-elevation of 1mm = 5 points
- concordant st-depression of in v1-v3 = 3 points
- discordant st-elevation of 5 mm = 2 points

A score of 3 or more has 90% specificity for myocardial infarction.

Cardiac biomarkers:

High-sensitive cardiac troponin T (HS-CTn T) is currently the preferred biomarker for myocardial damage because of their high sensitivity and specificity. Cardiac troponin T and I (cTnT and cTnI) is the best alternative and CK-MB if cardiac troponin assays are not available.

CK-MB, because of its more rapid appearance and disappearance from the blood, can be used in patients presenting early after symptom onset, to time the onset of injury if the troponin is increased and to detect re-infarction later in the hospital course. CK-MB appears in serum within approximately 3 hours after the onset of infarction, reaches peak levels at 12 to 24 hours, and has a mean duration of activity of 1 to 3 days.

The preferred biomarker to detect myocardial injury is cardiac troponin. The level starts to rise 3 to 12 hours after the onset of ischemia, peaks at 12 to 24 hours, and may remain elevated in cTnI for 7 to 10 days and cTnT for up to 10 to 14 days. The prolonged time course of the elevation in cTnT and cTnI is advantageous for the late diagnosis of MI.

Emergency room assessment and management:

The cornerstone of STEMI therapy is a rapid and accurate evaluation at first medical contact. A focused history and physical examination assessing the symptoms and signs should be quickly performed.

ECG should be obtained within the first 10 minutes of arrival at the emergency department.

If STEMI is diagnosed, the following measures should be administered:

1. Absolute bed rest.
2. Continuous hemodynamic monitoring and ready access to defibrillation should be available.
3. Intravenous (IV) access is mandatory.
4. Antiplatelet therapy:
   Aspirin ~ chewable tablet 300 mg stat.
   Clopidogrel ~ 300 mg orally if thrombolytic therapy (600 mg, if primary PCI) is planned.
5. Oxygen supplement if clinically significant hypoxemia (spo2 < 90 %.) Or if there is evidence of heart failure. Oxygen is not routinely indicated in acute STEMI.
6. Pain management: for STEMI patients with ongoing ischemic discomfort morphine sulphate (2 to 4 mg IV) is the analgesic of choice. It could be repeated at 5 to 15 minutes intervals with increment of 2 to 8 mg IV. IV pethidine with prochlorperazine can be considered.
7. Sublingual nitroglycerin 0.5 mg (can repeat every 5 minutes for a total of 3 doses, after that intravenous nitroglycerin should be considered.
8. ST elevation in the right-sided lead (rv3/rv4) in inferior MI indicates RV infarction. It should be treated initially with 1-2 liters of normal saline and/or inotropes, nitrate should be avoided.
9. Emergency echocardiography: in the acute phase when the diagnosis is in doubt emergency echocardiography may be useful, to rule out complications of MI and to see ejection fraction.
10. High-dose statin therapy (atorvastatin 40 / 80 mg or rosuvastatin 20 to 40 mg).

Reperfusion therapy:

The primary goal in the management of acute STEMI is to institute reperfusion therapy as soon as possible if patients present within less than 12 to 24 hrs of symptom onset. It may be either- primary PCI or thrombolytic therapy or a pharmaco-invasive strategy.

- Primary PCI is recommended if a patient can be transferred to primary PCI-capable hospital within 120 minutes of first medical contact. If the time duration is > 120 minutes or no such facility is available then fibrinolytic therapy should be initiated within 10 minutes of STEMI diagnosis.
- If primary PCI could not be done within the recommended time frame, then thrombolysis becomes the treatment of choice.
- Primary PCI is also indicated beyond 12 hrs in conditions like hemodynamic instability, cardiogenic shock, ongoing chest pain refractory to medical therapy, acute heart failure, life-threatening arrhythmia and cardiac arrest.
- It is recommended to transfer the patient for a coronary angiogram to PCI capable hospital within 2-24 hrs even after successful thrombolysis (pharmaco-invasive therapy) or for rescue PCI in case of failed thrombolysis.

Indication of thrombolytic therapy:

1. ST elevation as described above (STEMI)
2. Symptom onset less than 12 hrs before presentation
3. No contraindications

Table 36: Contraindications to fibrinolytic therapy

Absolute contraindications	Relative contraindications
▪ Previous intra-cranial hemorrhage (ICH) ▪ Stroke of unknown origin at any time ▪ Ischemic stroke in the past 6 months ▪ Central nervous system damage ▪ Malignant intracranial neoplasm ▪ Other intracranial lesions (aneurysm or av malformation) ▪ History of the closed head or facial trauma within 3 months ▪ Major trauma/surgery within the preceding 3 weeks suspected aortic dissection ▪ Active bleeding or known bleeding diathesis (excluding menses) ▪ Gastrointestinal bleeding within the past month non-compressible punctures in	▪ Previous ischemic stroke beyond 12 months ▪ Transient ischemic attack in the preceding 6 months ▪ Oral anticoagulation therapy ▪ Pregnancy or within 1 week postpartum ▪ Recent (2-4 weeks) internal bleeding ▪ Prolonged or traumatic CPR ▪ Active peptic ulcer (only if the ulcer is actively bleeding; if only stool occult blood positivity, may be considered for thrombolysis) ▪ Severe uncontrolled hypertension (SBP >180mm Hg and/or DBP > 110 mm Hg) ▪ Patients presenting with hypertension should be administered beta-blockers, nitroglycerin and analgesics promptly to lower blood pressure and reduce risk of ICH following thrombolysis ▪ Patients on warfarin therapy have higher rates of hemorrhage: higher the INR, the higher risk of advanced liver disease ▪ Infective endocarditis

Thrombolytic agents

Tenecteplase is fibrin specific, more potent, and can be repeated, a single dose hence is preferred.

Single dose IV bolus of tenecteplase:

- 30 mg if < 60 kg
- 35 mg if 60-70 kg
- 40 mg if 70-80 kg
- 45 mg if 80-90 kg
- 50 mg if ≥ 90 kg
- Half dose should be given if patient is >75 years

Streptokinase is cheaper (fibrin non-specific) and other agents are **alteplase and reteplase.**

The benefit of thrombolytic therapy appears to be greatest when agents are administered as early as possible, with the most dramatic results occurring when the drug is given less than 1 to 2 hours after symptom onset.

Criteria for successful thrombolysis: Resolution of ST-segment elevation at least 50% in 60-90 minutes, relief of ischemic symptoms, reperfusion arrhythmia and early peaking of cardiac enzymes indicate successful thrombolysis.

Routine medical therapies:

Antiplatelet therapy:

Aspirin is recommended indefinitely in all patients with STEMI (75–100mg). Clopidogrel, unless contraindicated, should be initiated upon presentation of STEMI. Loading dose of 300 to 600 mg orally, followed by 75 mg daily. (600 mg loading dose in a patient undergoing primary PCI). And this should be used along with aspirin, ideally at least for 12 months.

Antithrombin therapy:

Either unfractionated heparin/enoxaparin/fondaparinux

Unfractionated heparin: 60 u/kg IV bolus with a maximum of 4000 u followed by an IV infusion of 12 u/ kg with a maximum of 1000 u/hours for 24 to 48 hours. Target APTT: 50 to 70s or 1.5 to 2.0 times that of control to be monitored at 3,6,12 and 24 hours.

Enoxaparin:

- In patients <75 years of age: 30 mg iv bolus followed 15 minutes later by 1 mg/kg SC every 12 hours until hospital discharge or a maximum of 8 days. The first two doses should not exceed 100 mg
- In patients >75 years of age: no IV bolus. Start with the first SC dose of 0.75 mg/kg with a maximum of 75 mg for the first two SC doses
- In patients with creatinine clearance of <30 ml/min regardless of age the SC doses are given once every 24 hours.

Fondaparinux: 2.5 mg IV bolus; followed by a SC dose of 2.5 mg once daily for 8 days or till hospital discharge. Special attention must be given to proper dosing of antithrombotic in elderly and renal failure patients.

Beta-blocker (metoprolol succinate, bisoprolol, carvedilol): Oral beta-blockers should be initiated in the first 24 hours in patients with STEMI who do not have signs of heart failure, evidence of a low output state, increased risk for cardiogenic shock, or other contraindications in use of oral beta blockers (PR interval more than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease).

Renin-angiotensin-aldosterone system (RAAS) inhibitors (Spironolactone): Administered within the first 24 hours to all patients with STEMI with anterior location, HF, or ejection fraction (EF) less than or equal to 40%, unless contraindicated. ACE inhibitors are also reasonable for all patients with STEMI and no contraindications to their use

Angiotensin receptor blocker (ARB): It should be given to patients with STEMI who have indications but are intolerant of ACE inhibitors. It should also be used for all STEMI with LV systolic dysfunction with EF <35%.

Lipid management: High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use. Commonly used statins are atorvastatin 40-80 mg, and rosuvastatin 20-40 mg daily. Fasting lipid profile in patients with STEMI, preferably within 24 hour should be obtained.

Nitrates: It should not be given to patients with hypotension, marked bradycardia or tachycardia, RV infarction, or 5-phosphodiesterase inhibitor use within the previous 24 to 48 hours. There is no role for the routine use of oral nitrates in the convalescent phase of STEMI.

Calcium channel blockers: Calcium channel blockers may be useful to relieve ischemia, lower BP, or control the ventricular response rate of atrial fibrillation (AF) in patients who are intolerant of beta blockers. Caution is advised in patients with LV systolic dysfunction.

Risk assessment after STEMI

LVEF should be measured in all patients with STEMI by echocardiography.

Lifestyle modification and long-term therapy

- Smoking cessation
- Diet: low fat, low salt, food rich in fiber, and plenty of fruits and vegetables.
- Weight loss, if obese.
- Exercise-based cardiac rehabilitation
- Management of co-morbidity: blood sugar control, tight blood pressure control
- Dual antiplatelet therapy (DAPT), combining aspirin and a P2Y12 inhibitor (clopidogrel), is recommended in patients with STEMI who are undergoing primary PCI or thrombolysis (for up to 12months). Aspirin is recommended indefinitely in all patients with STEMI (75–100mg)
- Adherence to the treatment prescribed by the cardiologist/physician, which generally includes Betablockers, Statins and ACEI or ARBs.

Approach to patient with acute coronary syndrome

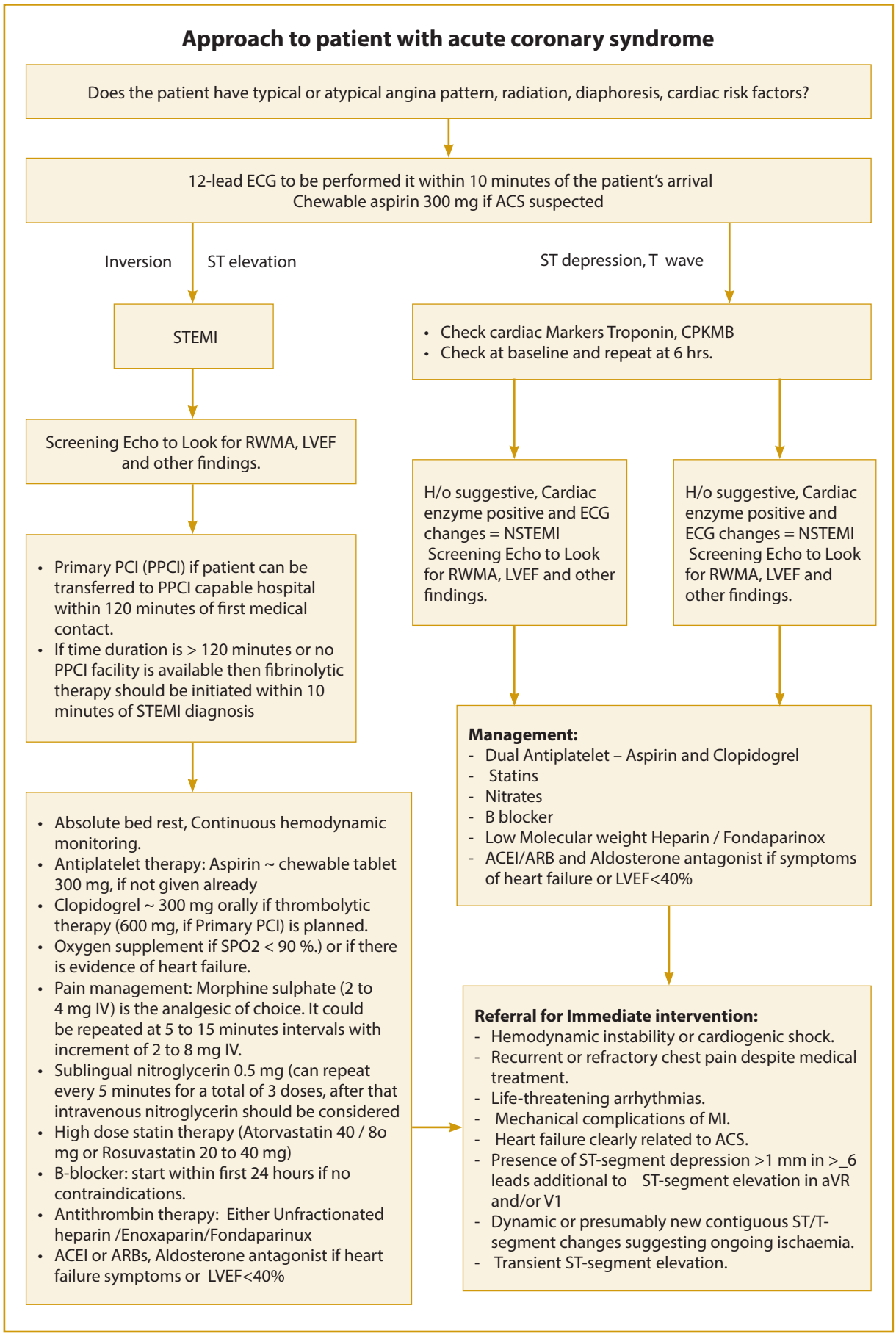


Table 37: Common causes of chest pain and their key features

Cause		Key features	
Cardiac	Angina	Retrosternal chest pressure, burning, or heaviness; Radiating occasionally to the neck, jaw, epigastrium, shoulders, left arm	Precipitated by exercise, cold weather, Or emotional stress; duration of 2-10 min
	Rest or unstable angina	Same as angina but severe	Same as angina, but may be more severe typically <20 min; lower tolerance for Exertion; crescendo pattern
	Acute myocardial infarction	Same as angina, but may be more severe	Sudden onset, usually lasting ≥30 min; Often associated with shortness of Breath, weakness, nausea, vomiting
	Pericarditis	Sharp, pleuritic pain aggravated by changes in position; highly variable duration	Pericardial friction rub
Vascular	Aortic dissection	Excruciating, ripping pain of sudden onset in the anterior aspect of the chest, often radiating to the back	Marked severity of unrelenting pain; usually occurs in the setting of hypertension or underlying connective tissue disorder such as Marfan's syndrome
	Pulmonary embolism	Sudden onset of dyspnea and pain, usually pleuritic with pulmonary infarction	Dyspnea, tachypnea, tachycardia, signs of right-sided heart failure
	Pulmonary hypertension	Substernal chest pressure, exacerbated by exertion	Pain associated with dyspnea and signs of pulmonary hypertension
Pulmonary	Pleuritis and/or pneumonia	Pleuritic pain, usually brief, over the involved area	Pain pleuritic and lateral to the midline, associated with dyspnea
	Tracheobronchitis	Burning discomfort in the midline location,	Associated with Cough
	Spontaneous pneumothorax	Sudden onset of unilateral pleuritic pain, with Dyspnea	Abrupt onset of dyspnea and pain
Gastrointestinal	Esophageal reflux	Burning substernal and epigastric discomfort, 10-60 min in duration	Aggravated by a large meal and Postprandial recumbency; relieved by antacid
	Peptic ulcer	Prolonged epigastric or substernal burning	Relieved by antacids or food
	Gallbladder disease	Prolonged epigastric or right upper quadrant pain	Unprovoked or following a meal
	Pancreatitis	Prolonged, intense epigastric and substernal pain	Risk factors, including alcohol, hypertriglyceridemia, medications
Musculo-skeletal	Costochondritis	Sudden onset of intense fleeting pain	May be reproduced by pressure over the affected joint swelling and inflammation over the costochondral joint
	Trauma or strain	Constant pain	Reproduced by palpation or movement of the chest wall or arm
	Cervical disc disease	Sudden onset of fleeting pain	May be reproduced with the movement of neck
Infectious	Herpes zoster	Prolonged burning pain in a dermatomal distribution	Vesicular rash, dermatomal distribution
Psychological	Panic disorder	Chest tightness or aching, often accompanied by dyspnea and lasting 30 min or more, unrelated to exertion or movement	Patient may have other evidence of an emotional disorder

Table 38: Recommended dosing regimens for long-term nitrate therapy

Nitroglycerine		
Sublingual tablet	0.3-0.6 mg	As needed, up to 3 doses 5 min apart
Spray	1 or 2 sprays	As needed, up to 3 doses 5 min apart
Isosorbide dinitrate		
Oral	10-40 mg	2 or 3 times daily
Oral sustained release	80-120 mg	Once or twice daily (eccentric schedule)
Isosorbide 5-mononitrate		
Oral	20 mg	Twice daily (given 7-8 hr apart)
Oral sustained release	30-240 mg	Once daily

Table 39: Doses of commonly use Beta-blockers and calcium channel antagonists

Drugs	Dose
Beta blockers	
Metoprolol tartaraate	50-100 mg BID
Metoprolol succinate	50-200 mg/day
Atenolol	50-100 mg/day
Propanolol	80-320 mg/ day (BID-TID)
Calcium channel blocker	
Diltiazem /SR	30-90 mg TID-QID SR: 60-180 mg BID
Verapamil/SR	80-120 mg TID-QID SR: 180-480 mg/day
Amlodipine	2.5 to 10 mg

Table 40: Drugs doses of ACEI/ARB, Beta-blocker, and Aldosterone antagonist use in post-myocardial infarction ACEI/ARBS

Drug	Starting dose	Target dose
Enalapril	2.5mg twice daily	10mg twice daily
Ramipril	1.25mg once daily	10mg once daily
Valsartan	40mg twice daily	160mg twice daily
Losartan	25mg daily	150mg daily
Irbesartan	150 once daily	300mg once daily

Contraindications to the use of ACEI and ARB are bilateral renal stenosis, history of angioedema, pregnancy and known allergy to the drugs. Caution and seek specialist advice when serum potassium of >5mmol/l and serum creatinine >2.25mg/dl and symptomatic hypotension. Half the ACEI/ARB dose if creatinine increases more than 50% compared to baseline. Stop ACEI/ARB if the increase is more than 100% and serum potassium is more than 5.5 mmol/l.

Beta-blockers

Drug	Starting dose	Target dose
Carvedilol	3.125 twice daily	25 mg twice daily
Metoprolol succinate	25mg once daily	200mg once daily
Bisoprolol	1.25mg once daily	10mg once daily
Irbesartan	150 once daily	300mg once daily

Aldosterone antagonists

Drug	Starting dose	Target dose
Spironolactone	12.5 to 25mg once daily	25mg once daily
Eplerenone	25mg once daily	50mg once daily

Recommend an aldosterone antagonist in selected patients with class NYHA II to IV HFREF patients who can be monitored carefully for renal function and potassium concentration. Patients should have a serum creatinine of 2.5mg/dl or lower in men and 2.0 mg/dl or lower in women and the serum potassium should be <5.0meq/l.

4.7. CONGENITAL HEART DISEASES

Introduction

Congenital heart disease, is a problem in the structure of the heart that is present at birth, is "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance." The defect can involve the septum within the heart, outflow tracts, valves & great vessels in isolation or in combination sometimes resulting in a severe form of complex defect. Congenital Heart Disease can be Acyanotic or Cyanotic.

1. Acyanotic CHD (SpO_2 > 94% at room air)
2. Cyanotic CHD (the child has the potential to turn bluish discoloration at rest or during exertion, SpO_2 < 93% at room air)

Table 41: Acyanotic Congenital Heart Defects

Shunt lesions	Obstructive lesions
Ventricular Septal Defect (VSD)	Pulmonary Stenosis (PS)
Atrial Septal Defect (ASD)	Aortic Stenosis (AS)
Patent Ductus Arteriosus (PDA)	Coarctation of Aorta (CoA)

Cyanotic heart defects:

Cyanotic heart defects are usually complex and are usually associated with increased pulmonary blood flow (PBF) (Transposition physiology) or reduced PBF (VSD, PS physiology) or normal PBF.

Lesions with ↑ PBF	Lesions with ↓ PBF	Lesions Normal PBF
Transposition of Great Arteries (D-TGA)	Tetralogy of Fallot (TOF)	Unroofed Coronary Sinus

Approach to suspected congenital heart disease;

Ask History and Symptoms of the child

- Blue since birth/ soon after birth and persistent blue, worsened by crying.
- Poor feeding/ intermittent feeding, excessive sweating during feeding, crying and sleeping.
- Precordial bulge, Poor weight gain, exercise intolerance.
- Recurrent Lower Respiratory Tract Infection.
- Recurrent episodes of Heart Failure.
- Squatting, cyanotic spell, loss of consciousness.
- Chest pain, Shortness of breath and palpitation during rest and on exertion.

Assess the child

- Get the weight and height of the child.
- Examination of the child in supine position (look for Dysmorphic facies, presence of extracardiac congenital malformations, chest deformity, precordial activity, right ventricular heave, chest indrawing, raised JVP, swelling of abdomen and legs, palpable liver, clubbing on upper and lower limbs,
- Measure blood pressure,
- Feel all peripheral pulses
- Check SpO_2 of upper and lower limbs,
- Auscultate for heart rate, rhythm, gallop, cardiac murmur, respiratory rate, and chest crackles.

Estimate the likelihood of congenital heart disease:

Apply "Nadas' Criteria" to suspect Congenital Heart Defect:

Major criteria:

- Systolic murmur of grade 3 or more
- Diastolic murmur of any grade
- Central cyanosis
- Congestive HF

Minor criteria:

- Systolic murmur of less than grade 3
- Abnormal S2
- Abnormal ECG
- Abnormal CXR
- Abnormal BP

Presence of 1 major or 2 minor criteria suggests the presence of CHD.

Investigations

(a) Blood investigation: CBC, PCV.

(b) Electrocardiogram (ECG): To determine the HR, rhythm, conduction abnormality, cardiac axis, Atrial enlargement, and ventricular hypertrophy.

(c) Chest X-ray: To assess the size of the heart chambers, pulmonary vascularity.

Hyper cyanotic spells or Tet Spells:

Hypercyanotic spells occur in some children with unrepaired Tetralogy of Fallot and other Cyanotic CHD, most often in those several months up to 2 years of age, sudden episodes of profound cyanosis and hypoxia (hypercyanotic or "Tet" spells) may occur, which may be lethal.

Management of Hypercyanotic spells: Hypercyanotic spells require immediate intervention.

The first steps are to

- Place infants in a knee-chest position (older children usually squat spontaneously and do not develop hyper cyanotic spells)
- Establish a calm environment
- Give supplemental oxygen
- Give IV fluids for volume expansion

If the spell persists, standard medical therapy should be instituted that includes morphine, phenylephrine, and beta-blockers (propranolol or esmolol).

Table 42: Drugs for Hypercyanotic Spells

Drug	Route	Initial dose	Maximum dose
Morphine	IV, intramuscular, or subcutaneous	0.1 mg/kg	0.1 mg/kg
Phenylephrine	IV	5–20 mcg/kg every 10 to 15 minutes as needed Follow with infusion 0.1–0.5 mcg/kg/minute	Max bolus 500 mcg Max infusion 5 mcg/kg/minute
Propranolol	IV	0.015–0.02 mg/kg, titrate to effect	0.1–0.2 mg/kg
Esmolol	IV	100–500 mcg/kg over 1 minute Followed by infusion of 25–100 mcg/kg/minute	500 mcg/kg/minute

Counsel and Refer

All suspected cases of CHD should be referred to a tertiary cardiac center after proper counseling

4.8. HEART FAILURE

Introduction

Heart failure (HF) is a progressive clinical and pathophysiological syndrome in which the heart is unable to function adequately to meet the metabolic needs, to dispose of either systemic or pulmonary circulation, or a combination of both. The clinical diagnosis of HF requires the presence of symptoms and/or signs of HF, most often with reduced EF.

HF may arise from cardiac and non-cardiac causes. The causes of heart failure in children differ substantially from those found in the adult population. Cardiomyopathies are the most common causes of heart failure in children with structurally normal hearts. Common causes are volume or pressure overload or both which may be caused by congenital or acquired heart disease and myocardial diseases. Tachyarrhythmia and heart block can lead to heart failure at any age. Congenital heart diseases are the most common cause of HF in infancy. Beyond infancy, myocardial dysfunction due to various causes accounts for HF. Rare causes of HF include metabolic and endocrine disorders, anemia, pulmonary diseases, collagen vascular diseases, systemic or pulmonary hypertension, neuromuscular disorders, and drugs e.g., anthracyclines.

The modified Ross classification (Table 43) is the most widely accepted and used classification for heart failure in children. It is an empirical tool for grading the severity of hf but not for predicting mortality based on status at presentation.

NYHA classification of heart failure in adults

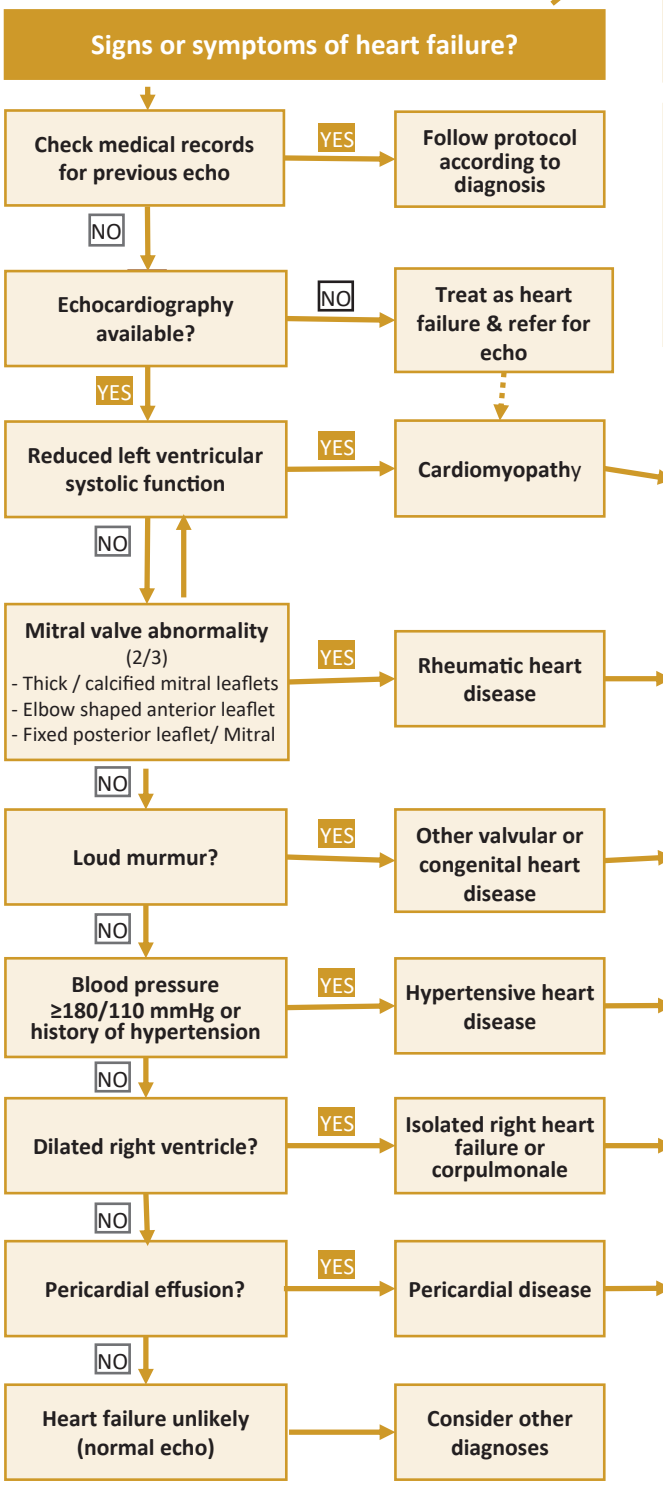
NYHA classification - the stages of heart failure:

- Class I - no symptoms and no limitation in ordinary physical activity, e.g. Shortness of breath when walking, climbing stairs, etc.
- Class II - mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- Class III - marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. Walking short distances (20-100 m), comfortable only at rest.
- Class IV - severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
- No NYHA class listed or unable to determine.

Table 43: The modified Ross classification of heart failure in children

Class of symptoms	Symptoms noted on history
Class I	No symptoms/limitations
Class II	Mild tachypnea/sweating during feeds in infants/dyspnea on exertion in older children but no growth failure
Class III	Significant tachypnea or sweating during feeds/marked dyspnea on exertion/ prolonged feeding time with growth failure
Class IV	Symptoms (tachypnea, retractions, grunting, and sweating) even at rest with growth failure

Protocol for Heart Failure Diagnosis and Management



NYHA Classification- The Stages of Heart Failure:

- **Class I -** No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
- **Class II -** Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- **Class III -** Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20—100 m).Comfortable only at rest.
- **Class IV -** Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
- **No NYHA class listed or unable to determine.**

Non-cardiomyopathy medications:

ASA 100mg daily
Penicillin V 250mg twice daily *or* **Penicillin IM inj**
Furosemide (contraindication: Cr >2.3)
Hydrochlorothiazide (HCTZ) (contraindication: Cr >2.3)
Amlodipine: 2.5-10 mg po od (goal BP <140/90 mmHg)
Nifedipine: 20-80 mg po od (goal BP <140/90 mmHg)

1) Furosemide if hypervolemic
2) ACEi (titrate to goal dose)
3) Beta-blocker (titrate to goal dose)
4) if max ACEi and BP not low: add spironolactone
5) Investigate & treat causes of cardiomyopathy
6) If peripartum: add ASA 81 mg od
7. Cardiology consultation after stabilization

1) Furosemide if hypervolemic
2) Beta blocker (goal HR 60-80 bpm)
3) Penicillin (secondary prophylaxis)
4) Cardiologist consultation after stabilization

1. Cardiologist consultation
2. Furosemide if hypervolemia
3. BP control
4. Consider penicillin for secondary prophylaxis if mitral valve thickening and calcification if present

1) Furosemide and/or HCTZ if hypervolemic
2) BP control: goal sBP <140 mmHg

1) Furosemide
2) Treat lung disease (asthma/COPD, TB) **if present**

1) Refer for pericardiocentesis if tamponade (low BP, tachycardic, IVC dilated)
2) Treat the cause (TB, HIV, cancer)

*Note that combined diagnoses are possible and can be made in consultation with an expert
*Family planning should be considered in all cases of heart failure affecting women of childbearing age

Table 44: Commonly used heart failure medications

Heart failure medications	Starting dose	Goal dose	Contraindication
Beta-blocker: Atenolol Beta-blocker: Carvedilol Beta-blocker: Metoprolol CR Beta-blocker: Bisoprolol	12.5 mg OD 6.25 mg BID 12.5 mg BID 2.5 mg OD	25 mg BID 25-50 mg BID 50-100 mg BID 10 mg OD	Heart rate <55, low doses in pregnancy (should not use atenolol in pregnancy)
Ace inhibitor: Captopril Ace inhibitor: Lisinopril Ace inhibitor: Enalapril Ace inhibitor: Ramipril	12.5 mg TID 5 mg OD 2.5 mg BID 2.5 mg OD	50 mg TID 20-40 mg OD 20 mg BID 10 mg OD	Creatinine (Cr) >2.3, SBP <100, pregnancy)
Angiotensin receptor blockers: Candesartan Angiotensin receptor blockers: Valsartan	8 mg OD 20-40 mg BID	32 mg OD 160 mg BID	Creatinine (Cr) >2.3, SBP <100, pregnancy
Aldosterone Antagonist: Spironolactone	12.5 mg daily	25 mg daily	Creatinine (Cr) >2.3 or k >5.5, pregnancy
Hydralazine	25 mg TID	75 mg TID	SBP <100 mm Hg
Isosorbide dinitrate (ISDN)	10 mg TID	40 mg TID	SBP <100 mm Hg or headache
Frusemide	20 mg OD	40 mg BID	

Referral to a cardiologist or tertiary care center should be done after initial stabilization of the patient.

CHAPTER-5

HEMOGLOBINOPATHIES

5.1. SICKLE CELL DISEASE

Introduction

Sickle cell disease (SCD) is a group of inherited red blood cell disorders that affect hemoglobin, the protein that carries oxygen throughout the body. The abnormal hemoglobin distorts RBC to become "sickle- shaped", thus the name Sickle cell Disease. The sickle cells have sharp edges and can cause blood vessels to get blocked, thus leading to inadequate blood supply to organs.

SCD is an autosomal recessive disorder, where an affected individual is homozygous for the abnormal gene.

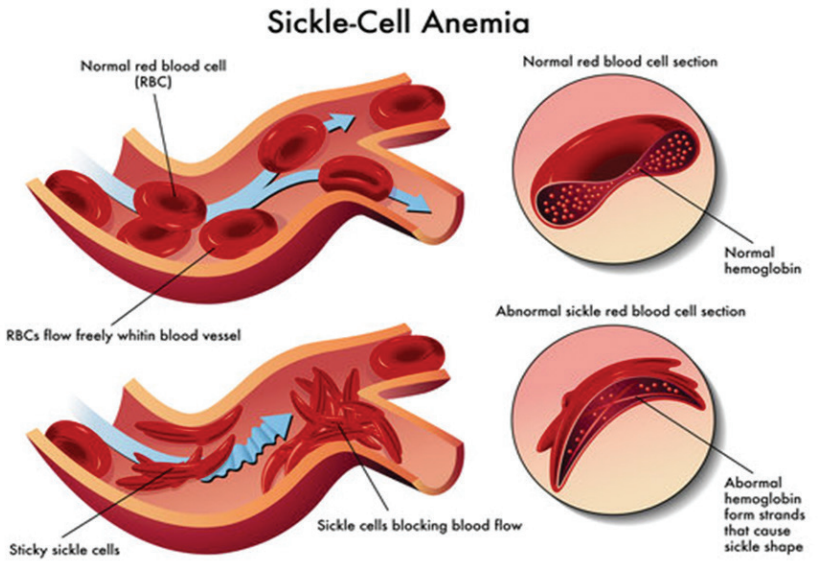


Figure 20: Pathogenesis of Sickle cell anemia

Genotypes in SCD

- SS (SCA)
- SC
- SBeta+
- SBeta0

Haplotypes in SCD

- Arab/India (AI) or Asian
- Benin (BEN)
- Senegal (SEN)
- Cameroon (CAM)
- Bantu (BAN)/Central African Republic (CAR)

Forms of Sickle Cell Disease

The commonest forms of SCD in our part of the world in order of prevalence are HbSS, HbSC, and HbSβ-thal.

- If a person inherits one sickle hemoglobin (HbS) from each parent, he/she will have HbSS
- If a person inherits one sickle hemoglobin (HbS) from one parent and another hemoglobin variant (HbC) from the other parent, he/she will have HbSC.

- If a person inherits one sickle hemoglobin (HbS) from one parent and another hemoglobin variant (Hb β-thalassemia) from another parent, he/she will have HbSβ-thal.
- It is worthy to note that SCD does not include the sickle cell trait also known as the carrier state (HbAS).

The Burden of Sickle Cell Disease

Sickle cell disease affects nearly 100 million people in the world and is responsible for over 50% of deaths in those with the most severe form of disease.

Over 300,000 children are born annually with SCD and over 70% of the births occur in Sub-Saharan Africa where a majority of them die before the age of 5 years as a result of the poor standard of management.

Globally, 5% of the population is carrier of various hemoglobinopathies

- The geographical distribution of sickle cell is mainly driven by two factors: The endemicity of malaria and population movements
- Depending on micro mapping in some communities 5 to 40% are carriers of hemoglobinopathies
  - Despite this magnitude up to a few years back, hemoglobinopathy was not a public health problem in Nepal, thinking it was a rare disease to be diagnosed in a tertiary level hospital and to be treated only by a specialist
- 20% of people in the Tharu community of Western Nepal at the community level are either diseased or carriers of either sickle or beta-thalassemia and an additional 20% in this community have low HbA2 which needs further exploration to rule out Iron deficiency or HbH disease

Signs and symptoms

Patients with Sickle Cell Disease (SCD) have inherited genes that lead to the presence of sickle cells (drepanocytes) in their blood. The clinical features arising from the presence of these sickle cells are protean affecting almost every system of the body and include:

- Anaemia
- Vaso-occlusive pain episodes
- Features of infections
- Splenomegaly
- Acute chest syndrome
- Stroke
- Leg ulcers
- Priapism
- Retinopathy
- Pulmonary hypertension
- Jaundice
- Cardiac dysfunction
- Sickle cell nephropathy

Various skeletal abnormalities are also associated with SCD and include:

1. Fronto-occipital bossing with striking gnathopathy
2. Stunted growth
3. Multifocal osteomyelitis
4. Long slender extremities
5. Avascular necrosis of the femoral head
6. Dactylitis (hand-foot syndrome)

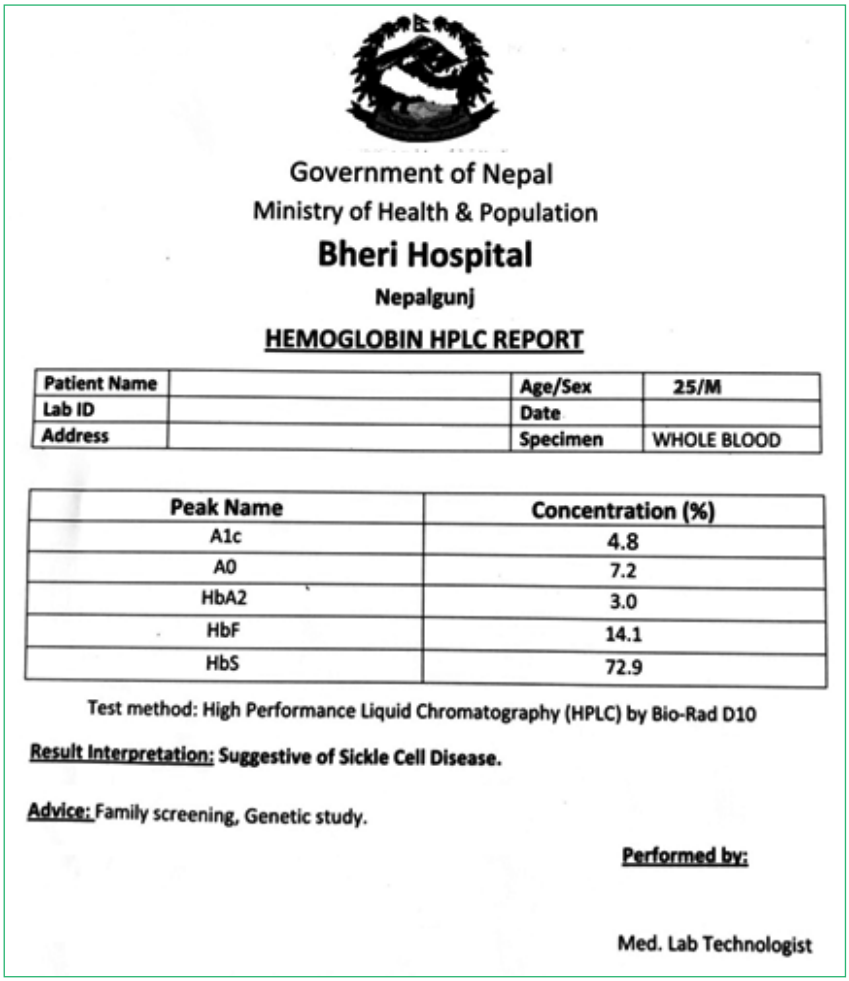
Pain is a defining feature of the disease with patients experiencing unpredictable recurrent, persistent pain throughout life resulting in frequent hospitalizations. Painful swelling of the hands and feet (dactylitis) can occur as early as six months of age and is often the feature that brings the affected child to medical attention.

The spectrum of clinical expression is heterogeneous with some people having mild disease while others present with severe complications. It is the presence of these clinical features that will alert one to the presence of the disease and prompt laboratory investigations to confirm the diagnosis.

Diagnosis

1. History of repeated anemia/jaundice
2. Episodes of pain and acute complications
3. Repeated infections
4. Family history
5. Laboratory testing

Diagnosis is confirmed by Hb Electrophoresis



Government of Nepal
Ministry of Health & Population
Bheri Hospital
Nepalgunj
HEMOGLOBIN HPLC REPORT

Patient Name		Age/Sex	25/M
Lab ID		Date	
Address		Specimen	WHOLE BLOOD

Peak Name	Concentration (%)
A1c	4.8
A0	7.2
HbA2	3.0
HbF	14.1
HbS	72.9

Test method: High Performance Liquid Chromatography (HPLC) by Bio-Rad D10

Result Interpretation: Suggestive of Sickle Cell Disease.

Advice: Family screening, Genetic study.

Performed by:

Med. Lab Technologist

Fig 21: Hb electrophoresis Report template of SCD

Significant aberration from classical electrophoretic patterns is not uncommon. So, electrophoresis patterns should always be interpreted in the context of clinical features, PBF, and transfusion history. Family screening may be needed in some cases.

Complications of SCD

Acute complications:

1) Acute vaso-occlusive crisis of SCD
2) Acute Chest Syndrome (ACS)
3) Sepsis
4) Aplastic crisis
5) Hyper hemolytic crisis
6) Acute hepatic crisis
7) Acute abdomen
8) Numb-Chin syndrome
9) Severe Anemia with anemic symptoms
10) Splenic Sequestration
11) Acute Stroke
12) Priapism

Treatment

The initial management should be done at the primary center and if the patient does not show signs of improvement, he/she should be referred to a higher center.

Acute vaso-occlusive crisis

1) I/V fluids
2) Antibiotics (eg: Inj. Ceftriaxone)
3) Analgesics –
   a. Inj. Ketorolac-30mg I/V QID)
   b. Inj. Morphine 3-5 mg I/V QID and SOS (gradually increase the dosage as per requirement)
4) Continue Folic acid
5) Continue Hydroxyurea (if no contraindication)
6) O_2 if necessary to maintain SpO_2>94 %
7) Counseling

Acute Chest Syndrome

1) I/V Fluids
2) Antibiotics(Inj Ceftriaxone and Azithromycin)
3) Analgesics
   a. Inj. Ketorolac-30mg I/V QID)
   b. Inj. Morphine 3-5 mg I/V QID and SOS (gradually increase the dosage as per requirement)
4) Inj. Heparin
5) Continue Folic acid taken previously
6) Continue Hydroxyurea (if no contraindication)
7) O_2 Therapy to maintain SpO_2 >94%
8) Blood transfusion

Sepsis

1) Investigations: Blood culture
2) I/V fluids
3) Antibiotics- Inj. Ceftriaxone. Change antibiotics according to culture sensitivity report
4) O_2 Therapy to maintain SpO_2 >94%

Note: *Pneumococcal sepsis is common so treatment of pneumococcal infection*

Salmonella osteomyelitis is common so treatment for salmonella osteomyelitis if the clinical condition demands

Aplastic crisis

1) Blood transfusion
2) Stop hydroxyurea
3) Continue folic acid

Hyper hemolytic crisis

1) Blood transfusion
2) Continue folic acid
3) Continue hydroxyurea

Acute hepatic crisis

1) I/V fluids
2) Blood transfusion
3) Antibiotics (e.g.Inj. Ceftriaxone)
4) Rule out other causes of hepatitis (Hepatitis A, E, herbal medicines)
5) Continue folic acid
6) Continue hydroxyurea
7) Analgesics

Acute abdomen

1) I/V fluids
2) Nil Per Oral (NPO)
3) Antibiotics (Ceftriaxone and Metronidazole)
4) Monitor vitals and continue supportive care
5) Rule out other causes of acute abdomen (Surgical causes like acute appendicitis, perforation of hollow viscus, peritonitis, Cholecystitis, and gynecological and obstetrical causes if female)

Numb-chin Syndrome

1) Rule out tetanus, local infection of the jaw
2) Muscle relaxants -Tizanidine
3) Continue folic acid
4) Continue hydroxyurea
5) Multivitamins tablets
6) Counseling

Severe anemia with anemic symptoms

1) Blood transfusion (top-up)
2) Continue tab folic acid
3) Continue hydroxyurea (If no contraindication)

Splenic sequestration

1) I/V fluids
2) Blood transfusion

Acute Stroke

1) Stabilization of the patient

Priapism

1) Correct dehydration
2) Analgesics as per need

Special situations in SCD

- Surgery: Pre-operative HbS should be <30%, top-up transfusion or exchange transfusion might be needed to achieve HbS<30%
- Pregnancy:
  - Hold Hydroxyurea 3 months before planning pregnancy,
  - Tab Aspirin 75 mg OD during pregnancy.
  - The risk of acute crisis is higher, thus frequent monitoring is needed.

Chronic Complications of SCD

Avascular necrosis of the femur and humerus

- Look for gait, and ask about any difficulties in walking,
- X-ray hip can show avascular necrosis of the femur. MRI hip can show early changes. Refer to the orthopedic surgeon.

Jaundice

Hemolysis is a common cause of jaundice in sickle cell disease. Other causes are hepatic cholestasis, choledocholithiasis, hepatic crisis, and viral hepatitis.

Cardiomyopathy

Long-term sickle cell disease can cause cardiomyopathy.

Pulmonary hypertension

Retinopathy

Yearly screening by an ophthalmologist is necessary

Nephropathy

Yearly screening is necessary by blood urea, serum creatinine and urinary protein excretion

Secondary hemochromatosis

Table 45: Recommendations on common health topics related to sickle cell disease

Health Topic	Recommendations
Prevention of infection	▪ Oral penicillin prophylaxis till 5years of age in all children with HbSS or HbSß°-thalassemia. Dose - 125mg for age<3 years and 250 mg for age ≥ 3 years twice daily ▪ Discontinue prophylactic penicillin in children with HbSS or HbSß°-thalassemia at age 5 unless they have had a splenectomy or invasive pneumococcal infection. Before discontinuation of penicillin prophylaxis, ensure completion of recommended pneumococcal vaccination series. ▪ Penicillin prophylaxis is not recommended for children with HbSC disease and HbSß+ - thalassemia unless they have had a splenectomy. Ensure that people of all ages with SCD have been vaccinated against Streptococcus pneumoniae, Haemophilus Influenzae type b, and meningococcus. ▪ Remind people with SCD, their families, and caregivers to seek immediate medical attention whenever fever (temperature>100.4°F or 38°C) occurs, due to the risk for severe bacterial infections.
Renal disease	Screen all individuals with SCD, beginning by age 10, for proteinuria. ▪ If the result is negative ⟶ annual screening ▪ If the result is positive ⟶ first-morning void urine albumin-creatinine ratio, refer to a nephrologist if abnormal
Heart disease	Consider annual echocardiography for adults with SCD. Routine echocardiography and ECG screening is not recommended for children with SCD.
Hypertension	▪ In adults with SCD, screen for hypertension and treatment to lower systolic blood pressure < 140mm Hg and diastolic blood pressure < 90mm Hg according to national guidelines. ▪ In children with SCD, measure blood pressure and evaluate and treat hypertension according to national guidelines.
Retinopathy	Refer to an ophthalmologist to evaluate for retinopathy beginning at age 10 and continue annually. Refer people with suspected retinopathy to a retinal specialist.
Stroke	▪ In children with HbSS and HbSß°thalassemia, screen annually with TCD, beginning at age 2 and continuing till at least age 16. ▪ In children with abnormal (non-imaging TAMMV>200 cm/s in dICA, bifurcation or MCA) TCD results, begin chronic transfusion therapy aimed at preventing stroke. ▪ In children with genotypes other than SCA (e.g. HbSß+-thalassemia or HbSC), do not perform screening with TCD. ▪ Consider screening MRI for detection of silent cerebral infraction (SCI) in children and adults with HbSS and HbSß°-thalassemia. For children with SCI, offer chronic transfusion therapy for prevention of recurrent infarction.
Lung disease	▪ Assess for signs and symptoms of respiratory problems (such as asthma, COPD, restrictive lung disease, or obstructive sleep apnea) by history and physical examination. ▪ In patients with positive findings, further assessment by pulmonary function tests is recommended to determine the cause and develop a plan to address the problem. ▪ Do not screen asymptomatic children and adults with pulmonary function tests.
Contraception	Progestin-only contraceptives (pills, injections, and implants), levonorgestrel IUDs, and barrier methods have no restrictions or concerns for use in women with SCD.

Diagnosis

Any child who presents with the following features and is supported by family history and ethnicity should be suspected to have SCD.

Ethnicity: SCD is more prevalent in the Tharu community in Nepal (especially in Western Nepal).

Clinical Features:

- Recurrent anemia
- Recurrent Jaundice
- Recurrent joint and bone pain often aggravate in the winter or summer season.
- Recurrent infections/fever

Investigations:

- CBC, Reticulocyte count, PBS
- Hb electrophoresis (HPLC or Capillary electrophoresis), LFT, USG Abdomen

Screening and genetic counseling of sickle cell disease

- Infantile screening at the time of the first dose of MR vaccine (nine months of age) seems to be the best screening modality in Nepal in district hospital and level I hospitals. Early diagnosis and penicillin prophylaxis up to the age of 5 years has improved survival in SCD.

For counseling to be effective, the patient should know:

- What is Sickle Cell
- The difference between sickle cell trait and sickle cell disease
- That the severity of pain & frequency of crisis is unpredictable
- It can be a chronic debilitating disease
- It can be prevented with proper prenatal screening
- This is a genetic disorder
- BMT is the definitive treatment of SCD

Punnett Square uses

- A square diagram that is used to predict the genotypes of a particular cross or breeding
- Named after Reginald C. Punnett, who devised the approach in 1905
- Used by a biologist to determine the probability of offspring having a particular genotype
- Genotype: The genetic makeup of the organism, what you can find when you look at the DNA
- Phenotype: The physical makeup of the organism, the characteristics you can see

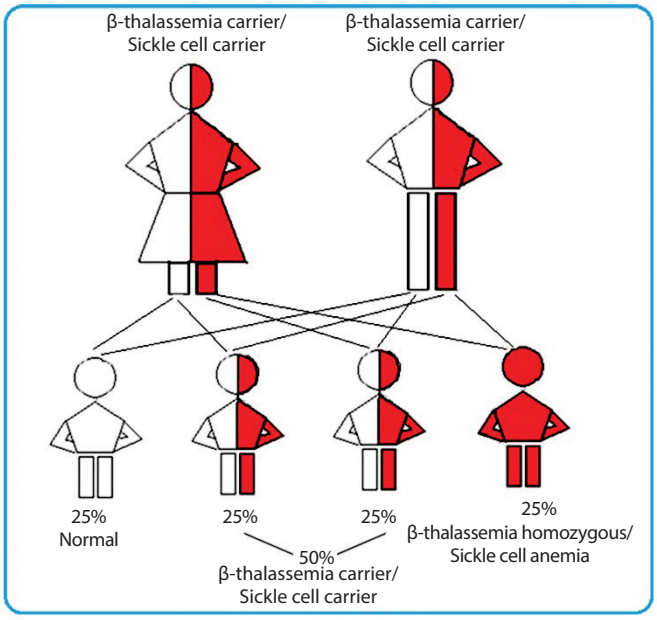


Figure 22: Punnett square for both parents as sickle cell or β-thalassemia carrier

- Both parents are beta-thalassemia or sickle cell carriers.
  - There is a 25% chance in every pregnancy that the baby will be normal, a 50% chance that the baby will be a carrier and a 25% chance that the baby will be affected with homozygous B-thalassemia or Sickle cell anemia.
- Both parents have homozygous B thalassemia or sickle cell anemia.
  - 100% chance in every pregnancy that the baby will have homozygous B-thalassemia or sickle cell anemia
- One parent is homozygous for B-thalassemia or has sickle cell anemia and the other is normal.
  - In every pregnancy will be a B-thalassemia or a sickle cell carrier. There is a 50% chance in every pregnancy that the baby will be a sickle cell carrier and a 50% chance that the baby will have homozygous sickle cell anemia.

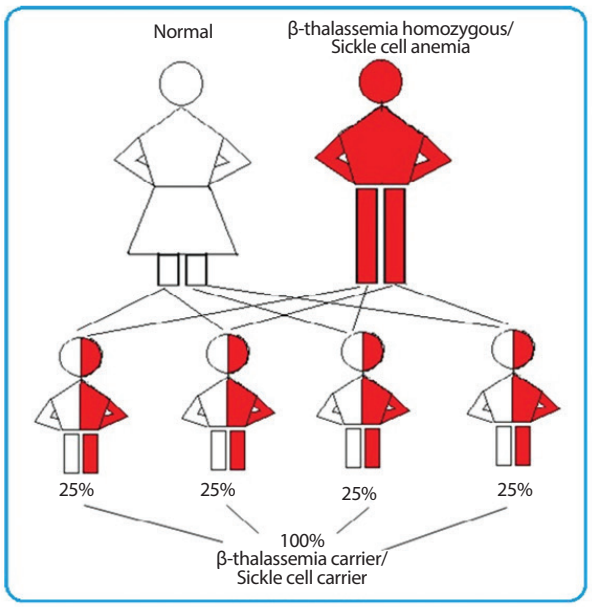


Figure 23: Punnett square for one parent is homozygous for sickle cell anemia or β-thalassemia and other is normal.

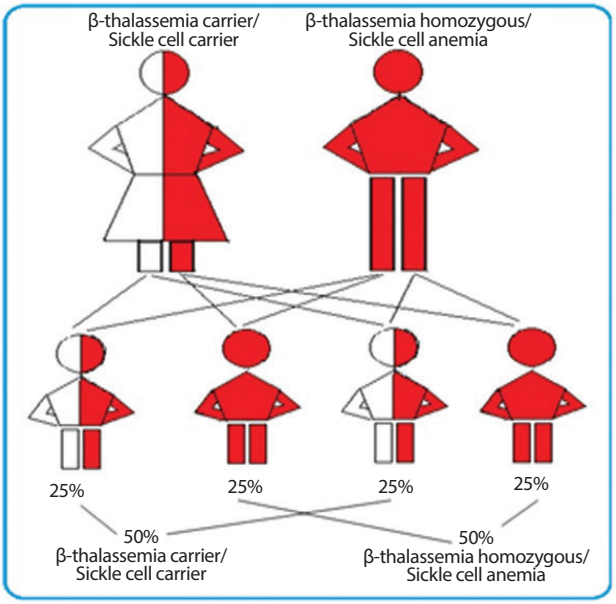


Figure 24: Punnett square for one parent is homozygous for sickle cell anemia or β-thalassemia and other is sickle cell or β-thalassemia carrier.

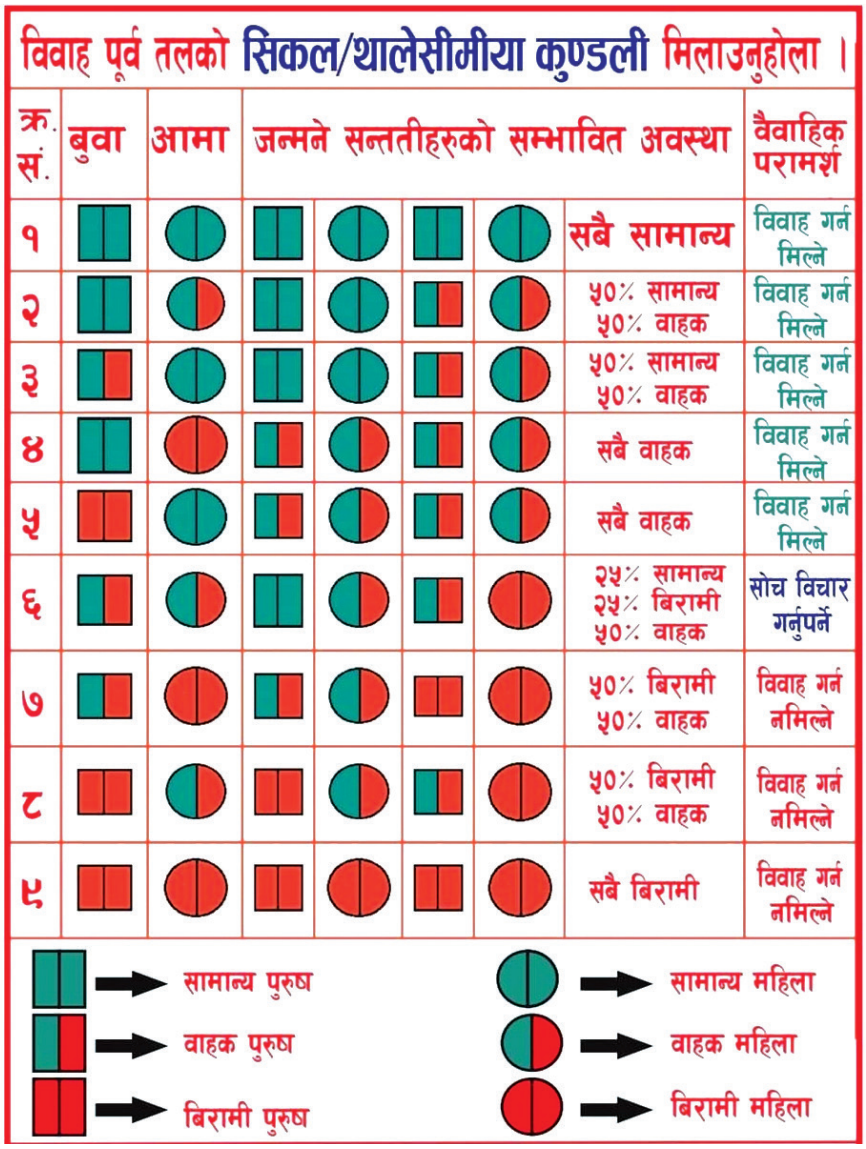


Figure 25: **Sickle/thalassemia kundali**

Management

Step 1: Tab. Folic Acid 1mg daily orally lifelong

Step 2: Cap. Hydroxyurea, start 15-20 mg/kg per day

Step 3: Use analgesics as per the WHO ladder for pain control

Step 4: Blood transfusion as per need

Step 5: Vaccination for capsulated organisms (Pneumococcal, Meningococcal, Haemophilus influenza b)

Step 6: Genetic counseling, family screening, pre-marital counseling

Step 7: Self care

Refer

- When SpO_2 is <94% and falling
- When patients are not improving
- Diagnosis is uncertain
- When pain control is difficult

Hydroxyurea(HU)

- Hydroxyurea reduces vaso-occlusive events such as pain episodes and acute chest syndrome in people with sickle cell disease (SCD).
- Indications

Children

- Infants <9 months with HbSS or sickle B0 thalassemia who are symptomatic (e.g., dactylitis, acute pain episodes)
- Infants >9 months, children, and adolescents with HbSS or sickle beta0 thalassemia of any clinical severity.

Adults with SCD

- Three or more hospitalization for a vaso-occlusive crisis in the past 12 months
- Severe or recurrent acute chest syndrome
- Sickle cell-associated pain that affects daily activities and quality of life

Evaluation of patient before initiating hydroxyurea

- Explain the indication, aims, benefits that can be expected, and possible side effects of hydroxyurea therapy to the patient- include possible supportive family members (spouse, children, parents)
- Order appropriate laboratory exams: CBC (including MCV, Neutrophil, platelets). RFT, LFT, Pregnancy test for women, baseline quantitative HbF by HPLC.
- Prescribe contraceptive methods, and if the patients intend to have children stress the need for a planned pregnancy
  - Dose: 15-20 mg/kg/day, rounded up to the nearest 500 mg; 5-10mg/kg/day if the chronic kidney disease; pills can be taken as a single dose or multiple smaller doses.
- Monitoring: CBC, RFT, and LFT every four weeks until MTD (Maximum tolerated dose) also measure HbF every 3 months afterward.
- MTD: Highest dose at which neutrophil count is above 2000/µl (may reach 1250/µl in young adults), with platelet and reticulocyte count above 80,000/ µl.
- Dose escalation: Increase 5 mg/kg/day every 8 weeks until MTD is reached.
- Toxicity: If neutrophil is <2000/µl (depending on age), platelet<80,000/µl or reticulocytes <80,000/ µl, stop hydroxyurea, monitor CBC weekly until recovery and restart HU at dose 5mg/kg/day lower than previously.
- Maximum dose: 35 mg/kg/day or MTD
- Minimum duration of treatment: 6 months

Cautions while prescribing hydroxyurea

- Double up doses if a patient misses a dose
- Stop HU during hospitalization or acute illness
- Stop HU if there is a lack of increase of MCV or fetal Hemoglobin

Pain management in SCD

- Acute pain: NSAIDs, Morphine
- Chronic pain: NSAIDs, Tricyclic antidepressants
- Acute on chronic pain: NSAIDs, Morphine, Tricyclic antidepressants

5.2. THALASSEMIA

Introduction

- Thalassemia is the name for a group of disorders of hemoglobin characterized by diminished or absent production of alpha or beta globin chains, the two protein subunits of the hemoglobin molecule.
- This inherited disorder derives its name from the Greek "Thalassa" (sea) and "Haema" (blood), referring to its discovery among people living around the Mediterranean Sea.
- It also occurs in high frequencies in parts of Africa, the Asian sub-continent, Southeast Asia, and the Middle East.
- Thalassemia is mainly divided into alpha-thalassemia (defective or absent alpha-chain synthesis) and beta-thalassemia (defective or absent beta-chain synthesis).

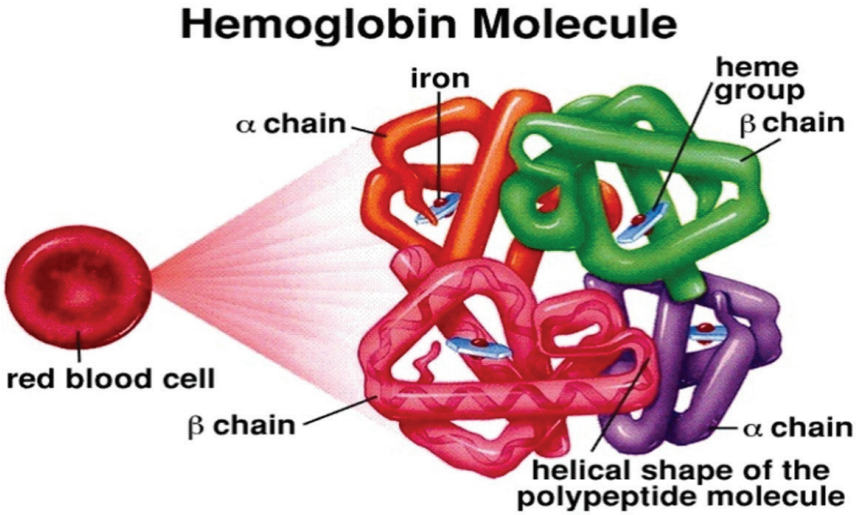


Figure 26: **Structure of Haemoglobin**

Figure 27: **Global distribution of beta Thalassemia**

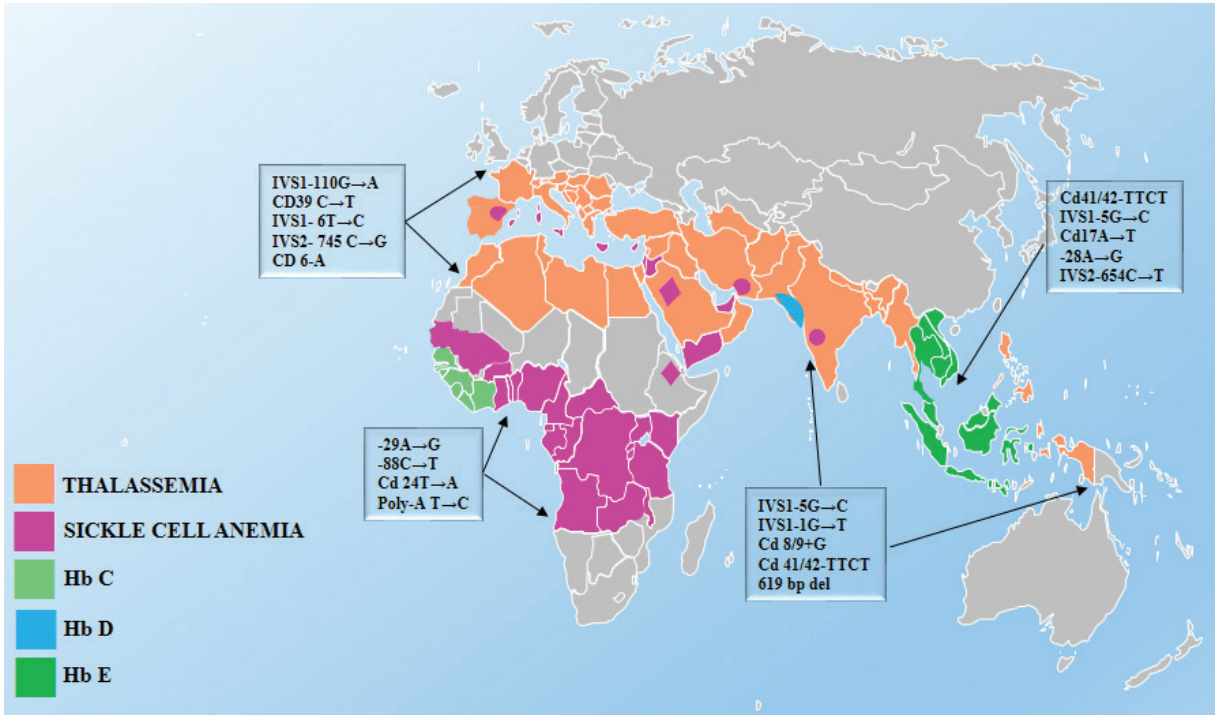


Figure 28: **Global distribution of alpha Thalassaemia**

Thalassemia in Nepal

Beta thalassemia is common in Nepal in all ethnic groups but more in the Terai region mainly in Tharu and other castes. Alpha Thalassemia is common in Tharus of western Nepal. HbE is common in Rajbansi of eastern Nepal. Total transfusion-dependent thalassemic patients are approximately 1,000 and among them, only one-fourth are registered in Nepal Thalassemia Society. Most of the thalassemia patients in Nepal are either under transfused, or on inadequate iron chelation and lack comprehensive management. Newborn screening and premarital screening are not in practice. Some community screening that has been done in western Nepal shows a 5% beta thalassemia trait in the community (Tharu community). We need to do micro mapping for accurate stratification of thalassemia in the different ethnic communities. Prenatal diagnosis is available only in the capital of the country and is lacking in places where a majority of thalassemics reside.

Molecular Basis and Classification

The alpha-globin gene cluster is on chromosome 16 and the beta-globin gene cluster is on chromosome 11. These gene clusters include regulatory regions as well as distinct genes for embryonic, fetal (for β-like globins), and adult versions of the α-like and β-like globins. Thalassemic mutations can affect any of these genes, but the most common forms of thalassemia occur due to defects in the α and β globin genes and their related regulatory sequences. The main subtypes of alpha thalassemia are presented in the following tables.

Table 46: Subtypes of alpha thalassemia

Genotype	α-globin gene number*	Name	Phenotype
αα/αα	4	Normal state	None
αα/α-	3	Silent carrier	None (values for Hb and MCV may be near the lower limits for normal
--/αα or -α/α-	2	Thalassemia trait	Thalassemia minor: asymptomatic, mild microcytic anemia
--/α-	1	HbH disease	Thalassemia intermedia: mild to moderate microcytic anemia
--/αcsα	1	Hb H-Constant spring	Thalassemia intermedia: moderate to severe microcytic anemia
--/--	0	Alpha thalassemia major	

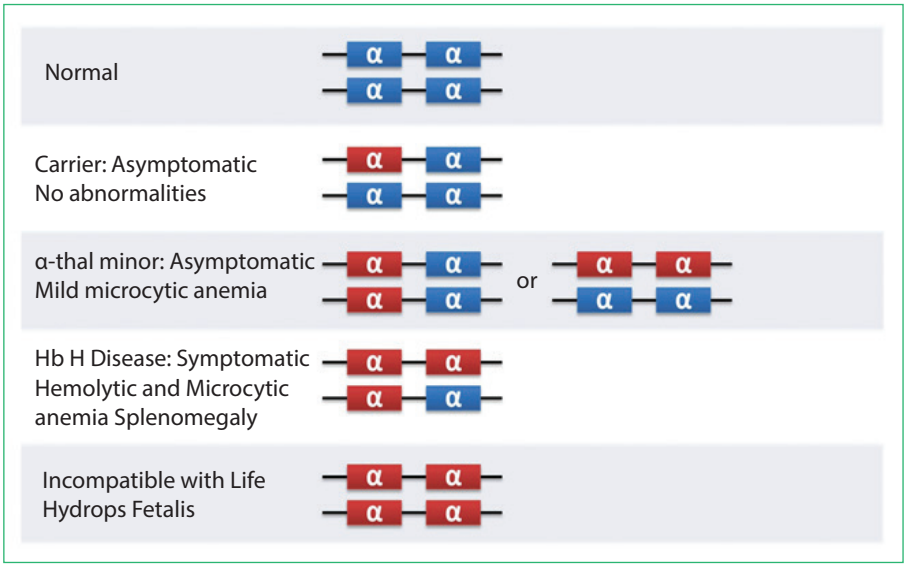


Figure 29: Alpha thalassemia genetics and clinical consequences

Beta thalassemia

- Beta thalassemia results mostly from over 200 point mutations, but deletions can also cause thalassemia.
- These point mutations affect gene regulation and expression to varying degrees. Beta-globin is normally synthesized from two beta-globin genes (one on each copy of chromosome 11).
- If a mutation abolishes the expression of beta-globin, it is classified as a beta-zero (β0) thalassemia allele while reduced or partial expression is classified as a beta-plus (β+) thalassemia allele.
- Clinically important thalassemia variants can also occur due to interactions of structural beta-globin variants (especially Hb E, βE) with β0 or β+ thalassemia mutations.

Table 47: Common genotypes and basic classification of beta thalassemia

Common genotypes	Name	Phenotype
β/ β	Normal	None
β/ β0 β/ β+	Beta thalassemia trait	Thalassemia minor, asymptomatic, mild microcytic hypochromic anemia
β +/ β+ β +/ β0 βE/ β+ βE/ β0	Beta thalassemia intermedia	Variable severity Mild to moderate anemia Possible extramedullary hematopoiesis Iron overload
β 0/ β0	Beta thalassemia major(cooley's Anemia)	Severe anemia Transfusion dependence Extramedullary hematopoiesis Iron overload

Abbreviation: β0: a β-thalassemia mutation that eliminates globin transcription or translation
β+: a β-thalassemia mutation that decreases globin transcription or translation
βE: a β-globin mutation that results in Hb E.

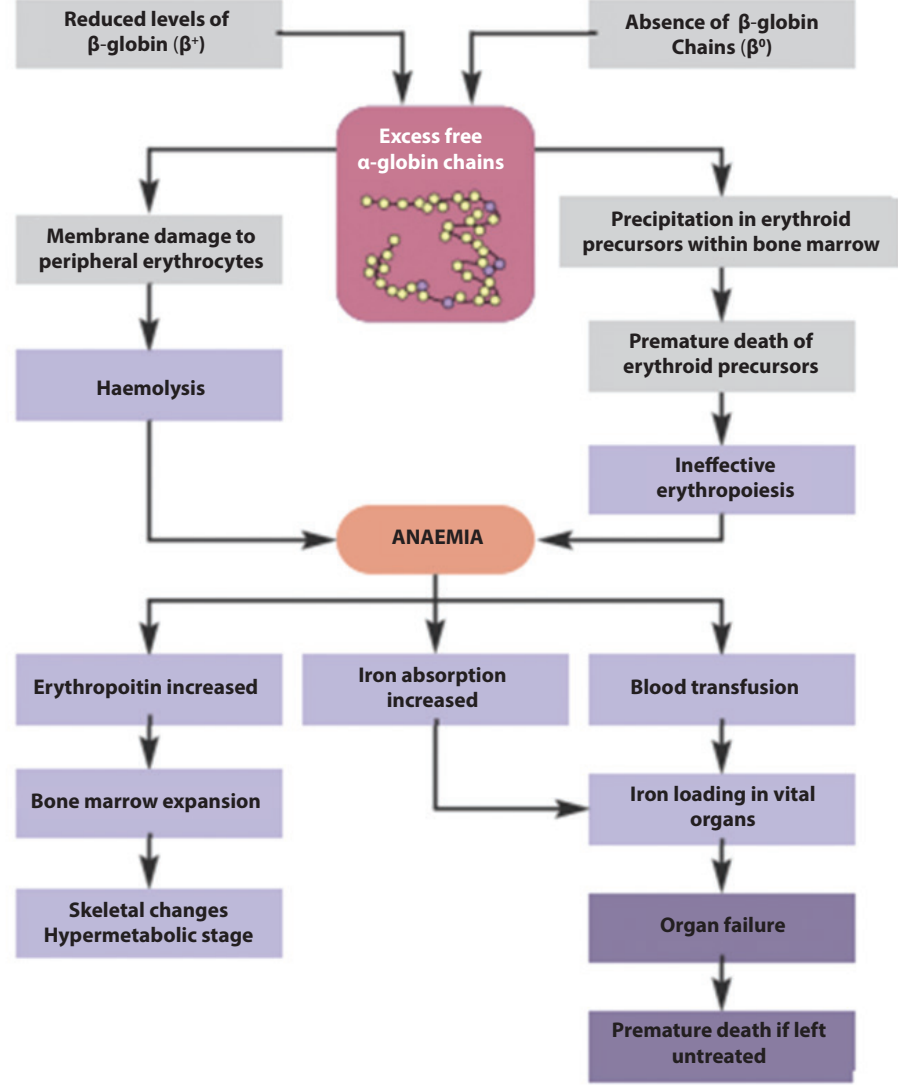


Figure 30: Alpha thalassemia genetics and clinical consequences

Signs and symptoms

Clinical features of thalassemia necessarily mean clinical features of symptomatic thalassemias, namely transfusion-dependent thalassemia (thalassemia major and thalassemia intermedia). Thalassemia major and intermedia present generally almost similar features but in a significantly varying spectrum of severity. There is different genotype-phenotype variation in the clinical features of thalassemia.

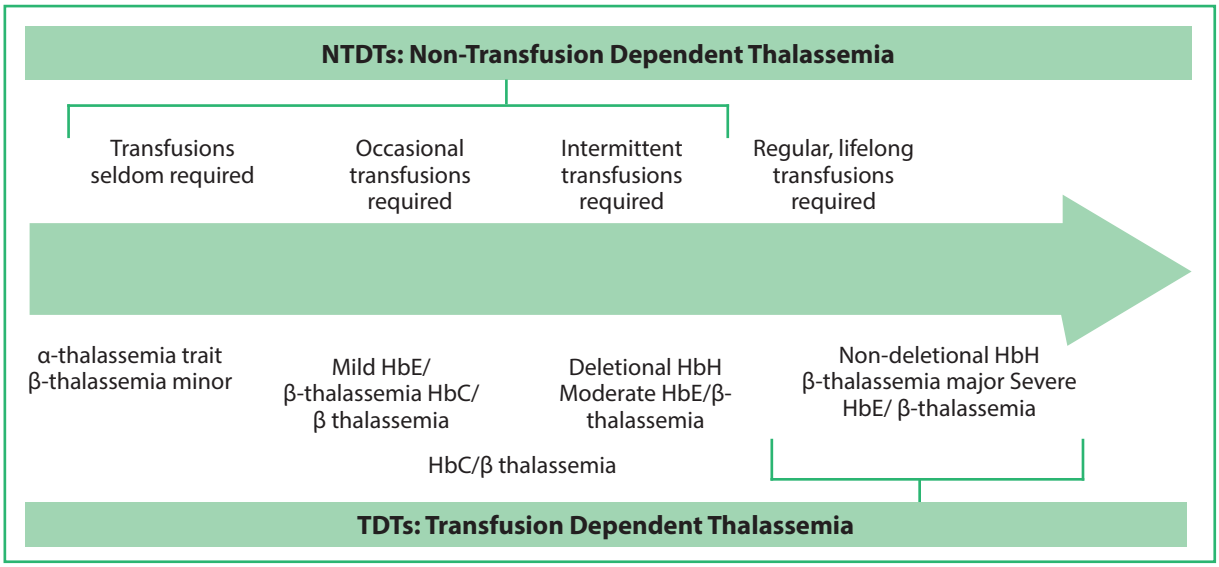


Figure 31: Clinical spectrum of thalassemia

Beta –Thalassemia minor:

- Usually no signs or symptoms except for mild persistent anemia not responding to hematinics

  Beta-Thalassemia Major: usually manifests after 6 months of age
  - Pallor, fatigue, irritability,jaundice
  - Growth retardation
  - Recurrent infections
  - Bony abnormalities, hemolytic facies (Typical facial changes: frontal bossing, prominent maxilla, zygoma, depressed nasal bridge.)
  - Enlarged spleen and liver
  - Delayed sexual development

Figure 32: Clinical spectrum of thalassemia

Diagnosis

Any child with following features should be suspected of thalassemia and investigated accordingly

- History of repeated anemia
- Failure to thrive
- Repeated infections
- Repeated jaundice
- Family history of thalassemia/anemia with jaundice

Investigations

- Hb electrophoresis
- Genetic testing

Significant aberration from a classical electrophoretic pattern is not uncommon. So, electrophoresis patterns should always be interpreted in the context of clinical features, PBF, and transfusion history. Parent screening may be needed in some cases.

Additional laboratory diagnosis

- Serum bilirubin: total (raised but not >5 mg/dl), direct (normal unless complicated) & indirect (raised)
- Reticulocyte count: reticulocytosis
- Serum ferritin: usually raised

Genetic diagnosis of beta thalassemia

- Sanger sequencing of HBB gene
- Generally not needed
- Must for prenatal diagnosis

Management

Current, most effective, and evidence-based management strategies can be

- Chronic transfusion therapy
- Iron chelation,
- Supportive care
- Induction of fetal Hb, in selected patients (Thalassemia intermedia)
- Splenectomy (if indicated)
- Gene therapy
- Bone marrow transplantation

Table 48: Standard care and screening guidelines for thalassemia intermedia and major

Assessment	Ages	Frequency	Comments
Bone mineral density	≥10	Yearly	DEXA scan or quantitative CT
Tanner stage	10-20	Yearly	Perform yearly starting at age 10 and continuing until breast or gonadal tanner stage 5 or age 20.
Liver iron content	All	Yearly	MRI method (R2,T2) or liver biopsy
Cardiac T2	≥10	Yearly	To be performed when available for patients with biochemical evidence of iron overload or age 10 years older
Cardiac studies	≥10	Yearly	Echocardiography and/or cardiac function by MRI; indicate the need to assess for pulmonary hypertension when ordering an echocardiogram
CBC plus differential	All	Yearly (minimum)	If transfused, preceding each transfusion
Blood chemistries	All	Yearly	BUN, creatinine, calcium, magnesium, phosphorus, and zinc
LFTs	All	Yearly	ALT,AST, total bilirubin, albumin
Ferritin	All	Six monthly (minimum)	If transfused, preceding each transfusion
HIV	All	Yearly	Only for transfused participants starting at the first transfusion
Hepatitis testing (Hepatitis B, Hepatitis C)	All	Yearly	Only for transfused participants starting at the first transfusion, HBV serology. HCV serology and PCR
Serum glucose	≥10	Yearly	12 h fasting
Endocrine panel I	≥6	Yearly	TSH, Free T4, Parathyroid hormone, 25-hydroxy vitamin D, and 1,2 dihydroxy vitamin D levels
Endocrine panel II	≥10	Yearly	Testosterone (males only), FSH and LH(males and females), and estradiol (females only)
Opthalmology and Audiology testing	Children and adults	Yearly	All patients undergoing chelation. Auditory testing necessary for those on deferoxamine

Recommended blood products

- Patients with transfusion-dependent thalassemia should preferably receive leuco-reduced packed red blood cells.
- Special blood products may be needed for special populations, such as washed red cells for patients with repeated severe allergic transfusion reactions
- Cryopreserved (frozen) red cells for patients who have unusual red cell antibodies or who are missing common red cell antigens.

Transfusion programs

The treatment for thalassemia major involves lifelong regular blood transfusions, usually administered every two to five weeks. This transfusion regimen

- Promotes normal growth, allows normal physical activities
- Adequately suppresses bone marrow activity in most patients

Blood transfusion requires informed consent

- Haemovigilance and adverse events reporting are key to the safety of blood transfusion.
- Careful donor selection and screening, favoring voluntary, regular, non-remunerated blood donors
- Target pre-transfusion hemoglobin level of 11.0-12.0 g/dl may be appropriate for

- Patients with heart disease
- Clinically significant extra medullary hematopoiesis or
- Other medical conditions, and for those patients who do not achieve adequate suppression of bone marrow activity at the lower hemoglobin level.

- Younger children may require a fraction of a unit to avoid under or over-transfusion.
  - For such children, 15-20ml/kg of packed RBC should be given
- Patients with cardiac failure or very low initial hemoglobin levels should always receive smaller amounts of red cells typically 5-10ml/kg in children.
- A careful record of transfused blood should be maintained for each patient, including the volume or weight of the administered units, the hematocrit of the units or the average hematocrit of units with similar anticoagulant-preservative solutions, and the patient's weight.

Transfusion and the spleen

- The transfusion requirements in non-splenectomized patients are generally higher than in splenectomized patients. Specific thresholds of annual transfusion requirements that would lead to consideration of splenectomy are difficult to establish
- Splenectomy may be considered one of several strategies to reduce the rate of iron-loading.

Adverse Reactions of transfusion

Blood transfusion exposes the patient to a variety of risks and adverse events. To minimize adverse events strict hemovigilance should be observed.

- Non-hemolytic febrile transfusion (NHFTR) is common and can be decreased by leukoreduction.
- Allergic reactions
- Acute hemolytic reactions (HTR)
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated graft-versus-host disease (TA-GVHD)
- Transfusion-associated circulatory overload (TACO)
- Transfusion-transmitted infections (TTI)

Recommendations for blood transfusions

- Confirm the diagnosis of thalassemia
- At each transfusion, give ABO, Rh(D) compatible blood.

Complications of Thalassemia

Complications can be grouped as

1) Transfusion-transmitted infections
2) Iron overload
3) Toxicities of iron chelation therapy
4) Bacterial infections
5) Cardiac complications
6) Liver complications
7) Bone complications
8) Other complications
   - Infections: Yersinia, parvovirus B19
   - Dental complications
   - Growth retardation

IRON OVERLOAD: PATHOPHYSIOLOGY, DIAGNOSIS AND MONITORING

Pathophysiology of iron overload

- Iron overload occurs when serum & organ iron level is increased over a sustained period, either as a result of red blood cell transfusions or increased absorption of iron through the gastrointestinal (GI) tract.
- The major cause of iron overload in TDT is transfusion while increased GI absorption is a major cause of non-transfusion-dependent thalassemia (NTDT).
- When thalassemia major patients receive a regular blood transfusion, iron overload is inevitable because the human body lacks a mechanism to excrete excess iron. Iron accumulation is toxic to many tissues causing heart failure, cirrhosis, liver cancer, growth retardation, and multiple endocrine abnormalities.

Diagnosis and monitoring of iron overload

The diagnosis and monitoring of iron overload are based on the complementary use of various parameters but the most frequently used and cost-effective parameter is a measurement of serum ferritin levels.

Serum ferritin (SF)

- SF concentration should be measured at least every 6 months (1-3 months). The ferritin level should be maintained between 500-1000 µg/l. Measuring the trends in SF over at least 3 months is a more reliable indicator for adjusting therapy than the use of single values.
- SF may not reflect total body iron levels or organ-specific levels in some patients since it fluctuates in response to inflammation, abnormal liver function, and metabolic deficiencies.
- Falling ferritin is usually due to falling levels of total body iron. In contrast, persistent high ferritin or increasing ferritin levels could be due to inflammation or liver disease.

IRON CHELATION

Aims of iron chelation therapy

- Preventive therapy: to maintain safe levels of body iron at all times, by balancing iron intake from a blood transfusion with iron excretion by chelation (iron balance).
- Rescue therapy: to remove excess iron stored in the body organs.
- Emergency therapy: to urgently intensify iron chelation in case of iron-induced heart failure.
- Dose adjustment of therapy: to adjust dosing and treatment regimens to changing circumstances identified by careful monitoring of body iron and its distribution; monitoring is important to avoid: a) under chelation with increased iron toxicity; or b) over-chelation and increased chelator toxicity.
- Adherence to therapy: to adhere to the prescribed regular regimen; intermittent high-dose chelation can induce negative iron balance but does not provide continuous protection from labile iron and also risks increased toxicity from the iron chelator.

Sources of chelatable iron: Only a small fraction of body iron is available for iron chelation at any moment. This is because iron chelators interact with low molecular weight 'labile' iron pools more rapidly than with iron stored as ferritin or haemosiderin.

Table 49: Iron chelators

Agent	Route half-life	Dose and regimen	Common or typical adverse effects
Deferoxamine	IV or SQ 8-10 min	30-40mg/kg/day over 8-12 hours 5-7 days/week	Anaphylaxis Local irritation Retinopathy Hearing loss Renal dysfunction Hepatic dysfunction
Deferasirox First line if available	Oral 12-18 h	20-40 mg/kg/day Once daily	Diarrhea Rash Proteinuria Renal dysfunction Hepatic dysfunction
Deferiprone	Oral 1.5-4h	75-100 mg/kg/day 3 divided doses daily	Arthralgia Arthropathy Agranulocytosis Renal dysfunction Hepatic dysfunction

Supportive management

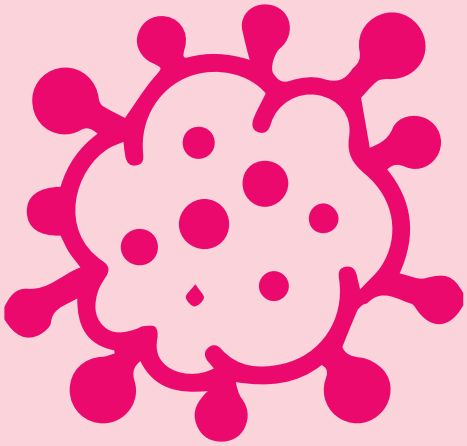
- Tab. Folic Acid 1 mg daily lifelong
- Calcium and vitamin D supplements
- Proper nutritional support
- Self Care

Prevention of Thalassemia

- Especially important in beta-thalassemia
- Highly cost-effective
- Carrier (trait) screening by Hb HPLC of mass and/or targeted group (ethnic group/premarital age group) and
- General population education

CHAPTER-6

CANCER



Introduction

Cancer refers to a large number of diseases characterized by the development of abnormal cells that divide uncontrollably and can infiltrate and destroy normal body tissue. The abnormal growth of cells can result in tumor (solid) formation. They can be benign or malignant tumors. If tumors have the potential to spread throughout the body, which is a process known as metastasis then they are known as cancer. However, not all cancers present necessarily as tumors such as leukemia and some lymphomas (liquid cancers).

Carcinoma in Situ and Invasive Carcinoma

Carcinoma "in situ" means cancer in place. These cells have transitioned to be cancerous, but they have not yet invaded the adjacent tissues. Note that, in the illustration below, the in situ cancer is still confined to the epithelial layer from which it arose. If left untreated, the in situ cancer may remain confined to the epithelial layer indefinitely, but it may acquire additional mutations that enable it to progress to invasive cancer.

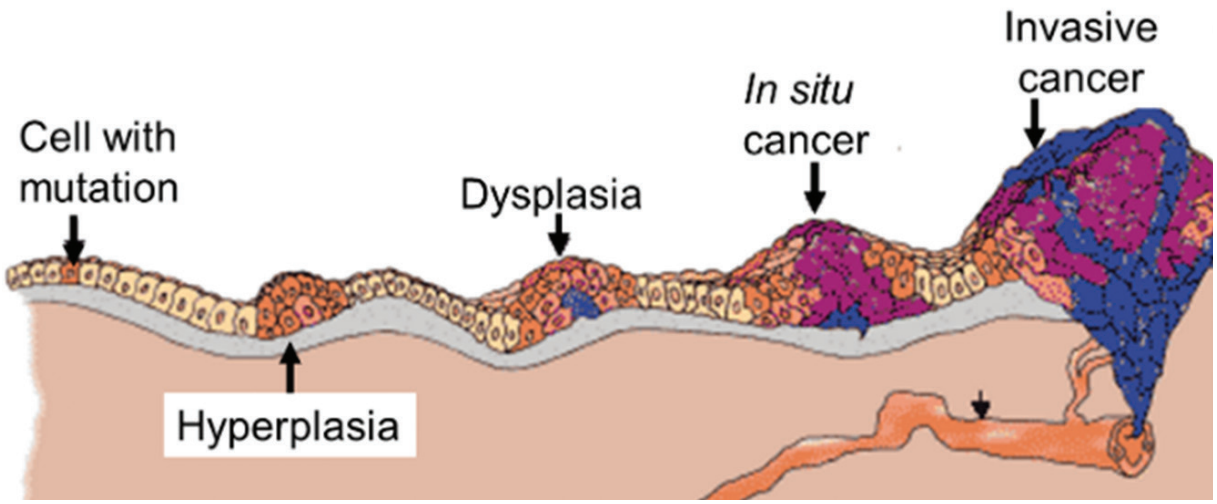


Figure 33: Etiopathogenesis of Cancer

The progression begins with a mutation that makes the cell more likely to divide. The altered cell and its descendants grow and divide too often, a condition called hyperplasia. At some point, one of these cells experiences another mutation that further increases its tendency to divide; this cell's descendants divide excessively and look abnormal, a condition called dysplasia. As time passes, one of the cells experiences yet another mutation, causing very abnormal structure, loss of differentiation, and loss of contact between the cells; however, it is still confined to the epithelial layer from which it arose, so it is called cancer in situ. The in situ cancer may remain contained indefinitely, but additional mutations may occur that enable it to invade neighboring tissues and shed cells into the blood or lymph, the tumor is said to be an invasive cancer (malignant). The escaped cells may establish new tumors (metastases) at other locations in the body.

Epidemiology

Cancer ranks as a leading cause of death and an important barrier to increasing life expectancy in every country of the world. According to estimates from the World Health Organization (WHO) in 2019, cancer is the first or second leading cause of death before the age of 70 years in 112 of 183 countries and ranks third or fourth in a further 23 countries. Cancer's rising prominence as a leading cause of death partly reflects marked decline in mortality rates of stroke and coronary heart disease, relative to cancer, in many countries.

In Nepal, the World Health Organization (WHO) estimates that NCDs account for 66% of all deaths, 9% of which are attributable to cancer (2016). According to estimates of the Global Cancer Observatory (GLOBOCAN) of the International Agency for Research on Cancer (IARC), there were 20,508 new cancer cases (8943 in men and 11,565 in women) and 13,629 cancer deaths (6244 in men and 7385 in women) in 2020.

Table 50: Common cancers in Nepal

Childhood Cancers	Female Cancers	Male Cancers	Combined (Male+Female)
Hematological (Leukemia/ Lymphomas)	Cervical Cancers	Lung cancers	Lung cancers
Sarcomas (Bony/ soft Tissue)	Breast Cancers	Stomach Cancers	Cervical cancers
Central Nervous system Tumors	Lung Cancers	Colorectal Cancers	Breast cancers
Retinoblastomas	Gall Bladder Cancers	Oral Cavity Cancers	Stomach cancers
Renal Tumours (Wilm's Tumor)	Ovarian Cancers	Thyroid Cancers	Colorectal cancers

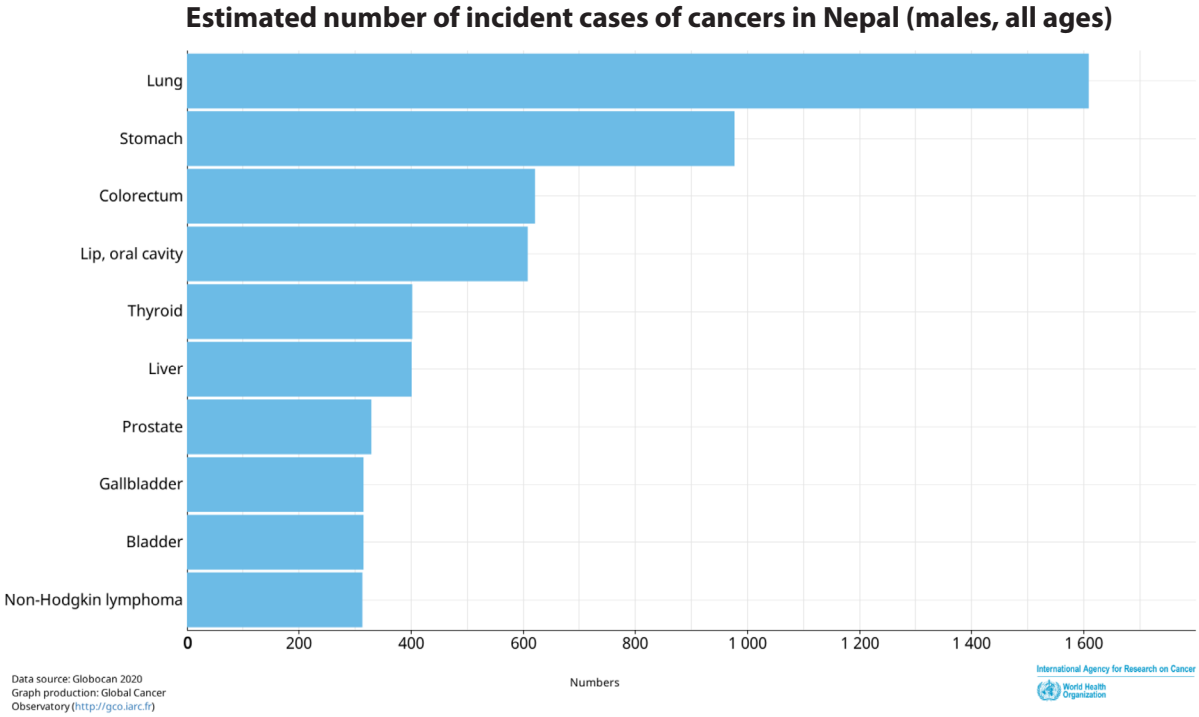


Figure 34: Estimated number of incident cases of males for Cancer in Nepal

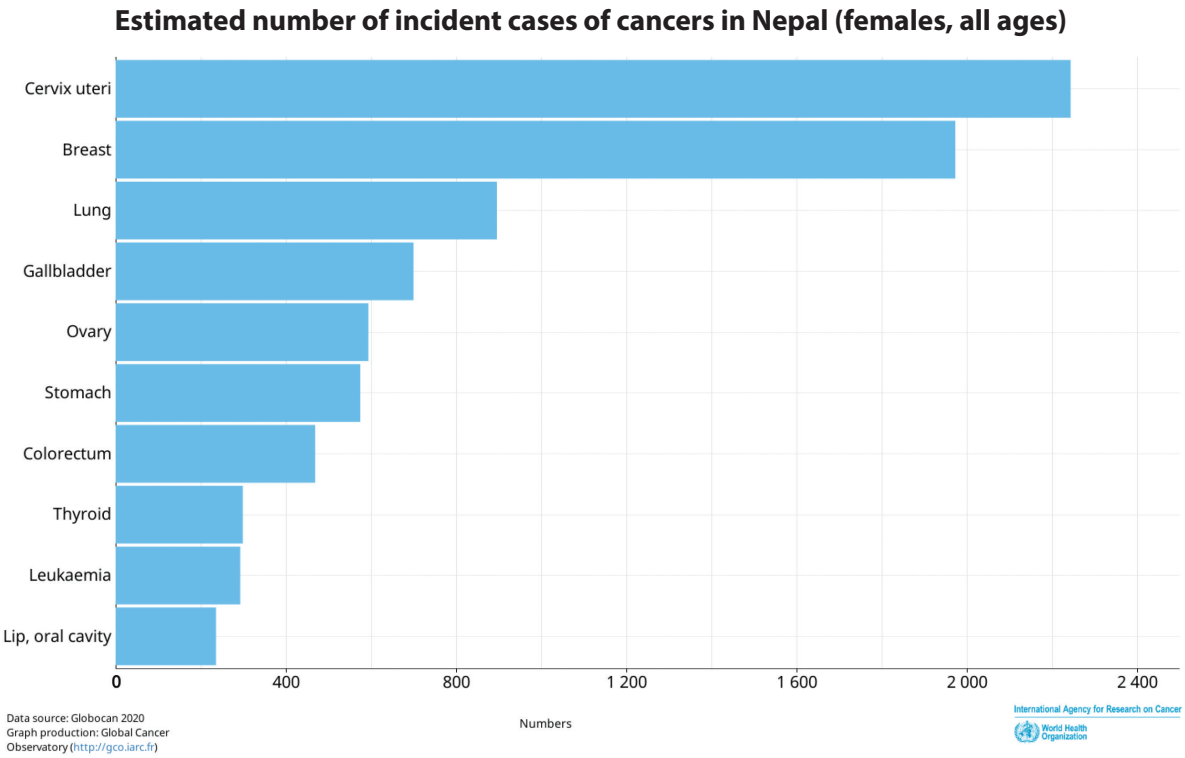


Figure 35: Estimated number of incident cases of females for Cancer in Nepal

Women are more affected because of the cervical cancer burden (2244 new cases), which ranks first, followed by breast cancer (1973 new cases) and lung cancer (896 new cases). In terms of incidence, the three most frequent cancer sites for men are lung (1609 cases), stomach (977 cases) and colorectal (621 cases). According to the same source, the estimated number of new childhood cancer cases is 485 in children aged 0–14 years and 829 cases in the age group 0-19 years.

Etiopathology

- Tobacco and related/ Chemical Carcinogens
- Oncogenic viruses include the Epstein –Barr virus, hepatitis B virus, Human Papilloma Virus (HPV), herpes virus, and hepatitis C virus.
- BMI and Obesity
- Alcohol Consumption
- Ionizing Radiation
- Heterocyclic Amines & Polycyclic Aromatic Hydrocarbons (chemicals formed from the cooking of muscle meats (beef, pork, fowl, and fish)
- Heredity (retinoblastoma, breast cancer, colorectal cancer, endometrial and ovarian cancer)
- AIDS-Related Cancers

Myths about Cancer

- **Cancer is always fatal:** Modern medicine has made huge strides in cancer treatment. Cancer is no longer the death sentence it once was. Early diagnosis and detection greatly improves the survival rate.
- **Cancer is contagious:** Unlike most common diseases that are caused by viruses, bacteria, or other microorganisms, cancer is caused by changes in cellular DNA. These changes are often random. In most people, these mutated cells are destroyed by cell death mechanisms but if these mechanisms fail, then it develops into cancer. While cancer can spread within the body, it cannot be transmitted from one person to another.

- **Radiotherapy and Chemotherapy will kill you:** While these treatments can be physically and mentally exhausting but they are life-saving treatments. Some side-effects are to be expected. In case of fears or doubts regarding cancer treatment, one should talk to the doctor before refusing the treatment entirely. It could be a matter of life and death.
- **I have no family history of cancer, so I won't get cancer:** A family history of cancer does increase your chance of developing the disease. However, this does not mean that if you have no family history of cancer you won't get the disease. Genetic mutations can be random, caused by environmental factors such as radiation exposure and pollution, and lifestyle factors such as smoking, obesity, excessive drinking, and poor dietary habits.
- **All lumps are cancer:** A majority of lumps that are detected during screenings and medical examinations are benign or another condition entirely such as a cyst. A doctor will conduct tests to determine if a growth is benign, precancerous, or cancerous.

Signs and Symptoms

There are no common symptoms or signs for all cancers; at early stage most cancers are asymptomatic. When they become symptomatic, each cancer can present with different signs and symptoms according to the site (local effect), type and stage as well as other constitutional symptoms. However, the following symptoms and signs should alert every clinician to suspect possible cancer and make appropriate investigations and referrals.

Symptoms

- PV discharge/bleeding: cervical cancer
- Palpable breast lump: Breast cancer
- Neck nodes: Head and neck cancers /Lymphomas
- Oral sores/ulcerations: Oral cancers
- Chronic cough/Hemoptysis: Lung cancers
- Difficulty urinating (weak stream): Prostate cancer
- Persistent vomiting, nausea, early satiety: Stomach or pancreatic cancer,
- Difficulty defecating or blood in stool: Colon or rectal cancer
- Passage of blood in urine: urinary bladder cancer
- Persistent headache, change in mental function, focal weakness: Brain tumor
- Whitish hue to the pupils, squint, pain, bulging eyes: Retinoblastoma

Signs

- Unexplained loss of weight or loss of appetite.
- Persistent fatigue, nausea, or vomiting.
- Persistent low-grade fever, either constant or intermittent.
- Repeated infection.
- Unexplained abdominal or bone pain.
- Features associated with Paraneoplastic syndrome. (e.g. symptomatic hyponatremia)

Principles of Screening, Early Detection, Diagnosis and Treatment

The purpose of screening an asymptomatic individual is to detect early evidence of an abnormality or abnormalities such as pre-malignant changes (e.g. by Pap test) or early invasive malignancy (e.g. by mammography) in order to recommend preventive strategies or treatment that will provide a better health outcome than if the disease were diagnosed at a later stage.

Early detection of cancer greatly increases the chances of successful treatment. Two components of early detection of cancer are early diagnosis and screening. Early diagnosis focuses on detecting symptomatic patients as early as possible, while screening consists of testing healthy individuals to identify those having cancers before any symptoms appear.

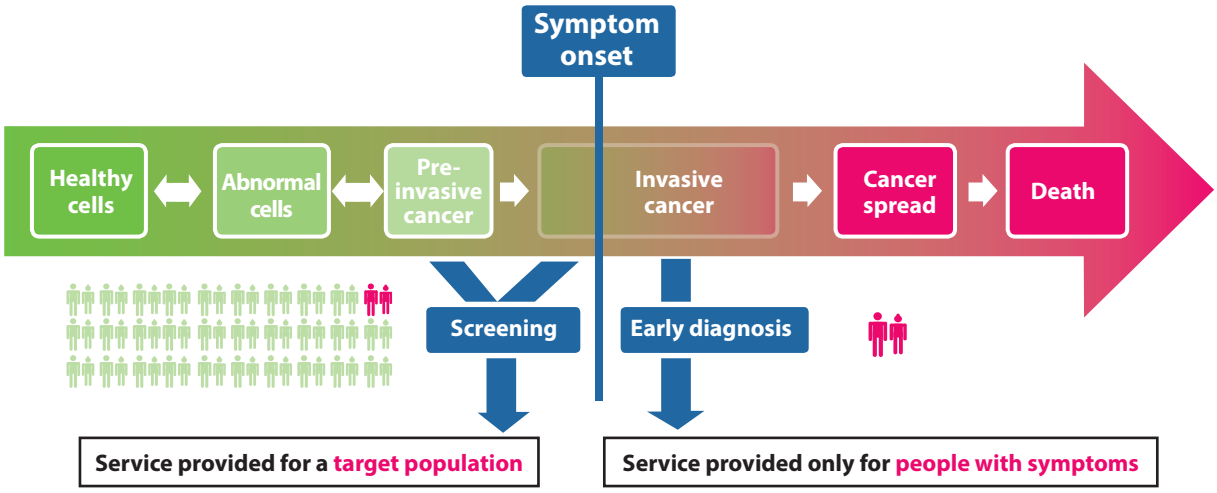


Figure 36: Principles of Screening, Early Detection, Diagnosis and Treatment

Principles of Diagnosis and Staging

The diagnosis of cancer is mostly confirmed by biopsy, and imaging techniques are used for cancer staging. The technique involved in staging of the cancer includes CT-scan, MRI, Functional scans like PET-CT and at times surgery.

Principles of treatment

Curing cancer requires eliminating all cancer cells. The intent of treatment includes curative and palliative treatment depending on the stage of the disease.

Various treatments for cancer include:

- Surgery (for local and local-regional disease and at times palliation of symptoms)
- Radiation therapy (for local and local-regional disease and at times palliation of symptoms)
- Chemotherapy (for systemic disease including some localized disease like germ cell tumor and retinoblastoma, used both for curative and palliative treatment)
- Hormonal therapy (for selected cancers, e.g., prostate, breast, endometrium)
- Immunotherapy
- Monoclonal antibodies. (Targeted drugs that exploit the growing knowledge of cellular and molecular biology)
- Palliative Care

6.1. CHILDHOOD CANCER

The WHO Global Initiative for childhood cancer (Cure All) has defined childhood cancers as the group of cancer that arises between birth and 19 years of age. Pediatric malignancies differ greatly from adult malignancies in both prognosis and distribution by histology and tumor site.

Lymphohematopoietic cancers (i.e., Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Hodgkin and Non-Hodgkin lymphomas) account for approximately 40%, central nervous system cancers for approximately 30%, and embryonal tumors and sarcomas for approximately 10% among the broad categories of childhood cancers.

Limited preventable measures and the high curability of childhood cancers, make early detection the key to the cure of childhood cancers. It requires strong public and health professional awareness, with timely and robust referral processes linked to high-quality clinical services.

Early Warning Signs of Childhood Cancer

One of the causes of disparity in the outcome of childhood cancer among high-income and low- and middle income countries is delayed diagnosis which is partly due to a lack of awareness among healthcare workers about early warning signs and symptoms. Early warning signs, also referred to as the "St SILUAN warning signs", is an effective method to aid early detection, as 85% of pediatric cancers are associated with the following signs:

Table 51: St SILUAN warning signs of Childhood Cancer

S	SEEK medical help early for ongoing symptoms
I	EYE White spot in the eye, new squint, sudden blindness or bulging eyeball
L	LUMP on the stomach, pelvis, head, arms, legs, testicle or glands
U	UNEXPLAINED fever present for over 2 weeks, weight loss, fatigue, pale appearance, easy bruising and bleeding
A	ACHING bones, joints, back and easy fractures
N	NEUROLOGICAL signs a change in walk balance or speech, regression, continuous headaches with/ without vomiting and an enlarged head

Patients with the above signs and symptoms should be referred to the tertiary center after proper initial stabilization of the patient for further management.

Leukemia

Acute leukemia represents a clonal expansion and arrest at a specific stage of myeloid or lymphoid hematopoiesis.

The common type of leukemia in children are:

- Acute lymphoblastic leukemia (ALL)
- B-cell acute lymphoblastic leukemia (B-ALL)
- T-cell acute lymphoblastic leukemia (T-ALL)
- Acute myeloblastic leukemia (AML)

Clinical manifestations

The initial presenting symptoms of leukemia are usually nonspecific.

- Anorexia, fatigue, malaise, irritability and intermittent low-grade fever -common
- Bruising, petechiae, purpura, mucosal bleeding from various sites - common
- Bone or joint pain may be present which might be for several months, may be localized predominantly to the bones or joints, and may include joint swelling. Bone pain might be severe and can wake the patient at night.
- Organ infiltration can cause
  - lymphadenopathy,
  - hepatosplenomegaly,
  - testicular enlargement,
  - central nervous system (CNS) involvement (cranial neuropathies, seizures).

Diagnosis:

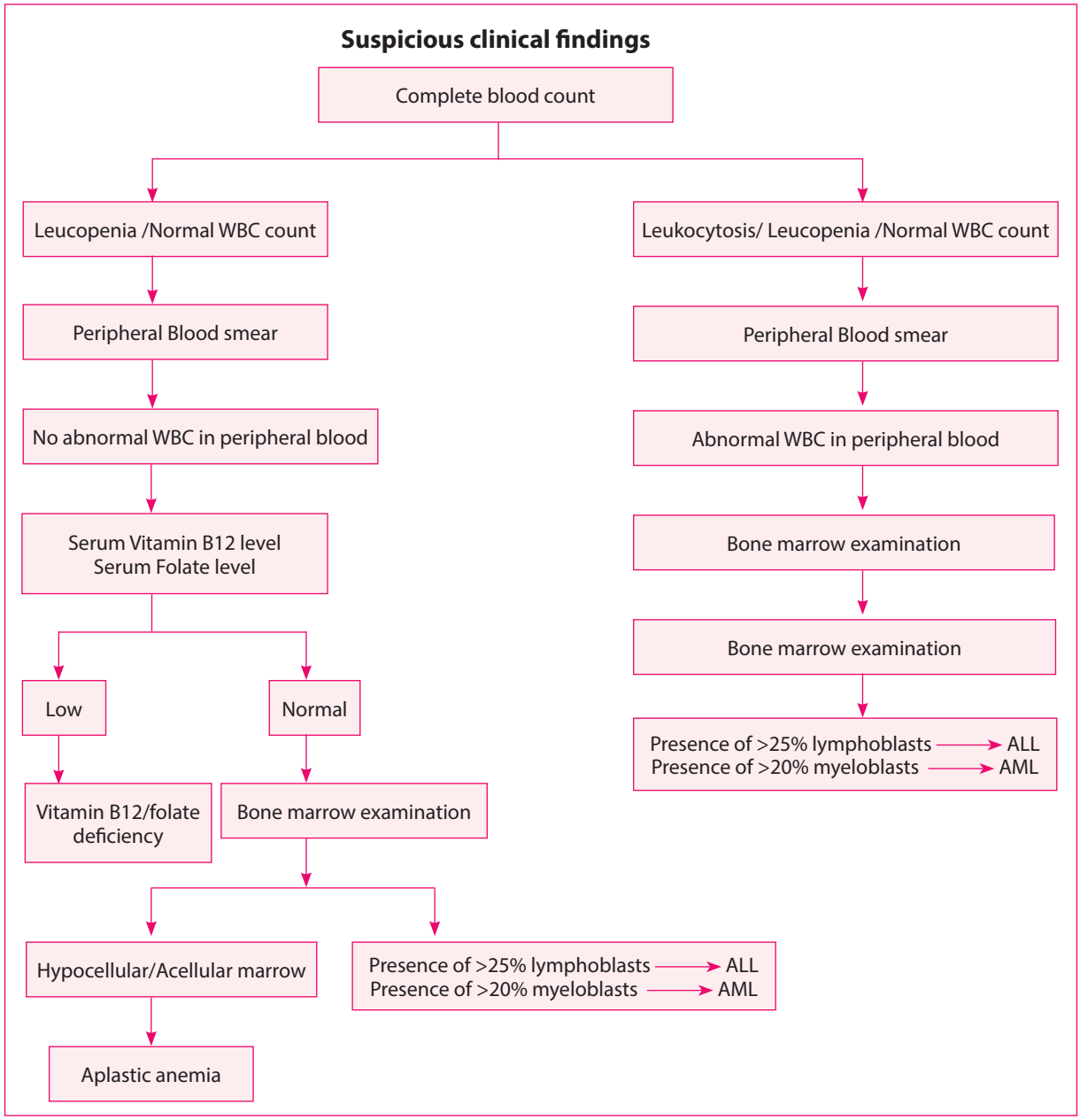


Figure 37: Algorithm for diagnosis of Childhood Cancer

Treatment:

Components

- Treatment of the primary disease by chemotherapeutic agents
- Supportive care
- Management of oncological emergencies

Treatment of the primary disease

- The single most important prognostic factor in leukemia is the treatment: without effective therapy the disease is fatal.

Supportive care

- The vast improvement in outcomes of children with malignancies is not only due to improvement in the treatment but also improvement in supportive care.

Management of oncological emergencies

- Oncological emergencies can occur as the initial manifestation of cancer, as a side effect of therapy, or at the time of progression or recurrence of the disease.

In any child suspected to have leukemia, stabilize the patient before transfer to a tertiary center.

1. Start intravenous fluids (potassium free)- Normal saline 125ml/m2/hour.
2. Start Tab. Allopurinol 10mg/kg/day in 3 divided doses
3. If anemia is severe, transfuse Packed Red Cell Concentrate (PRBC) 15ml/kg over 4 hours. Do not give prophylactic steroids before or during transfusion.

Note: *Do not transfuse PRBC if the patient has hyperleukocytosis unless anemia is severe, transfuse PRBC 5ml/kg over 4hours*

4. Consult and inform the oncologist regarding stabilization and transfer.

Lymphoma:

Lymphomas are malignancies that arise from lymphatic system. The common lymphomas in children are

- Non-Hodgkin Lymphoma
- Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL)

Pediatric NHL is usually high grade in contrast to adult lymphomas and can present as an oncological emergency.

Clinical manifestations:

Depend mainly on the pathologic subtype of disease and site of involvement. As pediatric NHL are very aggressive tumors with high mitotic index, they can present as potential clinical emergencies due to rapidly growing masses:

- Superior/inferior vena cava obstruction,
- Acute airway obstruction,
- Spinal cord compression,
- Pericardial tamponade,
- Intussusception/intestinal obstruction,
- Central nervous system (CNS) complications.
- Tumor lysis syndrome.

Diagnosis:

Tissue diagnosis is essential before starting therapy. If the patient's clinical condition is unstable, such as superior vena cava syndrome, the diagnosis should be made with a least invasive method.

Treatment:

The primary modality of treatment of pediatric NHL is multi-agent systemic chemotherapy.

If features of superior vena cava syndrome are present, the patient should be kept in the most comfortable position with minimal intervention. Patients may need empiric treatment as lifesaving therapy before transfer.

First-line treatment in emergent situations is high-dose steroids.

- IV methylprednisolone 1 mg/kg per dose up to every 6 hours or equivalent dose of steroids.

Stabilize the patient before transfer to a higher center.

Hodgkin Lymphoma (HL)

It is a malignancy of the lymphoreticular system and is the most common cancer in adolescents. It has been associated with infectious agents: Epstein-Barr virus, Human Herpes virus, and Cytomegalovirus.

Clinical manifestations:

Patients typically present with painless, non-tender, firm, rubbery, cervical or supraclavicular lymphadenopathy and usually some degree of mediastinal involvement. Systemic symptoms, classified as B symptoms, that are considered important in staging are unexplained fever >38°C (100.4°F), weight loss >10% of total body weight over 6 months, and drenching night sweats.

Diagnosis:

Histological examination of the affected lymph node. Immunohistochemistry is advised wherever feasible. Staging investigations are essential before starting the therapy.

Treatment:

Multi-agent systemic therapy is the core of the treatment of HL. With the use of current therapeutic regimens, patients with favorable prognostic factors and early-stage disease have an event-free survival (EFS) of 85–90% and overall survival (OS) at 5 year of >95%.

Retinoblastoma:

Most common intraocular tumor in children. It can be either hereditary or sporadic. Hereditary cases usually present at a younger age and are multifocal and bilateral, whereas sporadic cases usually present in older children, who tend to have unilateral, unifocal involvement.

Clinical presentation:

- Classical presentation- white pupillary reflex or leukocoria
- Strabismus often is an initial presenting complaint. Decreased vision, orbital inflammation, hyphema, and pupil irregularity can occur with advancing disease.
- Pain can occur if secondary glaucoma is present

Treatment:

- The primary goal of treatment is always cure; the secondary goals include preserving vision and the eye itself and decreasing the risk of late side effects, mainly secondary malignancies. Enucleation is performed if useful vision cannot be salvaged.
- Any child with white pupillary reflex should be immediately referred to a tertiary eye care center so that proper treatment can be started and vision can be salvaged.
- It is essential to counsel the parents that timely treatment can prevent visual loss.
- Tumors of the Central Nervous System (CNS):
- Primary CNS tumors are a heterogeneous group of diseases with the highest morbidity—primarily neurologic—of all malignancies in children. Outcomes have improved over time with innovations in neurosurgery, radiation therapy, chemotherapy, and immune therapy.

Clinical presentation:

The clinical presentation of the patient with a brain tumor depends on tumor location, tumor type, and patient age. In young children, the diagnosis of a brain tumor may be delayed because the symptoms are similar to more common illnesses, such as gastrointestinal disorders, with associated vomiting.

General signs and symptoms of intracranial tumors:

- Headache: headache can present as irritability; often worse in the morning, improving throughout the day.
- Vomiting, seizures
- Disturbances of gait and balance – common in infratentorial tumors
- Hemiparesis, focal sensory weakness - common in supratentorial tumors
- Cranial nerve abnormalities
- Impaired vision, diplopia (sixth nerve palsy), intermittent strabismus, visual field disturbances
- Papilledema from increased Intracranial Pressure (ICP) may present as intermittent blurred vision.
- Mental disturbances: somnolence, irritability, personality or behavioral change, change in school performance.
- Endocrine abnormalities

Diagnosis:

The evaluation of a patient in whom a brain tumor is suspected is an emergency. The initial evaluation should include a complete history, physical (including ophthalmic) examination, and neurologic assessment with neuroimaging. For primary brain tumors, MRI with and without gadolinium is the neuroimaging standard.

Treatment:

Comprises of multimodality therapy including surgery, radiation and chemotherapy depending upon the subtype of tumor and age of the patient.

If the patient has features of raised ICP, measures to decrease ICP should be done before transfer.

- Elevate headend by 15-30® in the midline
- Hyperosmolar therapy – if features of impending brain herniation
  - Inj. Mannitol- 0.5-1g/kg infused over 10mins or
  - Inj. 3% sodium chloride – 1-3mL/kg, maximum 250ml over 10mins.

Wilms tumor (Nephroblastoma):

Most common primary renal tumor in children. Most cases are unilateral but few cases are bilateral. It is usually sporadic but can be familial. The most common sites of metastases are the lungs, regional lymph nodes and liver.

Clinical presentation:

- Incidental detection of abdominal mass – most common presentation
- Abdominal pain
- Gross hematuria
- Constitutional symptoms – fever, anorexia and weight loss

Diagnosis:

- Ultrasonography abdomen – initial screening
- CT abdomen and thorax- to define the extent of disease, integrity of contralateral kidney and metastases
- Histopathological examination of the biopsy specimen

Treatment:

Risk-adapted multimodality therapy forms the basis of treatment of Wilms tumor and is one of the malignancies of childhood with very good outcomes.

Management of Oncological Emergencies

Survival in children with cancer has increased dramatically not only due to advances in therapy but also to advances in supportive care and an improved ability to manage life-threatening complications.

The various oncological emergencies are:

- Metabolic emergencies- Hyperleukocytosis, Tumor Lysis Syndrome (TLS)
- Cardiothoracic emergencies- Superior vena cava Syndrome (SVCS) and/or Superior Mediastinal Syndrome (SMS)
- Acute abdominal processes;
- Treatment-related emergencies

A. Metabolic Emergencies:

More common in hematological malignancies like leukemia, lymphoma.
The most critical step in the prevention of metabolic emergencies is hydration.

Hyperleukocytosis:

Total white cell count >100,000/mm3. It can lead to tachypnoea, blurred vision, confusion, oliguria, hemorrhage, and thrombosis. Urgent treatment is required to prevent complications.

Tumor Lysis Syndrome:

Metabolic abnormalities that result from the death of tumor cells with release of their contents into the circulation. The classic triad includes hyperuricemia, hyperphosphatemia, and hyperkalemia.

Table 52: Treatment of Metabolic Emergencies

Objectives	Management guidelines
1. Monitor for Tumor Lysis Syndrome	▪ Strict intake/output monitoring ▪ Check CBC, renal function, uric acid, phosphorus, and calcium daily
2. Promote excretion of intracellular metabolites	▪ Intravenous hydration- Inj. Normal saline 3L/m2/day (Do not add potassium) ▪ Maintain urine output>100ml/m2/hour
3. Reduce Uric acid	▪ Allopurinol 10mg/kg/day (max.-800mg/day)
4. Reduce potassium	▪ Potassium infusion should be avoided unless dangerously low ▪ Diuretics can be used
5. Reduce phosphorus	▪ Use Phosphate binders if available - Aluminum hydroxide- 150mg/kg/day in divided doses every 6-8 h - Sevelamer hydrochloride- 400 mg twice daily for older children)
6. Raise calcium	▪ Low phosphate diet ▪ If symptomatic hypocalcemia: 0.5-1.0mL/kg of 10% calcium gluconate over 10mins

B. Cardiothoracic emergencies

Superior Venacava Syndrome (SVCS) and/or Superior Mediastinal Syndrome (SMS): due to compression of superior venacava with/ without tracheal compression by anterior mediastinal mass. It presents with signs of respiratory distress, distended neck veins, swelling of upper extremities, and conjunctival congestion.

Management

- Extreme care should be taken in handling the patient.
  The following may precipitate respiratory arrest:
  - supine or recumbent position (as for CT or operative procedures),
  - drugs that cause intercoastal muscle relaxation (anxiolytics, sedatives)
  - anxiety/ stress.
- Diagnosis should be made quickly in the least invasive manner possible
  - Chest X-ray and CT scan chest to delineate the mass (if tolerated)
  - Blood investigations- Complete blood count, Peripheral blood smear, renal function test, serum calcium, phosphorus, uric acid.
  - In case of hyperleukocytosis- send peripheral blood for flow cytometry (avoid bone marrow examination)
- Patients may need empiric treatment as a lifesaving measure.
  - First-line treatment in emergent situations is high-dose steroids.
    - IV methylprednisolone 1 mg/kg per dose up to every 6 hours.

This will treat hematologic malignancies as well as decrease airway edema.

- The patient should be stabilized before transfer to a higher center.
- IV hydration should be started and continued during transfer.

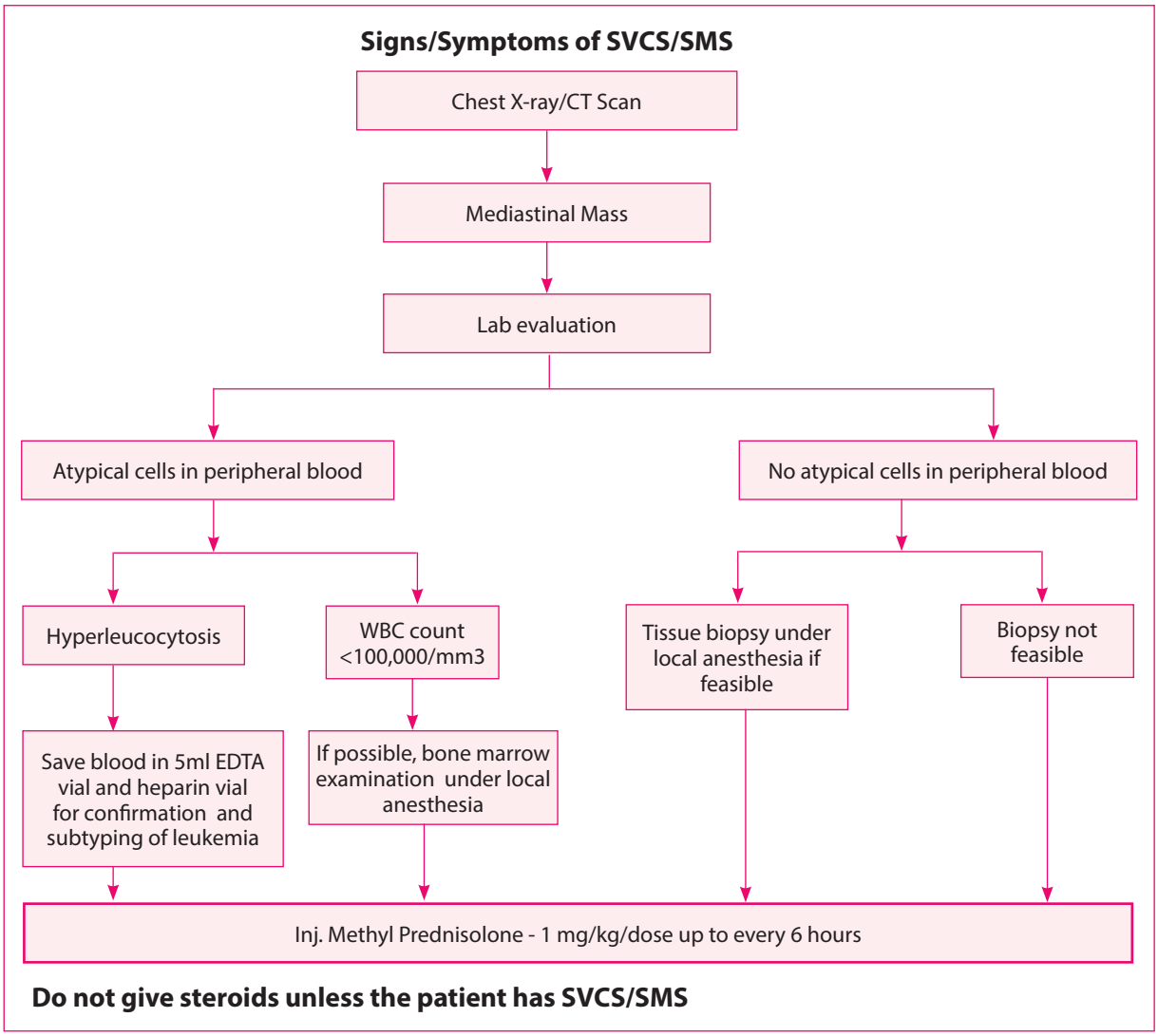


Figure 38: Management of SVS/SMS before transfer to higher center

C. Abdominal emergencies

Can occur as a part of the presentation of disease or due to toxicity from therapy. When a patient with malignancy on therapy presents with signs and symptoms of abdominal process, evaluate the following:

- Detail history and gentle examination, including mouth and perirectal area. The classic signs of an acute abdomen may be muted in a neutropenic patient or a patient on steroids.
- Lab tests-
  - CBC, blood culture, urine culture, amylase, lipase, electrolytes
- Abdominal imaging

Table 53: Evaluation and management of common causes of abdominal pain in oncology patient

Diagnosis	Signs/symptoms	Clinical risk factors	Evaluation	Management
Typhlitis	Acute abdominal pain, diarrhoea, hypotension, bloody diarrhea	Severe myelosuppression	Abdominal X-ray (free gas or thickened bowel loop)	- Bowel rest/NG drain - Broad-spectrum antibiotics (Gram negatives + anaerobes)
Pancreatitis	Abdominal pain, vomiting	L-asparaginase, Steroids, 6-MP	Amylase, Lipase, USG/CT abdomen	- Bowel rest/NG drain
Perirectal abscess	Erythema, Induration, pain with defecation	Severe myelosuppression, prolonged neutropenia	Perirectal examination	- Broad-spectrum antibiotics (Gram negatives + anaerobes) - Sitz baths
Constipation/ Ileus	Hard stool or no stool, pain, distended abdomen	Vincristine, dehydration	Abdominal X-ray	Stool softeners
Gastrointestinal hemorrhage	Black tarry stool, hematemesis	Chemotherapy, prolonged steroids	Oral examination, Endoscopy	IV antacids, bowel rest

D. Treatment related emergencies

1. Febrile Neutropenia

Any patient on chemotherapeutic agents when presents with fever, consider it a medical emergency.

- Send blood culture and start intravenous empirical antibiotics within 1hour of presentation to the hospital.
- The antibiotics should cover gram negative organisms (E. coli, Pseudomonas).
  - Inj. Piperacillin/Tazobactam – 90mg/kg/dose TID
  - Inj. Amikacin 15mg/kg/day
- The empirical antibiotics should be continued till blood culture reports are negative and patient is afebrile for at least 48hours.
- If the focus of infection is present, antibiotics should be continued accordingly.

Granulocyte Colony stimulating (G-CSF) should be avoided in patients with hematolymphoid malignancies unless life-threatening infection is present while can be used in patients with solid tumor and febrile neutropenia.

6.2. BREAST CANCER

Introduction:

Breast cancer is a malignant tumor that starts in the cells of the breast. Most breast cancers begin in the cells that line the ducts (ductal cancers). Some begin in the cells that line the lobules (lobular cancers), while a small number start in other tissues.

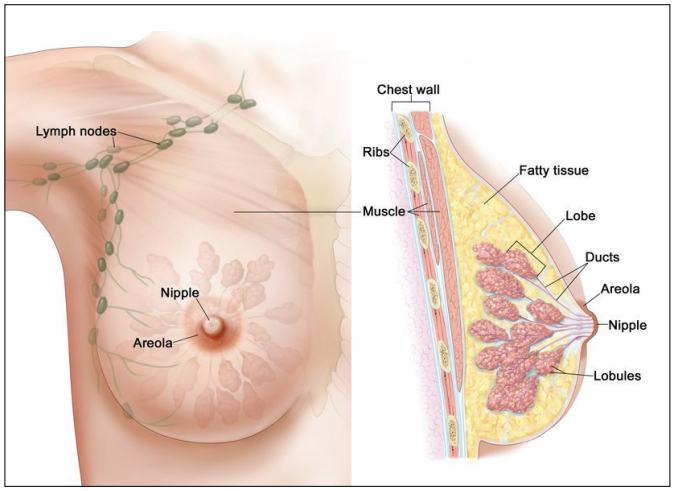


Figure 39: Anatomy of Breast

Benign breast lumps

Most breast lumps are not cancerous (benign). Still, some may need to be biopsied (sampled and viewed under a microscope) to prove they are not cancerous.

Fibrosis and cysts

Fibrosis is the formation of scar-like (fibrous) tissue, and cysts are fluid-filled sacs. These conditions are most often diagnosed based on symptoms, such as breast lumps, swelling, and tenderness or pain. These symptoms tend to be worse just before a woman's menstrual period is about to begin.

Fibro adenomas and Intraductal papillomas

Benign breast tumors such as fibro adenomas or intra-ductal papillomas are abnormal growths, but they are not cancerous and do not spread outside the breast to other organs. They are not life-threatening. Fibro adenomas are firm and mobile and appear to shift position and are commonly referred to as 'breast mice'. Still, some benign breast conditions are important because women with these conditions have a higher risk of developing breast cancer.

Etio-pathogenesis

Non-modifiable risk factors

- Gender: Female
- Aging: The risk of developing breast cancer increases as the person gets older. The scenario is changing now and younger patient with breast cancer is increasing in our country too.
- Genetic risk factors: About 5% to 10% of breast cancer cases are thought to be hereditary.
- Certain benign breast conditions: Fibrosis, cysts, fibroadenomas.

Modifiable risk factors

- Nulliparous: Women who have had no children or who had their first child after age 30 have a slightly higher breast cancer risk overall.
- Oral contraceptives: The risk is slightly increased.
- Hormone therapy after menopause: Hormone therapy with estrogen (often combined with progesterone)
- Not Breastfeeding: Some studies suggest that breastfeeding may slightly lower breast cancer risk.
- Drinking alcohol: The use of alcohol is linked to an increased risk of developing breast cancer. The risk increases with the amount and frequency of alcohol consumed.
- Overweight or obese: Being overweight or obese increases breast cancer risk.
- No Physical activity: Evidence is growing that physical inactivity increases breast cancer risk.
- Tobacco smoke: The risk is increased in smokers.

Signs and Symptoms

The most common symptom of breast cancer is a new lump or mass. A painless, hard mass that has irregular edges is more likely to be cancerous. They can sometimes be painful. For this reason, it is important to have any breast mass or lump or breast change checked by a healthcare professional experienced in diagnosing breast diseases. Possible symptoms of breast cancer include:

- Swelling of all or part of a breast (even if no distinct lump is felt)
- Skin irritation or dimpling
- Breast or nipple pain
- Nipple retraction (turning inward)
- Redness, scaliness, or thickening of the nipple or breast skin
- Nipple discharge (other than breast milk)

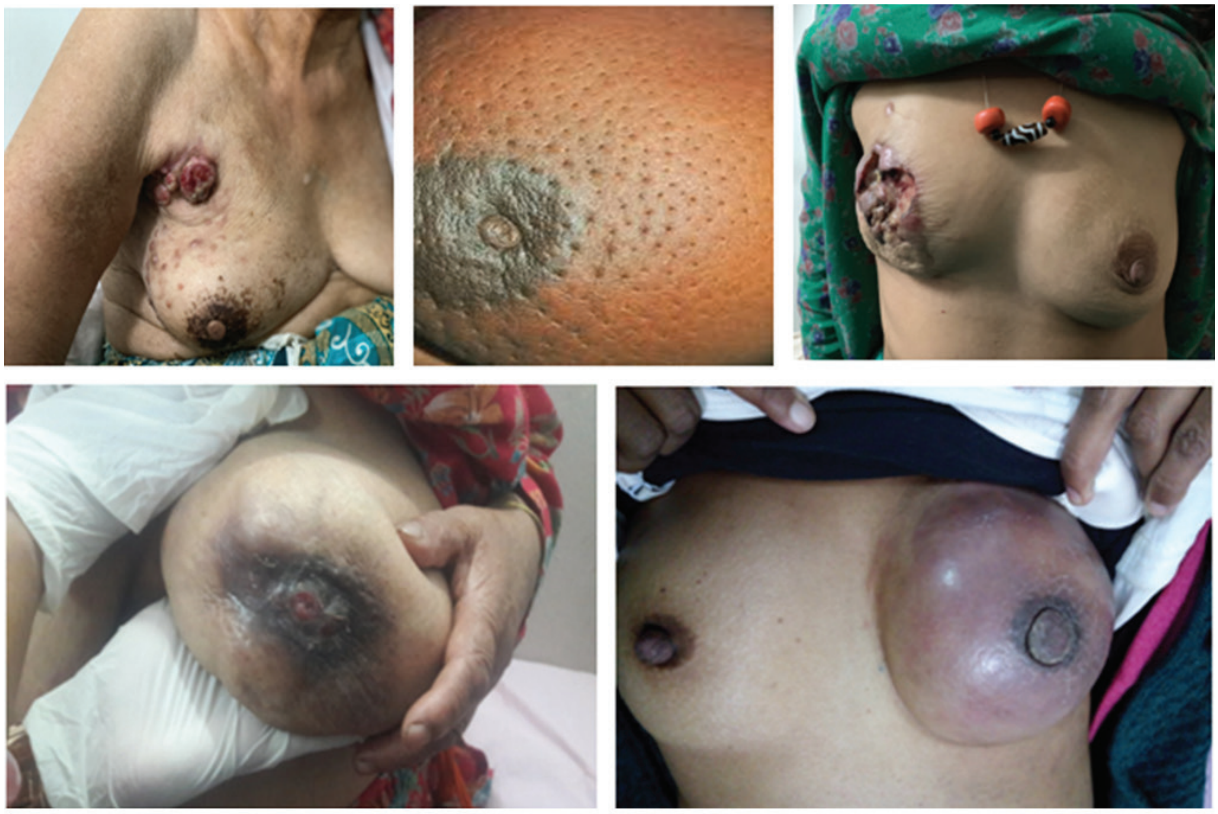


Figure 40: Presentation of Patients with Breast Cancer

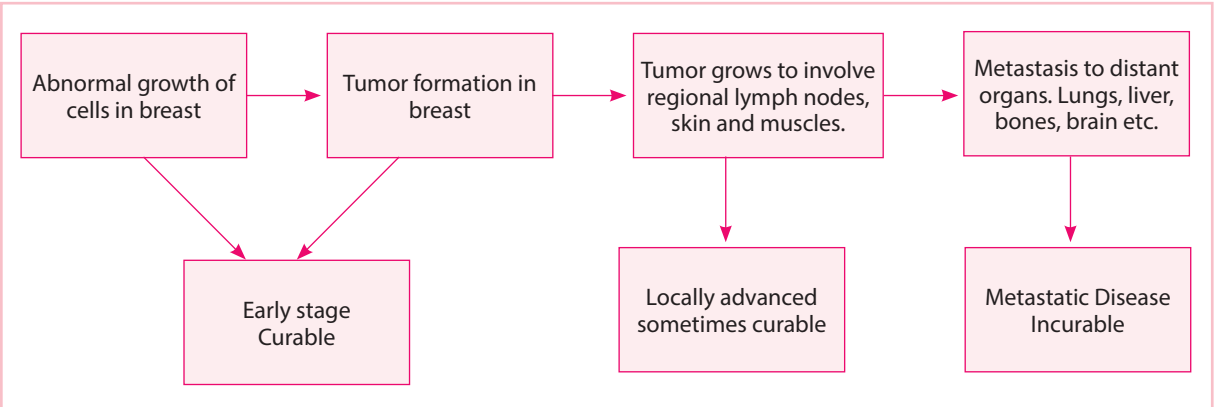


Figure 41: Breast Cancer Progression

Diagnosis

Triple Test

1. Clinical Exam: Examination of breast, axilla and supraclavicular region both sides by the physicians.
2. Imaging tests: Mammogram, Breast ultrasound, CT scan and MRI of the breast as applicable.
3. Pathology: A biopsy is done when mammograms, other imaging tests, or the physical exam finds a breast change (or abnormality) that is possibly cancer. A biopsy is the only way to tell if cancer is really present. Biopsy can be done through Core needle biopsy, Surgical (Incisional/ Excisional) biopsy.

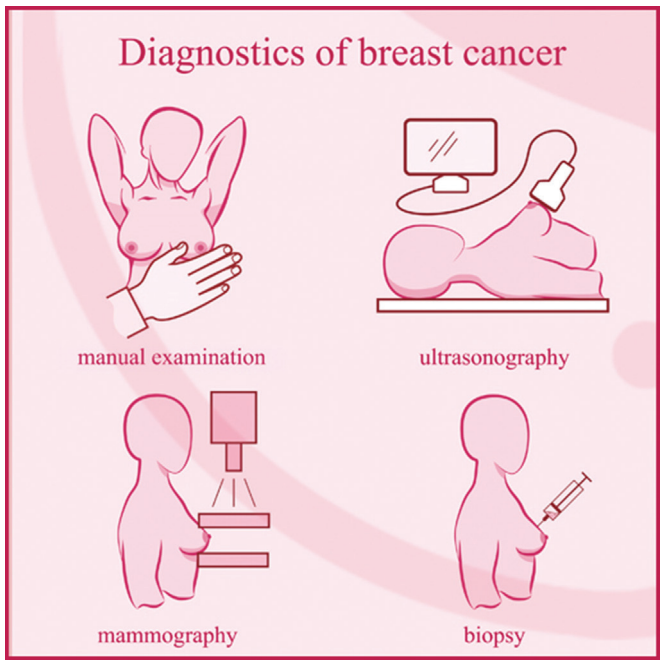


Figure 42: Diagnostics of Breast Cancer

Management

The treatment of breast cancer depends on the type and stage of the disease, the main types of treatment for breast cancer are:

- Surgery
- Radiation therapy
- Chemotherapy
- Hormone therapy
- Targeted therapy
- Bone-directed therapy (for bone metastases)

A practical approach to handle a patient with suspected breast cancer concerns at the level of health center and district hospital.

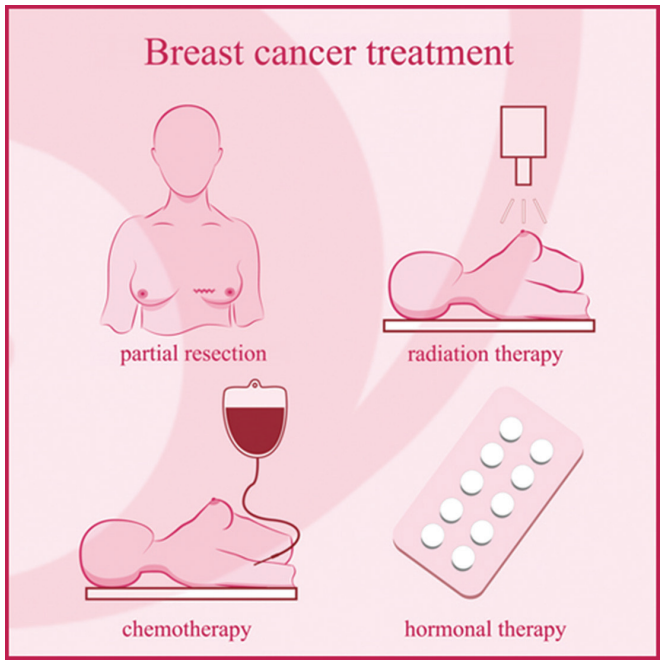


Figure 43: Breast cancer treatment

Questions to ask a patient with a breast concern.

- How long has she had the problem?
- Does she have any other symptoms? (e.g. Pain, nipple discharge, fevers)
- Has she been pregnant before?
- Is she pregnant or breastfeeding?
- Are symptoms related to the menstrual cycle?
- Does she have any personal history of breast cancer?
- Has she had this problem before or had treatment for this or other breast problems?
- Does she have any family history of breast cancer?

*Before examination, the male examiner must ensure the presence of a chaperone.

Breast Cancer Screening

Breast cancer screening focuses on providing timely access to cancer treatment by reducing barriers to care and/or improving access to effective diagnosis services. The goal is to increase the proportion of breast cancers identified at an early stage, allowing for more effective treatment to be used and reducing the risks of death from breast cancer. This section includes two important breast cancer screening techniques: Clinical Breast Examination and self-breast examination.

Clinical Breast Examination (CBE)

It is an examination of both breasts performed by a trained health professional. CBE can be used as a diagnostic test in a woman who has a breast lump or as a screening test in a woman during a screening program. CBE seems to be a promising approach for low-resource settings and could be implemented depending on the evidence from ongoing studies. Research is underway to evaluate CBE is a low-cost approach to breast cancer screening that can work in less affluent countries. Promising preliminary results show that the age-standardized incidence rate for advanced-stage breast cancer is lower in the screened group compared with the unscreened group.

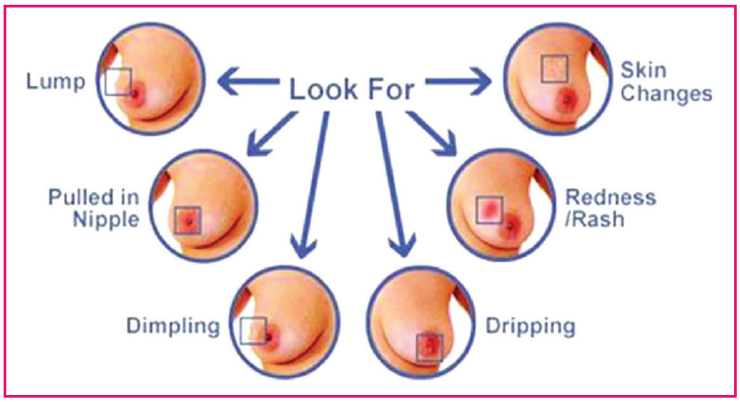


Figure 44: Clinical breast examination

Step 1: Visual inspection

Identify any visible abnormalities or asymmetry or nipple retraction

1. Patient should be naked from the waist up.
2. Patient sitting up, hands on either side of hips and pushing into hips down.
3. The patient has to raise her arms and press her hands together over her head.
4. Pay attention to the size, form, symmetry of the breast tissue, color and changes on the skin, condition of the nipple and nipple discharge.

Step 2: Nodal Examination (while sitting):

Identify any enlarged lymph nodes

1. Cervical nodes
2. Supra/infraclavicular nodes
3. Axillary nodes: Have the patient relax her arm, for example by resting it on the examiner's forearm

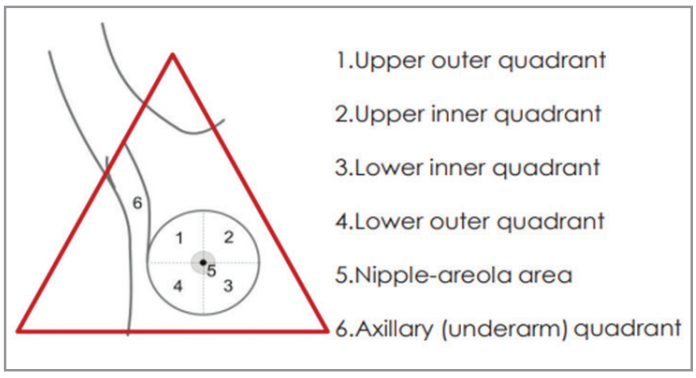


Figure 45: Location of tumors in different quadrants of breast

Step 3: Breast Palpation

Identify any abnormal masses, tenderness, or nipple discharge

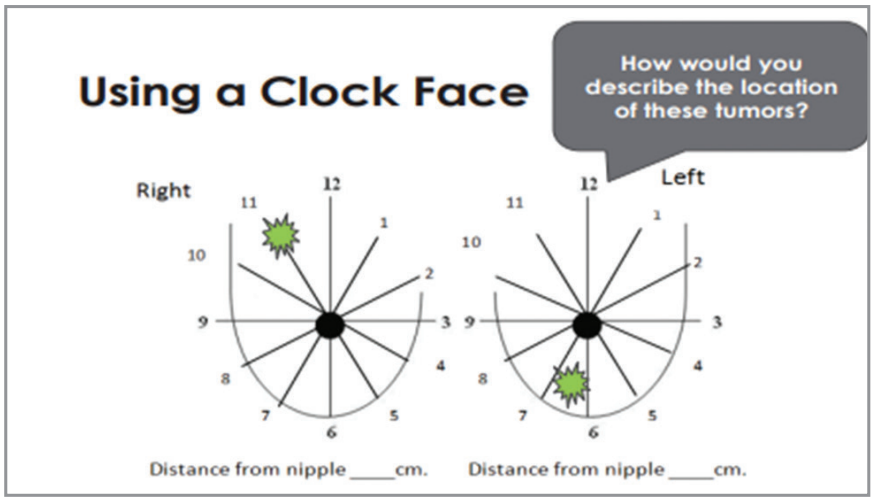


Figure 46: **Location of breast tumor using a clock face**

Table 54: **Difference between Malignant and Benign Breast lump**

Malignant	Benign
Hard Consistency	Smooth and rubbery
Painless(pain in 1/1000)	Often painful
Irregular edge	Well-defined
Fixation to skin or chest wall	Easily moves under the skin
Can cause dimpling of the skin	Skin dimpling unlikely
May have unilateral, bloody nipple discharge	May have yellow/green nipple discharge
Can have nipple retraction	No nipple retraction

Self-Breast-examination

There is no evidence of the effect of screening through breast self-examination. However, the practice of breast awareness has been seen to empower women, for taking responsibility for their health. Therefore, breast awareness is recommended for improving the rate of early diagnosis of breast cancer among women at risk.

Procedure of self-breast examination

Choose a time when the breasts are the least tender. Hormone levels fluctuate each month during the menstrual cycle, which causes changes in breast tissue. Swelling begins to decrease when the period starts. The best time to perform a self-exam for breast awareness is usually the week after the menstrual period ends.

Begin with a visual examination of your breasts. Sit or stand shirtless and braless in front of a mirror with your arms at your sides. To inspect your breasts visually, do the following:

- Face forward and look for puckering, dimpling, or changes in size, shape or symmetry.
- Check to see if your nipples are turned in (inverted).
- Inspect your breasts with your hands pressed down on your hips.
- Inspect your breasts with your arms raised overhead and the palms of your hands pressed together.
- Lift your breasts to see if the ridges along the bottom are symmetrical.

If you have a vision impairment that makes it difficult for you to visually inspect your breasts, ask a trusted friend or a family member to help you.

Next, use your hands to examine the breast

Common ways to perform the manual part of the breast exam include:

- **Lying down.** Choose a bed or other flat surface to lie down on your back. When lying down, the breast tissue spreads out, making it thinner and easier to feel.
- **In the shower.** Lather your fingers and breasts with soap to help your fingers glide more smoothly over your skin.
- **Use the pads of your fingers.** Use the pads, not the very tips, of your three middle fingers for the exam. If you have difficulty feeling with your finger pads, use another part of your hand that is more sensitive, such as your palm or the backs of your fingers.
- **Use different pressure levels.** Your goal is to feel different depths of the breast by using different levels of pressure to feel all the breast tissue. Use light pressure to feel the tissue closest to the skin, medium pressure to feel a little deeper, and firm pressure to feel the tissue closest to the chest and ribs. Be sure to use each pressure level before moving on to the next spot. If you're not sure how hard to press, talk with your doctor or nurse.
- **Take your time.** Don't rush. It may take several minutes to carefully examine your breasts.
- **Follow a pattern.** Use a methodical technique to ensure you examine your entire breast. For instance, imagine the face of a clock over your breast or the slices of a pie. Begin near your collarbone and examine that section, moving your fingers toward your nipple. Then move your fingers to the next section.

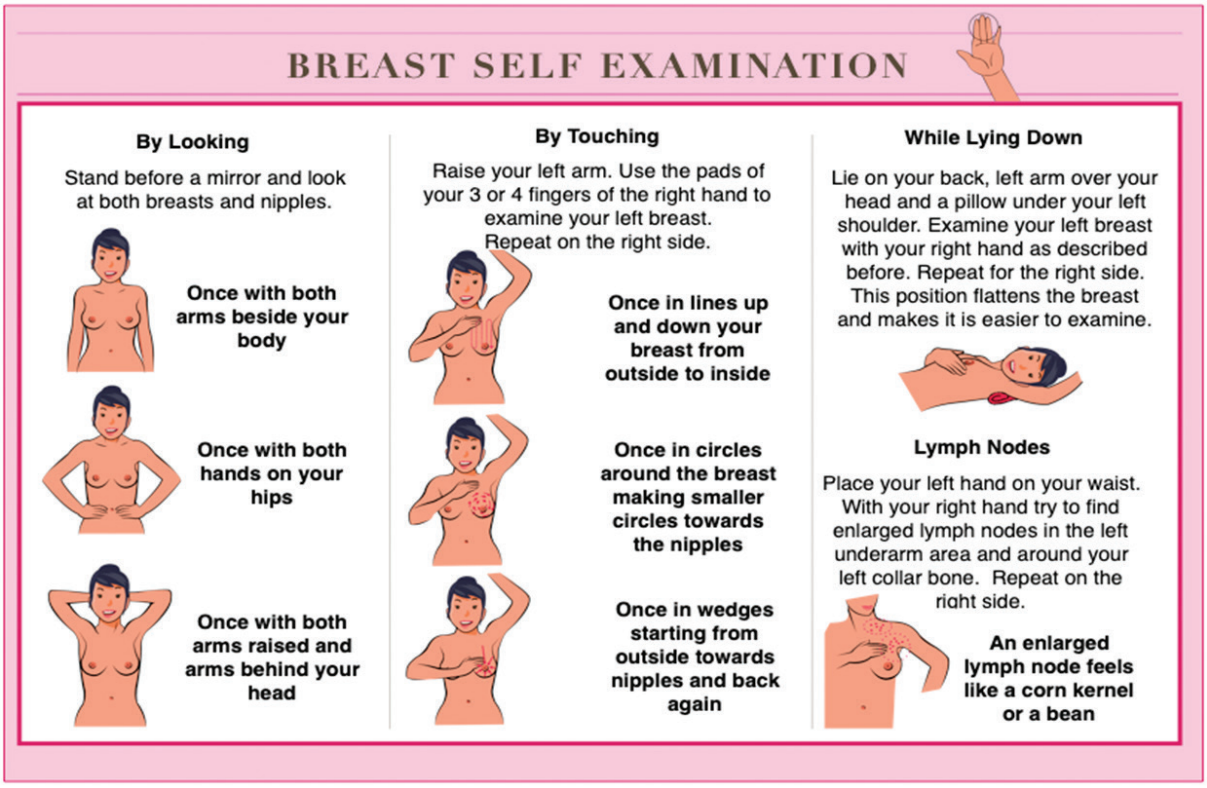


Figure 47: Breast self examination

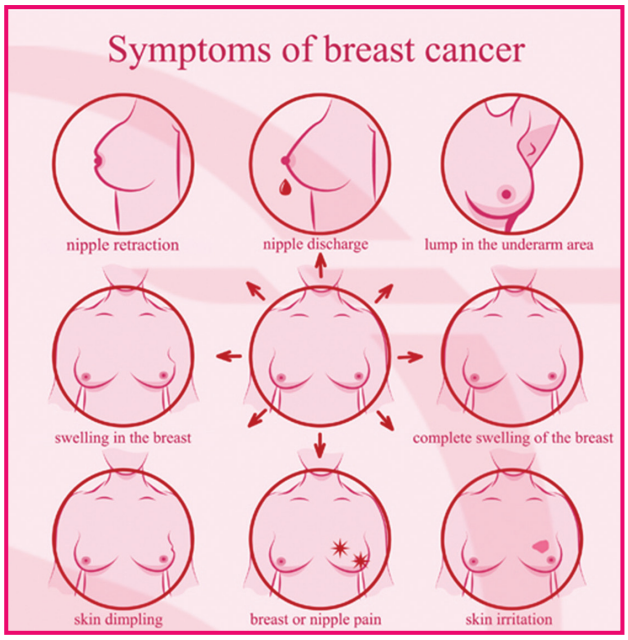


Figure 48: **Symptoms of breast cancer**

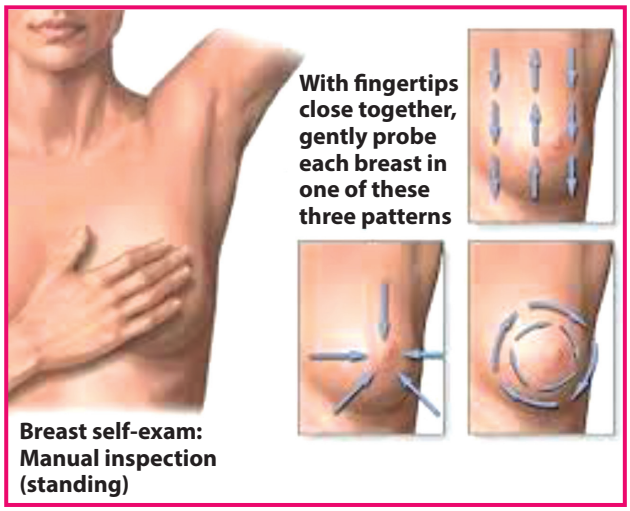


Figure 49: **Breast self-exam: manual inspection**

Results

Visit your doctor if you notice:

- Changes in the way your breasts look or feel, including thickening or prominent fullness that is different from the surrounding tissue
- A hard lump or knot near your underarm
- Dimples, puckers, bulges or ridges on the skin of your breast
- A recent change in a nipple to become pushed in (inverted) instead of sticking out
- Redness, warmth, swelling or pain
- Itching, scales, sores or rashes
- Bloody nipple discharge

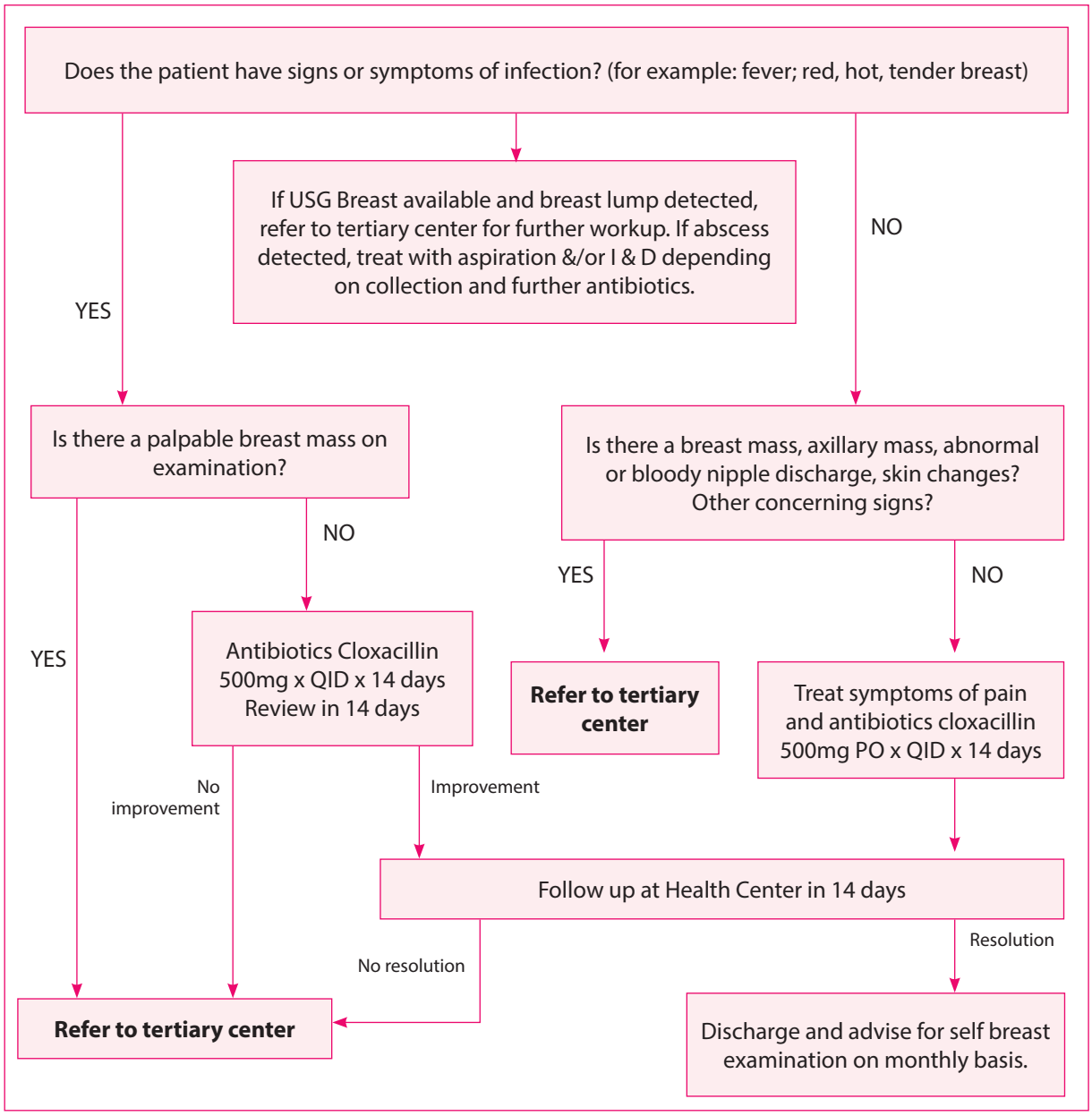


Figure 50: Approach to breast concerns in a breastfeeding patient

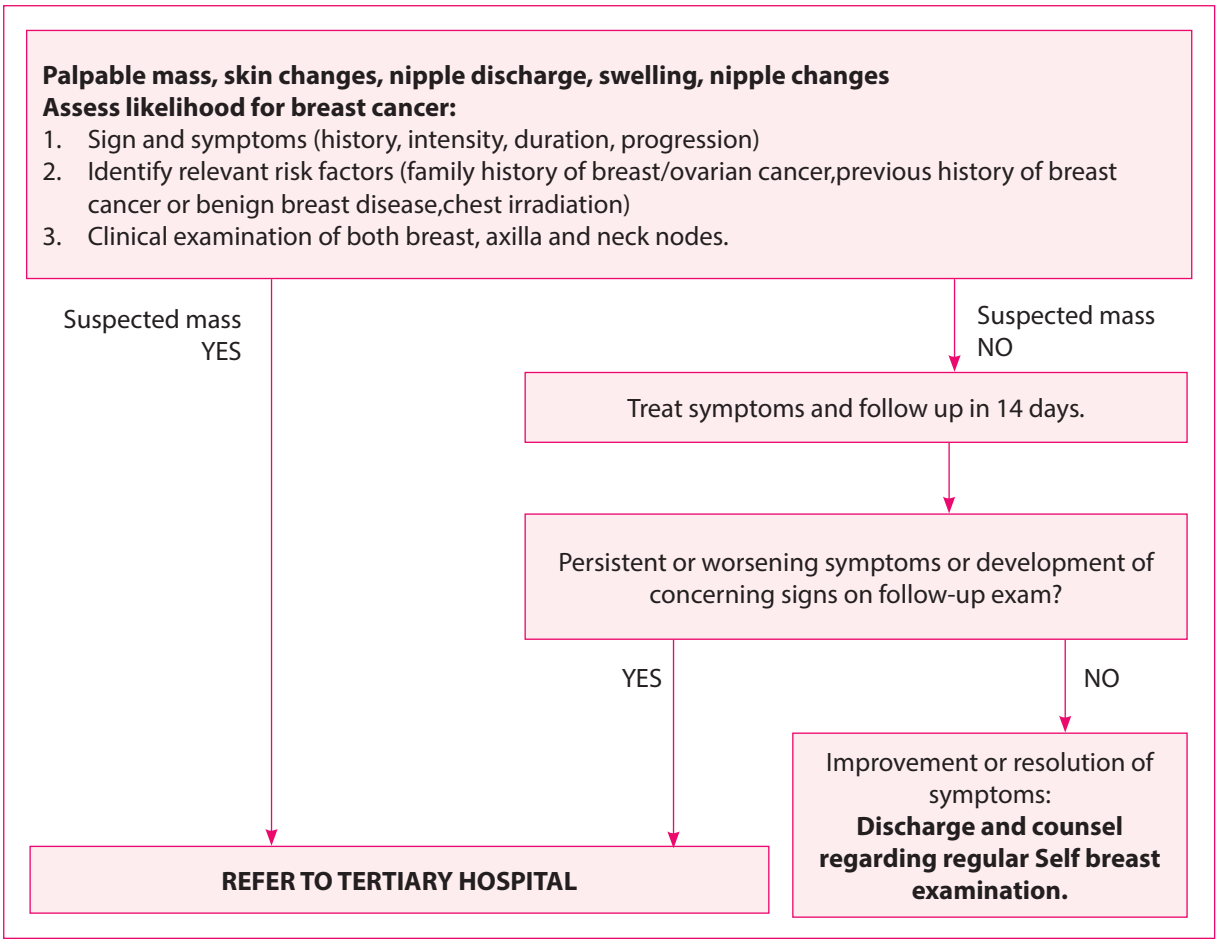


Figure 51: Approach to any women presenting with symptoms

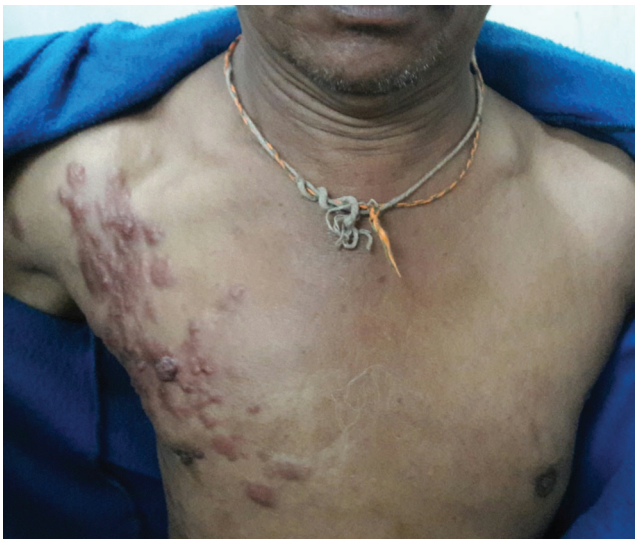


Figure 52: Male breast cancer

- Male breast cancer accounts for 1% of all cancers.
- Treatment is same as for female breast cancer.

6.3. ORAL CANCERS

Introduction

Oral cancers include cancers of the mucosal lip, tongue, gum, floor of the mouth, palate, and mouth. Oral cancer is considered a lifestyle disease. Behaviors such as alcohol consumption and smoking have been primarily associated with increased risk of oral cancer. Although globally declining in trend, the traditional habit of betel nut chewing is still prevalent in many parts of the world including Nepal and has been known to contribute to the risk. Early detection of oral cancer is important as a diagnosis at late stage would significantly increase the treatment cost and associated morbidity and mortality rates.

Etiopathology

Established Risk Factors

- Smoking tobacco - cigarettes, cigars, pipes, bidis
- Smokeless tobacco - chewing tobacco, and other unburnt products
- Chewing betel quid/pan/gutkha/pan masala
- High alcohol consumption (synergistic with tobacco)
- Prior history of the oral cavity or other aerodigestive tract cancer
- Excessive exposure to sunlight or radiation (for lip cancer)
- Age, in conjunction with other risks listed

Other Possible Risk Factors

- Diet lacking in fresh fruits and vegetables
- Viral infections, e.g. certain types of Human Papilloma Virus (HPVs) particularly for oropharyngeal cancers
- Immune deficiency disease or immune suppression
- Chronic wounds in the mouth (especially in those with major risk factors)

Prevention of Oral Cancers

Primary prevention aims to change behaviors (lifestyle) known to be associated with oral cancer. Below are listed the key messages for oral cancer prevention.

Table 55: Key Messages for Oral Cancer Prevention

Quit smoking or the use of any form of tobacco.
Discourage children and young adults from experimenting with harmful life styles and habit initiation.
Quit betel quid/areca/gutkha/chewing tobacco use.
Eat plenty of fresh fruits and green-yellow vegetables.
Keep within recommended guidelines for alcohol consumption.

Oral Cancer Screening and Mucosal Lesion Assessment

Patient History and Signs and Symptoms

The first step in screening for oral cancer is the completion of a patient history, which should include review of:

- General health history including a list of current medications and medication allergies
- Oral habits and lifestyle, with particular reference to quantity, frequency and duration of tobacco/tobacco product use and alcohol consumption
- Symptoms of oral pain or discomfort.

Visual Screening Examination

- **Head and Neck:** Head and neck examination for cervical lymph glands is carried out by standing behind the individual and slightly flexing and bending the neck to the side so that the sternocleidomastoid muscle becomes relaxed and palpation and identification of any enlarged nodes will be easier. The presence of neck masses is not an uncommon finding, especially in subjects with oral infections or cancer.
- **Lips:** Oral examination commences with the visual examination of the lips and the vermilion border and by palpation after removing any lipstick. The lip is usually smooth and pliable. Evert the lips and carefully inspect the labial mucosa. It should be smooth, soft and well-lubricated by minor salivary glands that can be palpated.
- **Buccal Mucosa:** The buccal mucosa is examined by stretching it with a pair of tongue depressors or mouth mirrors after the subject partially opens the mouth.
- **Tongue–Dorsal Surface:** The dorsal surface of the tongue is examined by asking the subject to protrude the tongue and attempt to touch the tip of the chin; alternatively the tip of the tongue may be held gently by the fingers and a gauze sponge.
- **Ventral Surface of Tongue and Floor of Mouth:** The ventral surface of the tongue and the floor of the mouth are most easily visualized by having the person touch the tip of the tongue to the roof of the mouth. A high level of clinical alertness is required when examining these sites, where oral cancers may be missed as red or white innocuous-looking lesions.
- **Gingivae:** The gingivae are examined with the mouth partially opened and the lips retracted with a mouth mirror, fingers or plastic lip retractor.
- **Hard Palate:** The anterior part of the hard palate is better visualized using an intraoral mirror.
- **Soft Palate:** The soft palate is examined by depressing the base of the tongue with a tongue depressor and asking the subject to say "aah".
- **Teeth:** Examination of the teeth should be the final part of the oral examination. Missing teeth and/or supernumerary teeth may be observed. Discolored cavities in the occlusal surfaces of teeth may be observed as a consequence of poor oral hygiene.

Lesion inspection

Evaluate the specific characteristics of each lesion with particular attention to size, color, texture and outline. Particular attention to predominantly white, red and white, ulcerated and/or indurated lesions is indicated. The examiner should be alert during the entire procedure to identify any change in color and/or texture of the mucous membrane, inflammatory areas, erythema, hyperpigmentation, macules, papules, white lesions, greyish white lesions, red lesions, induration, ulceration, swellings and growth in the oral mucosa.

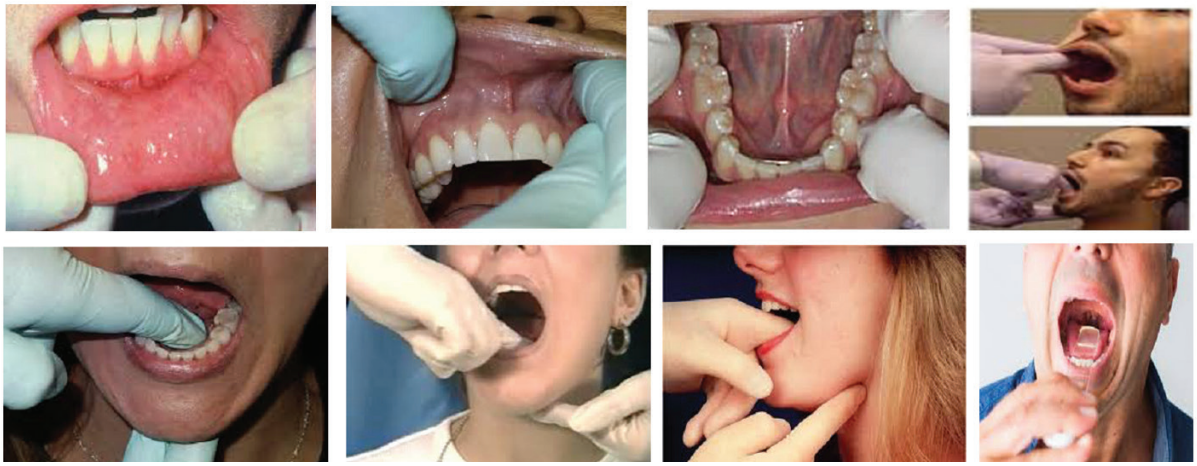


Figure 53: **Steps of oral cavity examination**

Figure 54: **Position and areas of neck examination**

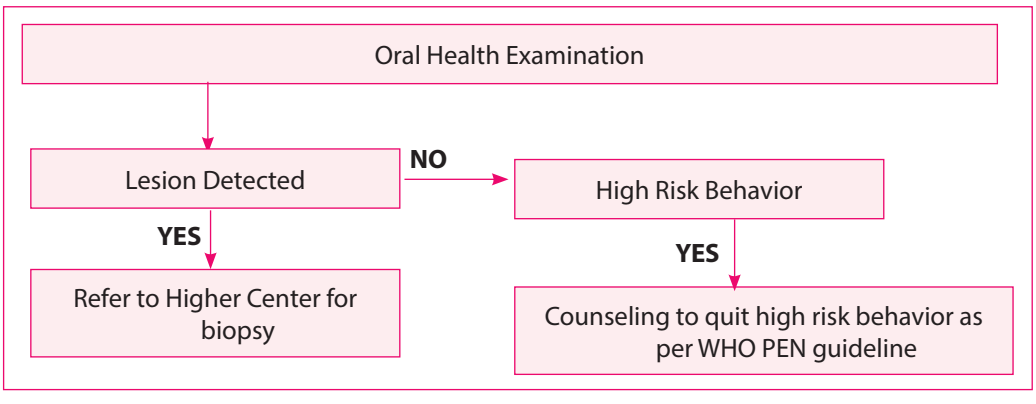


Figure 55: **Referral Pathway for oral cancer**

Common findings of oral examination

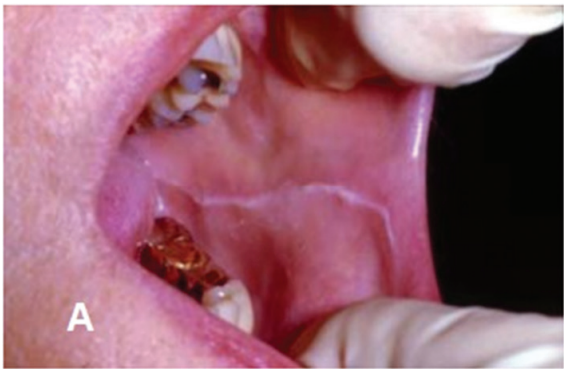


Figure 56: Linea alba (whitish line)

The whitish line is a common lesion that develops as a reaction to pressure of the soft tissue against the teeth. This readily identifiable lesion is termed linea alba (white line) and has no potential for cancer.

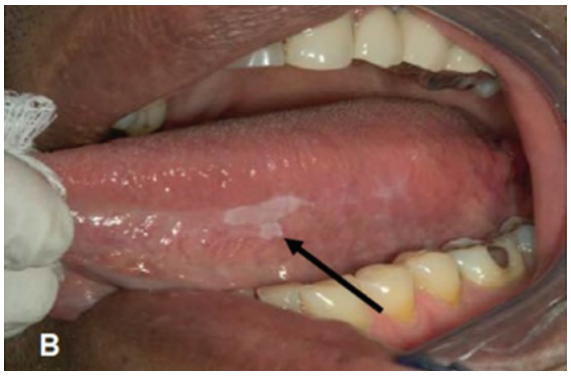


Figure 57: Leukoplakia on the left lateral tongue

Leukoplakia on the left lateral tongue in a non-smoker. The biopsy showed premalignant changes (dysplasia).

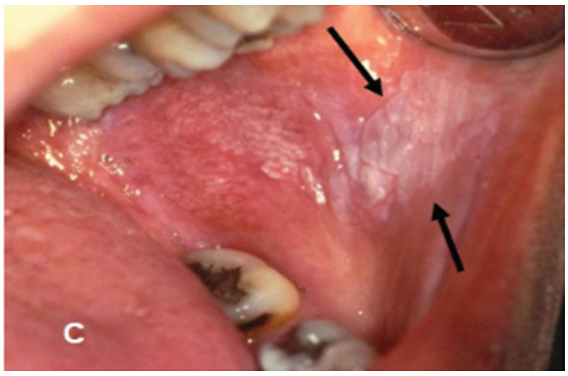


Figure 58: Leukoplakia of the cheek (buccal mucosa)

Leukoplakia of the cheek (buccal mucosa) in a smoker. The biopsy showed dysplasia

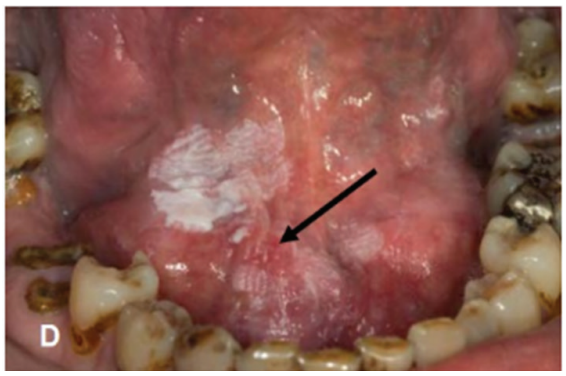


Figure 59: Erythroleukoplakia on the floor of the mouth

Erythroleukoplakia - red (arrow) and white areas in the floor of the mouth of a smoker that showed premalignant changes (dysplasia)

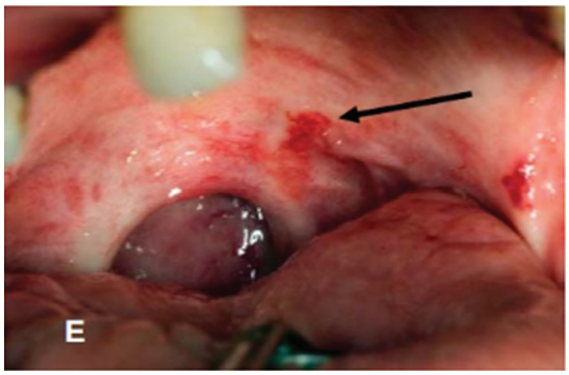


Figure 60: Erythroplakia on the soft palate

Erythroplakia- (arrow) on the soft palate. A biopsy revealed dysplasia

6.4. CERVICAL CANCER

Introduction

Cervical cancer starts in the cells lining the uterine cervix. The main types of cervical cancers are squamous cell carcinoma (common 90%) and adenocarcinoma (10%).

Etiopathogenesis

Human Papilloma Virus infection: The most important risk factor for cervical cancer is infection by the Human Papilloma Virus (HPV)

- High-risk sexual behaviour
- Early sexual activity
- Multiple sexual partners
- Human immunodeficiency virus (HIV), the virus that causes AIDS, damages the immune system and puts women at higher risk for HPV infections
- Smoking
- Unhealthy diet
- Having multiple full-term pregnancies
- Having a family history of cervical cancer

Signs and Symptoms

Women with early cervical cancers and pre-cancers usually have no symptoms. Symptoms often do not begin until the cancer becomes invasive and grows into nearby tissue. When this happens, the most common symptoms are:

1. Abnormal vaginal bleeding, such as bleeding after vaginal intercourse, peri-menopausal bleeding, bleeding and spotting between periods
2. An unusual discharge from the vagina – the discharge may contain some blood and may occur between your periods or after menopause.
3. Pain during intercourse.

Diagnosis

1. Pap's Smear/cytology-based screening
2. Visual Inspection with Acetic Acid (VIA)
3. High-risk Human Papilloma Virus testing (HrHPV)

Pap's Smear/Cytology based screening

Papsmear is recommended where technical and laboratory facilities are available for taking the Papsmear and providing the results. Although Pap smear is the golden standard for cervical cancer screening it is not appropriate as a tool for large-scale national screening programs in developing countries such as Nepal where resources are limited.

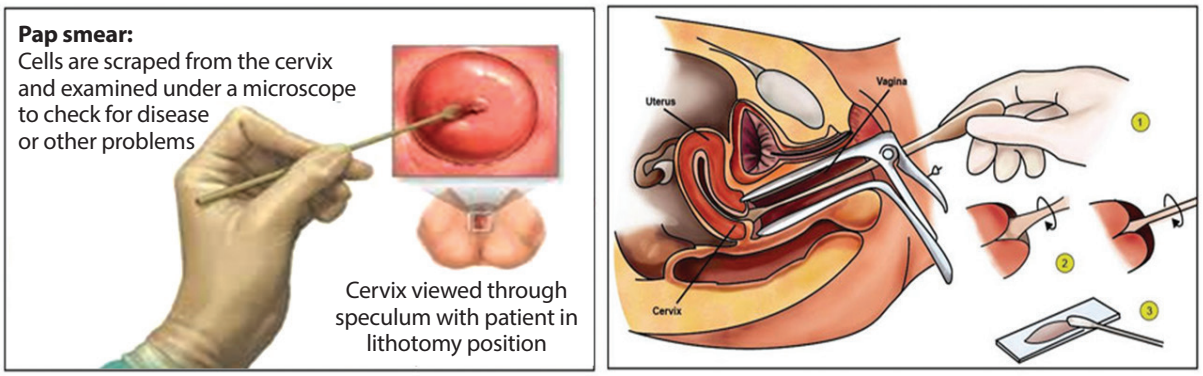


Figure 61: **Pap Smear Test**

Visual Inspection with Acetic Acid (VIA):

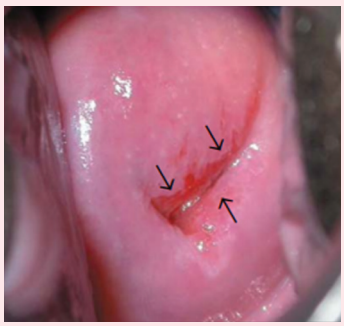
The National Guideline for Cervical Cancer Prevention and Screening in Nepal-2010 mandates that VIA will be used at all levels from the primary health care centre (PHCC) to the tertiary level. The test can be performed with a satisfactory standard by the trained health workers and the nursing staff in the primary care setting. The results are immediately available and further management can be decided.

Visual inspection of the cervix using acetic acid means looking at the cervix with a naked unaided eye to detect abnormalities after the application of dilute (3–5%) acetic acid or vinegar. The abnormal area turns aceto white, which shows that it may have precancerous lesions. VIA is the recommended practice for low resource settings compared to other screening tests such as Pap smear because:

- It is safe, inexpensive and easy to perform;
- The test performance is similar to other tests used for cervical cancer screening;
- It is non-invasive and effectively identifies many precancerous lesions;
- It can be learned and provided by almost all health professionals at all levels of the healthcare system;
- It provides immediate results on which decisions about management (treatment or referral) are based;
- Most equipment and supplies for this service are locally available; and
- Instant treatment (cryotherapy or Thermal ablation) can be linked to this type of screening to offer women screening and treatment in a single visit.

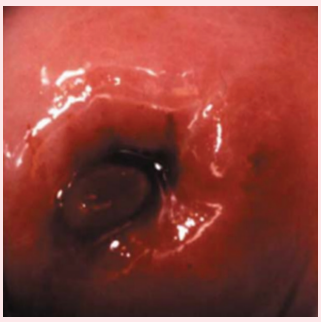
VIA negative (-):

VIA screening is reported as negative in the case of any of the following observations:



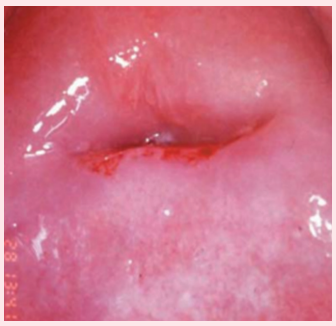
1) No acetowhite lesions are observed on the cervix.

VIA negative: No acetowhite area seen. Note the advancing edges of squamous metaplasia in the anterior and posterior lips (arrows)



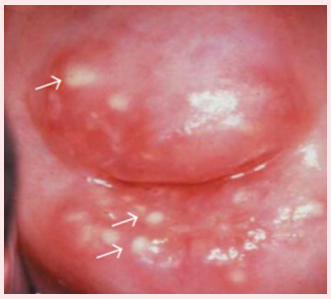
2) Polyps protrude from the cervix with bluish-white acetowhite areas.

VIA negative: No acetowhite area in the polyp or cervix.



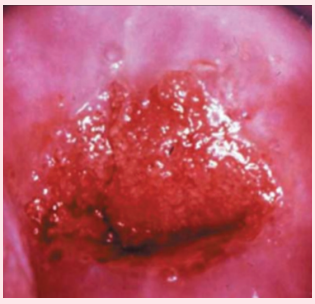
3) There are shiny, pinkish-white, cloudy white, bluish-white, faint patchy or doubtful lesions with ill-defined, indefinite margins, blending with the rest of the cervix.

VIA negative: There are ill-defined pinkish white and cloudy-white areas with indefinite margins blending with the rest of the epithelium. The squamocolumnar junction is fully visible.



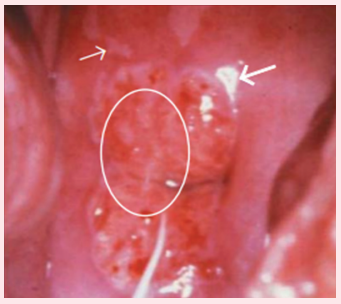
4) Nabothian cysts appear as button-like areas, as whitish acne or pimples.

VIA negative: The nabothian cysts appear as pimple- or button-like areas after the application of acetic acid.



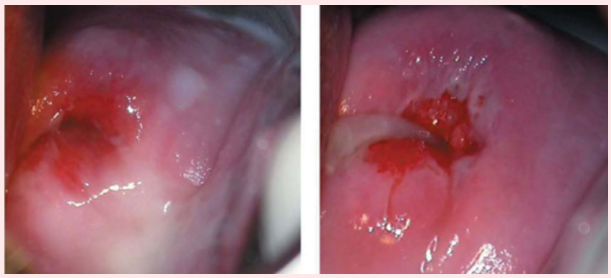
5) Dot-like areas are present in the endocervix, which are due to grapelike columnar epithelium staining with acetic acid.

VIA negative: There is dot-like acetowhitening in the columnar epithelium in the anterior lip. The squamocolumnar junction is fully visible.



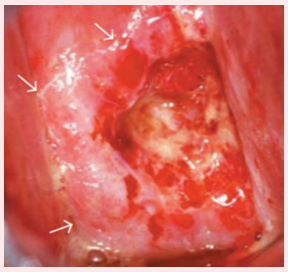
6) Angular, irregular, digitating acetowhite lesions, resembling geographical regions, distant (detached) from the squamocolumnar junction (satellite lesions). Streak-like acetowhitening is visible in the columnar epithelium.

VIA negative: There are pale white, satellite, geographical lesions with angular margins (narrow arrow) far away from the squamocolumnar junction (dense arrow). Note the streak-like acetowhitening in the columnar epithelium (within the oval area).



7) Faint line-like or ill-defined acetowhitening is seen at the squamocolumnar junction.

VIA negative: There is dense, thick, mucus on the cervix before the application of acetic acid. After the application of acetic acid, the mucus is cleared and the squamocolumnar junction becomes prominent.



8) There are ill-defined, patchy, pale, discontinuous, scattered acetowhite areas.

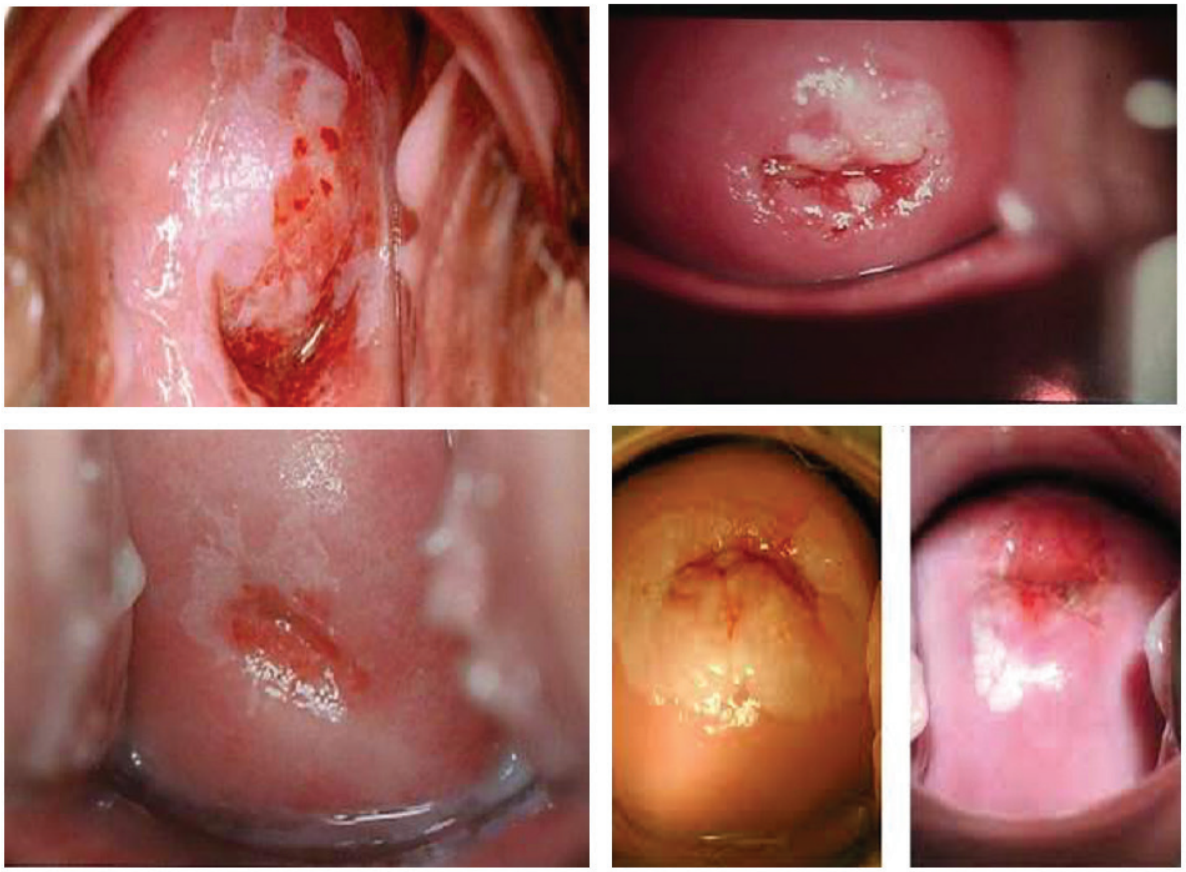
VIA negative: The cervix is unhealthy, inflamed with ulceration, necrosis, bleeding and inflammatory exudate. There is ill-defined, diffuse, pinkish-white acetowhitening with indefinite margins blending with the rest of epithelium (arrows).

Figure 62: VIA negative results

VIA Positive:

The VIA test outcome is reported as positive in any of the following situations:

1) There are distinct, well-defined, dense (opaque, dull- or oyster-white) aceto white areas with regular or irregular margins, close to or abutting the squamocolumnar junction in the transformation zone or close to the external os if the squamocolumnar junction is not visible.
2) Strikingly dense aceto white areas are seen in the columnar epithelium.
3) The entire cervix becomes densely white after the application of acetic acid.
4) Condyloma and leukoplakia occur close to the squamocolumnar junction, turning intensely white after the application of acetic acid.

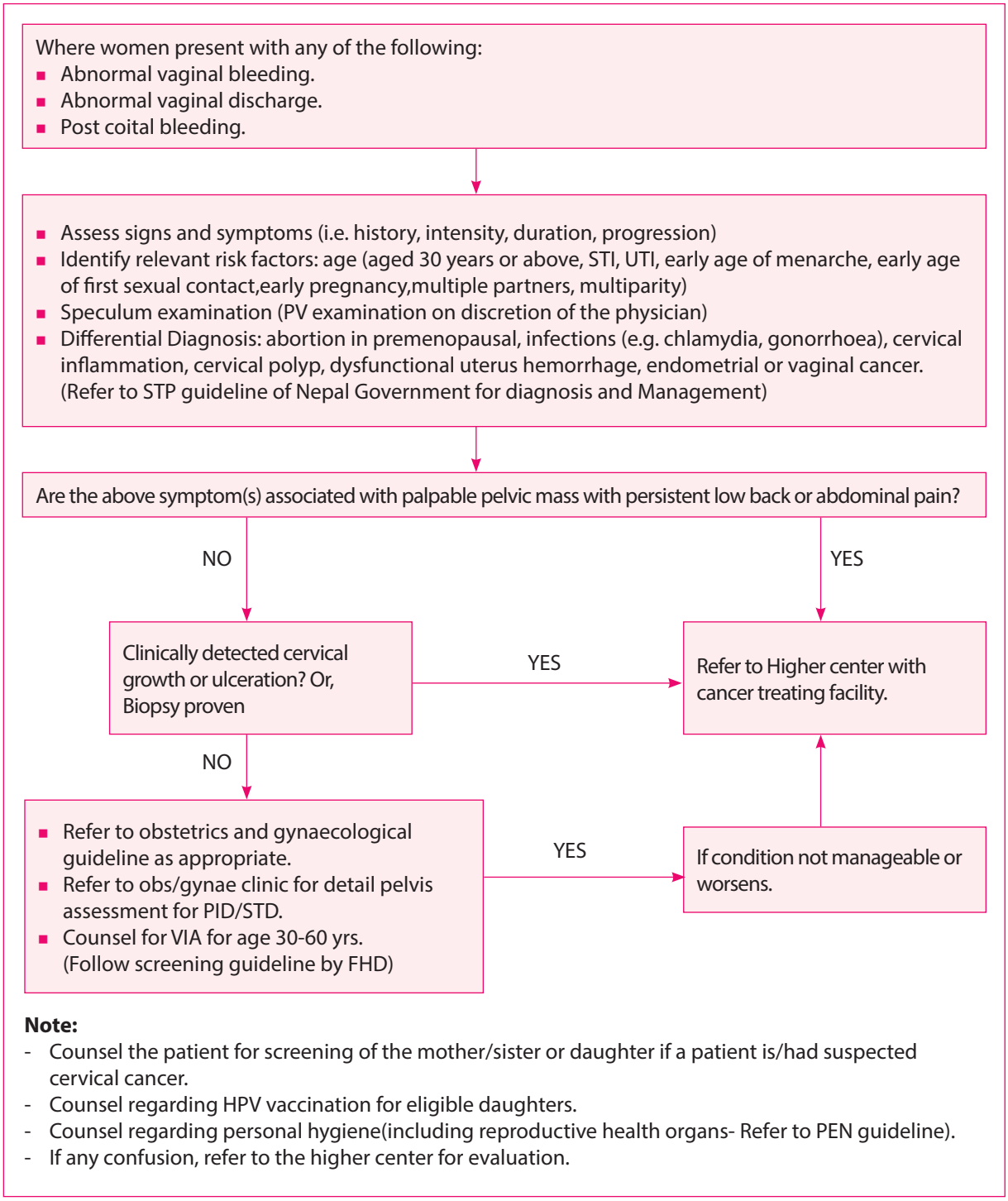


VIA positive: There is a well-defined, opaque acetowhite area, with irregular digitating margins, in the anterior

Figure 63: VIA positive results

High-risk Human Papilloma Virus Testing (HrHPV):

Cervical cancer is caused by HPV, a very common group of viruses, which have no symptoms that are easy to detect. Two high-risk HPV strains (16 and 18) cause more than 70% of cervical cancers but can be treated if detected early enough. So, alongside nationwide vaccination of girls against HPV, WHO recommends that countries ensure regular DNA-based testing for HPV to identify women who have or are at risk of cervical pre-cancer. DNA-based testing is also less prone to human errors, unlike tests that rely on visual inspection. HPV-DNA testing is an objective diagnostic, leaving no space for interpretation of results. Another benefit of HrHPV is that it can be self-performed by females which therefore can contribute to broadening the coverage of screening.



Note:

- Counsel the patient for screening of the mother/sister or daughter if a patient is/had suspected cervical cancer.
- Counsel regarding HPV vaccination for eligible daughters.
- Counsel regarding personal hygiene(including reproductive health organs- Refer to PEN guideline).
- If any confusion, refer to the higher center for evaluation.

Figure 64: Referral Pathway for cervical cancer

Management and Prevention

Depending on the type and stage of your cancer, you may need more than one type of treatment. Common types of treatments for cervical cancer include:

- Surgery
- Radiation therapy
- Chemotherapy
- Targeted-therapy

Prevention Strategies for Cervical Cancer:

1. Primary Prevention: HPV Vaccination
2. Secondary Prevention: Screening and Treatment of Pre-invasive diseases
3. Treatment of Invasive disease by a multidisciplinary team.

1. Primary Prevention: HPV Vaccination

Vaccination of adolescent girls is the most effective long-term intervention for reducing the risk of developing cervical cancer. There is also strong evidence that high HPV vaccination coverage leads to the protection of unvaccinated individuals through herd immunity, further enhancing the protective effect for the community.

WHO's current guidelines recommend that young adolescent girls between 9 and 14 years receive two doses of vaccine to be fully protected.

Girls <15 years at the time of the first dose: 2-dose schedule (0, 6 months) is recommended. If the interval between doses is shorter than 5 months, then a third dose should be given at least 6 months after the first dose.

Girls/Females >15 years of age three dose is recommended (0, 2, 6 months)

In addition to HPV vaccination, a comprehensive prevention strategy must include:

- Age-appropriate information on sexual and reproductive health.
- Safer sexual practices – such as delaying sexual debut.
- Decreasing the number of sexual partners.
- Condom use.
- Cessation of tobacco use.

2. Secondary Prevention: Screening and treatment of pre-invasive disease

The national guidelines on cervical cancer screening and prevention (2010) call for screening at least 50 percent of women aged 30–60 years and for reducing the mortality due to cervical cancer by 10 percent with recommended screening among this group every five years. Cervical cancer screening is done by visual inspection of the cervix and by trained nurses or doctors using 5% diluted acetic acid. This approach is cost-effective as the early detection of lesions and early management by cryotherapy will usually prevent progression to cervical cancer.

VIA testing procedure, interpretation of the result and management of aceto white areas will be mandatory in centre trained for PEN Plus and close coordination for human resource development with FWD will be undertaken

VIA and treatment by cryotherapy as a Single Visit Approach (SVA)

Screening by VIA and immediate treatment of precancerous lesions in one visit to the screening and treatment service site is recommended wherever the resources and trained manpower are available.

Women with VIA-positive are eligible for SVA if:

- Acetowhite lesions cover less than 75% of the cervix (if more than 75% of the cervix is covered, further consultation with a Oncologists/Gynecologists should be done)
- No suspected invasive cancer.
- Lesion that does not extend to the endocervical canal.
- Lesion that extends less than 2 mm beyond the diameter of the cryotherapy probe.

Cryotherapy is not an appropriate treatment method if:

- Aceto white lesion is greater than 75% of the face of the cervix.
- Aceto white lesions extending into the endocervical canal or extending more than 2mm beyond the outer or inner edge of the cryotherapy probe.
- Aceto white lesion where the client requests alternate treatment to cryotherapy or requests additional diagnostic tests where invasive cancer is suspected.
- During the bimanual examination, an ovarian mass or fibroid is suspected.

Palliative Care

Palliative care (adults) - WHO definition for adults

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering using early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Intent of Palliative care:

- Provides relief from pain and other distressing symptoms;
- Affirms life and regards dying as a normal process;
- Intends neither to hasten nor postpone death;
- Integrates the psychological and spiritual aspects of patient care;
- Offers a support system to help patients live as actively as possible until death;
- Offers a support system to help the family cope during the patient's illness and in their bereavement;
- Uses a team approach to address the needs of patients and their families.

Bereavement counseling, if indicated;

- Will enhance quality of life, and may also positively influence the course of illness;
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications;
- Is equally important for both cancer and non-cancer diseases.

Palliative Care (children) - WHO definition for children

Palliative care for children represents a special, albeit closely related field to adult palliative care. The WHO definition of palliative care appropriate for children and their families is as follows; the principles apply to other pediatric chronic disorders:

- Palliative care for children is the active total care of the child's body, mind and spirit, and also involves giving support to the family;
- It begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease;
- Health providers must evaluate and alleviate a child's physical, psychological, and social distress;
- Effective palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources
- It can be successfully implemented even if resources are limited;
- It can be provided in tertiary care facilities, in community health centers and even in children's homes.

Terminal care

Palliative care is delivered at the very end of a patient's life i.e. in the last days or weeks of life. Palliative care may be also appropriate much earlier in the illness, including at diagnosis.

Specialist palliative care

Palliative care is delivered by health and social care professionals from a range of disciplines (often working in a multidisciplinary team) who have received extensive training in palliative care and who are working in palliative care for all or a large proportion of their time. Specialist palliative care may be provided in a specialist unit – such as a hospice or palliative care unit in a hospital. Specialists in

palliative care may be providing consulting services in hospitals or the community. Often specialists in palliative care will work across two or more sectors. Specialist palliative care will focus on patients who are the most complex and receive referrals from other healthcare professionals or provide clinical advice to other professionals as required. A substantial proportion of a specialist's time will be dedicated to providing education in palliative care, service development and research.

Generalist palliative care

Palliative care is delivered by health and social care professionals, whose primary clinical role is not the provision of palliative care. Professionals practicing generalist palliative care will have received basic training in palliative care (i.e. not to a specialist level) and will use palliative care principles in their work. They will be aware of the scope of palliative care, the limits of their competence and will refer to specialists when it is to the benefit of the patient.

Primary palliative care

This is a branch of generalist palliative care. It is provided in the primary care setting by general practitioners and primary care health workers – nurses, health assistants and Community Medical Assistants (CMA) who have received basic training in palliative care. In primary palliative care, professionals synthesize their primary and palliative care skills.

Community palliative care

Palliative care provided in the patient's home by trained health workers and trained volunteers, such as female community health volunteers (FCHVs), who support the family in their caring role.

Palliative medicine

This is palliative care delivered by a medically qualified professional with specialist training in palliative care.

Common symptoms in Advanced Cancer:

- Pain (96%)
- Breathlessness (70%)
- Fatigue (90%)
- Nausea and Vomiting (70%)

Patients typically experience more than one symptom at a time.

Pain

Pain is one of the most common symptoms seen in patients with advanced illness; including cancer. It is frequently not optimally managed.

Mc-Caffery's (1968) definition of pain: Pain is whatever the experiencing person says it is, existing whenever s/he says it does.

International Association for the Study of Pain (1979) defines as: Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Pain Assessment:

Pain should be considered as the "fifth vital sign." As with the other vital signs: pulse, blood pressure, respiration and temperature, pain needs to be assessed regularly. All patients should be evaluated for the presence of pain at every visit, and any new pain should be thoroughly evaluated. Initial

assessment should always start with the patient history, examination and occasionally, diagnostic examinations.

Questions to be included in the pain assessment are as follows –

- Where is the pain? (There may be more than one pain)
- How severe is the pain?
- What does it feel like? (E.g. aching, stabbing, cramping, burning, etc.)
- When did it start?
- Timing - Is the pain there all the time or does it come and go?
- Treatment - Has any treatment been tried and has it helped?
- Changing - What makes it better or worse (e.g. movement, eating, time of day, etc.)?
- Causing - What do you (the patient) think is causing the pain?

Pain Scoring Tools

Numerical Rating Scale (NRS) –

This is the most commonly used pain assessment tool. This enables the clinician to assess how severe the pain is and whether it is improving over time or getting worse. Ask the patients to score their pain with these words: "On a scale of zero to ten, where zero is no pain and ten is the worst pain imaginable, how would you score your pain now."

A. No pain (0)
B. Mild pain (1–3)
C. Moderate pain (4-6)
D. Severe pain (7–10)

Wong-Baker Faces Pain Rating Scale –

If the patient has difficulty in understanding the NRS e.g. children or the very old, the Wong-Baker Faces Pain Rating Scale may be used. Ask the patients to score their pain with these facial expressions: "On a scale of zero to five, where zero is no hurt and five is the hurts worst."

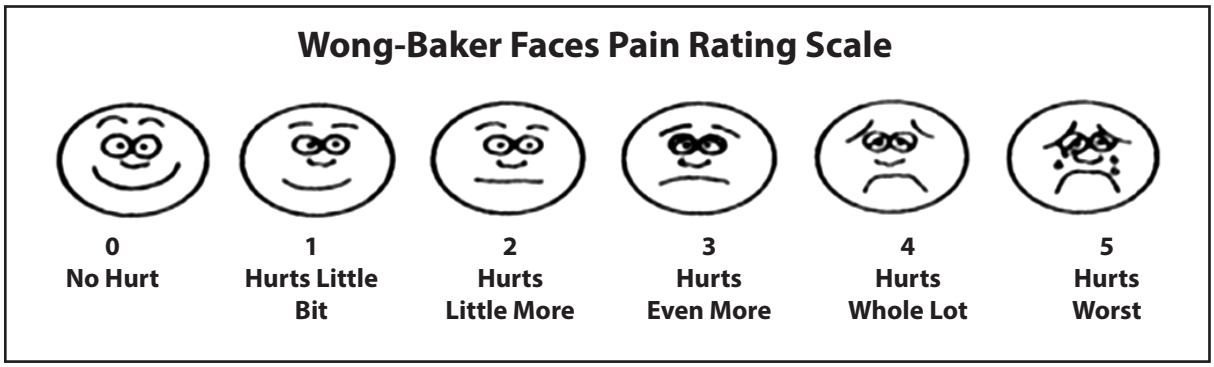


Figure 65: **Wong-Baker Faces Pain Rating Scale**

Five Fingers Scale

This can be particularly useful for patients who are being monitored for pain over several days as they learn how to measure their pain. Ask the patients to show how much pain they have by holding up different numbers of fingers. "On a scale of zero to five, where zero is no hurt and five is the hurts worst."

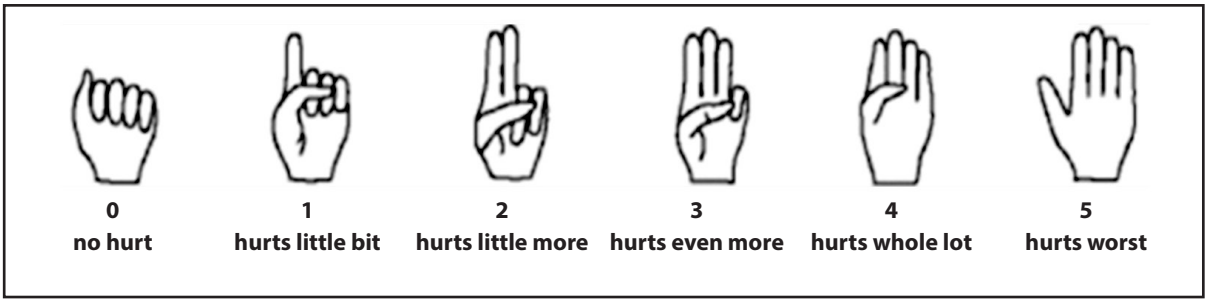


Figure 66: Five Fingers Scale for pain rating

Revised FLACC (Face, Legs, Activity, Cry, Consolability)

This tool is used to assess pain in non-verbal children and neurological impaired patients. This assessment is done by their behaviors. Behaviors associated with pain in this population include:

- Vocalizations (crying, moaning)
- Facial expression (grimacing)
- Consolability
- Interactivity(withdrawn)
- Diminished sleep
- Movement(restless, increased movement of extremities)
- Tone and posture (arching, stiffening)
- Physiological responses (diaphoresis, pallor, tachycardia)

Core pain behaviors are consistently identified in this population yet each child will display a unique set of behaviors. It is important to be vigilant about the possibility of pain in children with neurological impairments.

Goal of Pain Management:

The goal should be to achieve and maintain freedom from pain with usual, and maximal pain scores in the mild range (that is <4 on pain score). To reach this goal, medicine should be given "by the clock", that is every 4-6 hours, rather than on demand. Improving pain control lessens anxiety, depression, sleep disturbances, and feelings of physical un-wellness.

Management of Pain:

The WHO in 1986 established a stepwise system which is the backbone of the pharmacological approach. The goal was to provide treatment guidelines that healthcare practitioners could easily follow. These pain management guidelines suggest that the choice of analgesic pharmacotherapy should be based on the intensity of pain reported by the patient, not simply on its specific etiology. In the WHO guidelines, morphine remains the cornerstone for the management of cancer pain.

The three main principles of the WHO analgesic ladder are: "By the clock, by the mouth, by the ladder".

By the clock:

To maintain freedom from pain, drugs should be given "by the clock" or "around the clock" rather than only "on demand" (i.e. PRN). This means they are given on a regularly scheduled basis. The frequency will depend on whether it is a long- or short-acting preparation.

By the mouth:

The oral route is usually the preferred route for ease of use in a variety of care settings. However, it may not be possible for all patients (e.g. end-of-life, unconscious, swallowing issues). When the oral route is not feasible, the least invasive route should be considered (e.g. sub-lingual or sub-cutaneous before intra-venous.). The intra-muscular route should never be used.

By the ladder:

If pain occurs there should be prompt administration of drugs in the following order:

- non-opioids (e. g. acetaminophen)
- as necessary, mild opioids (e. g. codeine)
- then strong opioids (e. g. morphine or hydromorphone) until the patient is free of pain

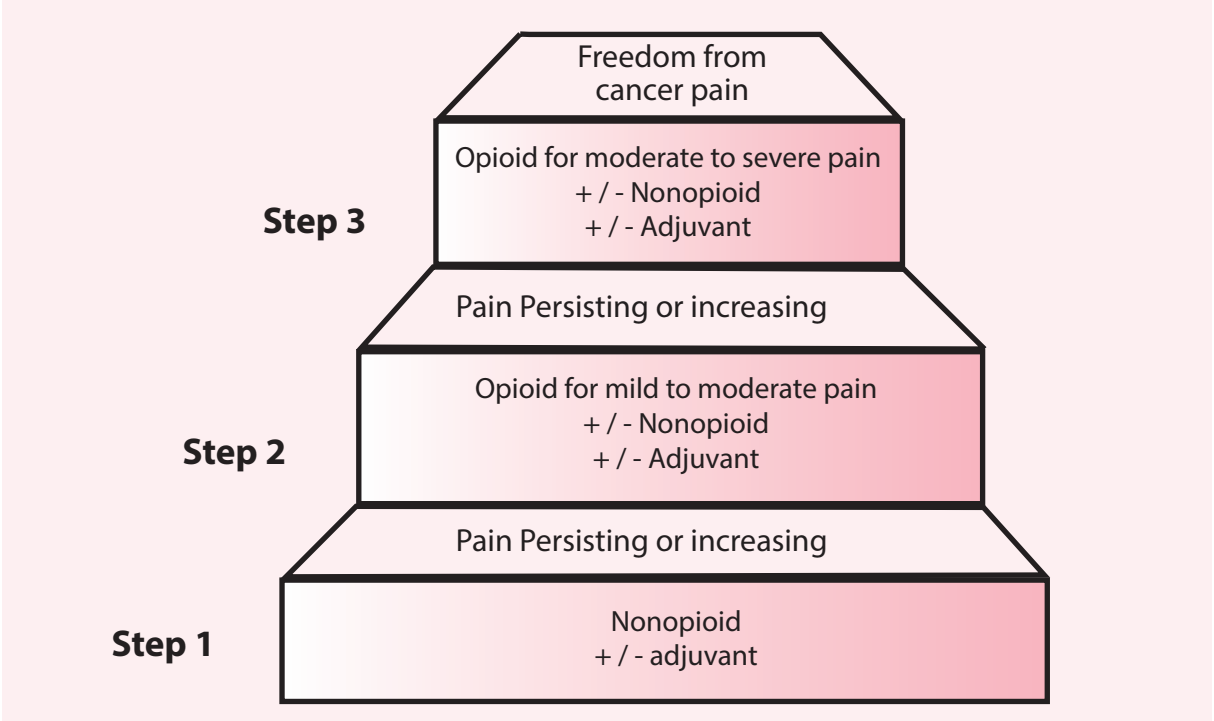


Figure 67: WHO Pain relief ladder

WHO 3 Steps Ladder for Pain Management

The other option is Two Steps Ladder where step two is omitted and weak opioids are not used.

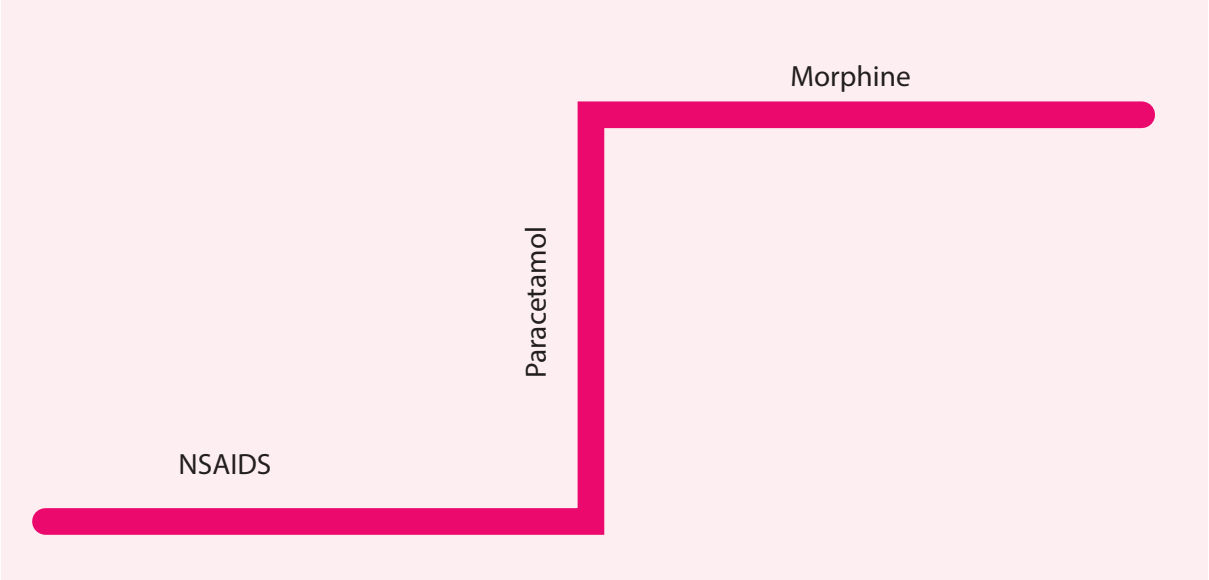


Figure 68: WHO 3 Steps Ladder for Pain Management

Non-Opioid Analgesics

A) Paracetamol(10-15mg/kg/day) 500-1000 mg up to every 6 hours. Upper limit 4gm/day

- Preferred route of administration is oral but IV can be given if needed for a short duration
- Caution: patients with liver disease

B) Non-steroidal anti-inflammatory drugs (NSAIDs)

Somatic pain: Bone metastases and soft tissue pain

- Cautions:
  - Patients with previous peptic ulcer disease, on steroids or anticoagulants, should also be given a gastric protectant while taking NSAIDs
  - Impaired renal function is a potentially serious side effect of any NSAIDs. It is more likely in patients with previous impaired renal function and those with dehydration. NSAIDs need to be used with care in the palliative care setting. It is suggested that renal function is checked when NSAIDs are commenced and rechecked after two weeks
  - Selective COX-2 inhibitors cause fewer gastric side effects
  - Ketorolac should be reserved for severe pain not responding to other drugs
  - Nimesulide is not recommended due to liver toxicity
  - Bronchospasm is possible in patients who are sensitive to NSAIDs (Ibuprofen, diclofenac, Naproxen, Meloxicam, Ketorolac).

Table 56: Non-opioid analgesics

Drug	Duration	Dose (child)	Dose (adult)	Frequency	Route	Maximum dose per day
Ibuprofen	8 hrs	6-10mg/kg/dose	400-800mg	TDS	PO	2400mg
Diclofenac	8hrs	2-5mg/kg/day	50mg	TDS	PO/SC/IM	150mg
Naproxen	8-12 hrs	5-7mg/kg/dose	250-500mg	BD	PO	1000mg
Meloxicam	24 hrs		7.5-15mg	OD	PO	15mg
Ketorolac	6 hrs	0.5-0.6mg/kg	10-30mg	TDS	PO/SC/IV	90mg

Opioid Analgesics:

These are divided into weak opioids (Step 2) and strong opioids (Step 3). All opioids have a similar spectrum of action and cause similar side effects, particularly constipation and sometimes nausea and vomiting. Opioids should therefore normally be prescribed with a laxative and with an antiemetic if nausea occurs.

Weak Opioids (Not used in Two Steps Ladder):

A) Codeine

- Codeine is a pro-drug that requires an enzyme for breakdown to morphine for pain relief.
- The recommended adult dose of codeine for pain relief is 15 mg to 60 mg every 4 to 6 hours as required, not to exceed 240 mg in one day
- 60mg oral codeine is equianalgesic to 10mg oral morphine
- Not preferred in pediatric patients

B) Tramadol

- The recommended dose of Tramadol is 50-100 mg (immediate release tablets) every 4-6 hours for pain.
- In pediatric age- 1-2 mg/kg/dose 4-6 hourly max 50-100mg
- The maximum dose is 400 mg/day
- 50 mg of oral Tramadol is equianalgesic to10mg of oral Morphine (5:1)
- 100 mg IV Tramadol is equianalgesic 10 mg IV morphine (10:1)
- Tramadol can cause dizziness as well as nausea and constipation.

Strong Opioids

Morphine

Morphine is the drug of choice for the management of moderate to severe pain. Internationally it is accepted as the 'gold standard' strong opioid in palliative care.

- It is effective by mouth, subcutaneously, IM and IV.
- Morphine is available in oral doses as:
- Sustained release tablets of 10mg, 30mg.
- Instant/immediate release tablets of 10mg.
- Syrup form: 5ml has 10mg morphine.
- In injectable form with 10mg in a 1 ml ampoule.

- It is relatively inexpensive and available in Nepal. Starting dose for opioid-naïve patients is oral morphine 5mg immediate release every 4 hours. If the patient's pain persists after the 4th dose, then the dose of morphine can be increased by 30-50%. When the daily dose is found to control the pain adequately, Prolonged Release (PR) morphine can be substituted for immediate-release morphine.
- Morphine PR is given every 12 hours.

How to calculate the dose of morphine PR:

Add up all the morphine given in the past 24 hours. That gives the total dose required in 24 hours. Then divide by 2 to give the 12 hourly doses. E.g. morphine 10mg given every 4 hours = 6x10mg in 24 hours = 60mg in 24 hours = 30mg every 12 hours. The dose of morphine PR is 30mg twice daily.

Pediatric dose: 0.2 to 0.3 mg /kg (10-15mg) initial dose, 4hrly PO/SL and IV/SC 0.1mg/kg.

Side effects of morphine include are constipation, nausea, and vomiting, sedation, dry mouth, sweating, hallucinations, myoclonus, urinary retention, pruritus, hyperalgesia etc.

Constipation is the most common side effect. The hand that writes opioids should also write laxatives. Morphine reduces gastrointestinal motility and secretion leading to constipation. A stimulant laxative like bisacodyle, reduces the ring contraction and facilitate propulsive activity.

Sedation and nausea usually resolve after a few days. A patient will need to be reassured and given an antiemetic if they experience nausea.

Physical dependence may develop but drug addiction to morphine in patients with palliative care is very rare.

Withdrawal symptoms when morphine is stopped or the dose is reduced are due to physical dependence. Therefore the morphine dose should only be reduced slowly whilst the patient adjusts to coming off morphine.

Respiratory depression is a very rare side effect in pain management when morphine is correctly titrated in palliative care. Naloxone is an antidote if respiratory depression develops. Dilute 400 micrograms (1amp) in 9ml normal saline and give 2.5ml (100 micrograms) IV every 1-2 minutes for titrating response.

Adjuvant Analgesics:

Adjuvant analgesics are medications not typically used for pain relief but they are effective for specific types of pain, notably bone and neuropathic pain. Primary among these agents are:

A) Steroids

- Steroids are used when pain is caused by pressure e.g. stretched liver capsule, raised intracranial pressure, pancoast tumor, etc.
- Dexamethasone 8-16mg per day in a single dose before noon, reduce dose by 2mg per day after 3 days if effective
- Stop the steroids after five days if there is no response

B) Antidepressants

- Antidepressants are used for neuropathic pain
- Amitriptyline 10-75mg at night start at the lowest dose and increase every 2-3 days until pain is controlled or side effects limit its use.

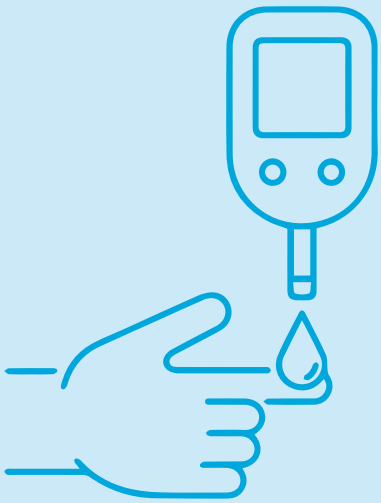
C) Anticonvulsants

- Anticonvulsants are used for neuropathic pain
- Gabapentin- Start 300mg at night and increase by 300mg every 2-3 days (300mg at night >> 300mg bd>> 300mg tds>> 600mg bd etc) maximum dose is 2400mg but if no benefit after 900mg it is unlikely that it will be effective.
- Pregabalin starts at a dose of 50 mg three times daily or 75 mg twice daily. Doses greater than 300 mg/day have not consistently shown additional benefit for the treatment of neuropathic pain conditions.

Caution for use: Renal impairment.

CHAPTER-7

DIABETES MELLITUS



7. DIABETES MELLITUS

Introduction

Diabetes mellitus (DM) refers to a group of disorders that share the common phenotype of hyperglycemia. Hyperglycemia associated with DM causes secondary changes in multiple organs increasing the burden on the individual with diabetes. The prevalence of diabetes mellitus in Nepal is estimated to be 8.5%.

Etiopathogenesis

DM is classified based on the pathogenic process leading to hyperglycemia:

- Type 1 DM develops as a result of autoimmunity against beta cells that produce insulin. This results in a complete or near-total insulin deficiency state.
- Type 2 DM may result from insulin resistance, impaired insulin secretion, or increased hepatic glucose production.

Note:
- Some individuals cannot be classified as having type 1 or type 2 diabetes mellitus at the time of diagnosis.
- The traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes only in children are no longer accurate, as both diseases occur in both age groups.

Although type 1 and type 2 diabetes mellitus are the two major categories of diabetes, other atypical forms of diabetes are increasingly recognized including:

- Maturity Onset Diabetes of Young (MODY),
- Latent Autoimmune Diabetes of Adulthood (LADA) and Ketosis-prone type 2 diabetes.

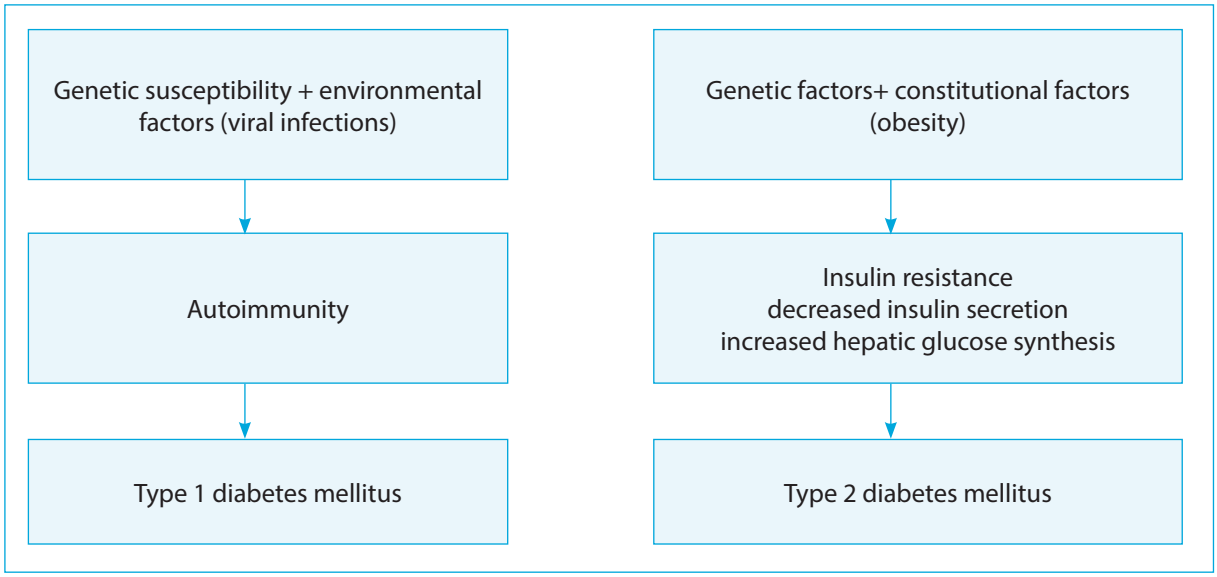


Figure 69: Etiopathogenesis of Diabetes Mellitus

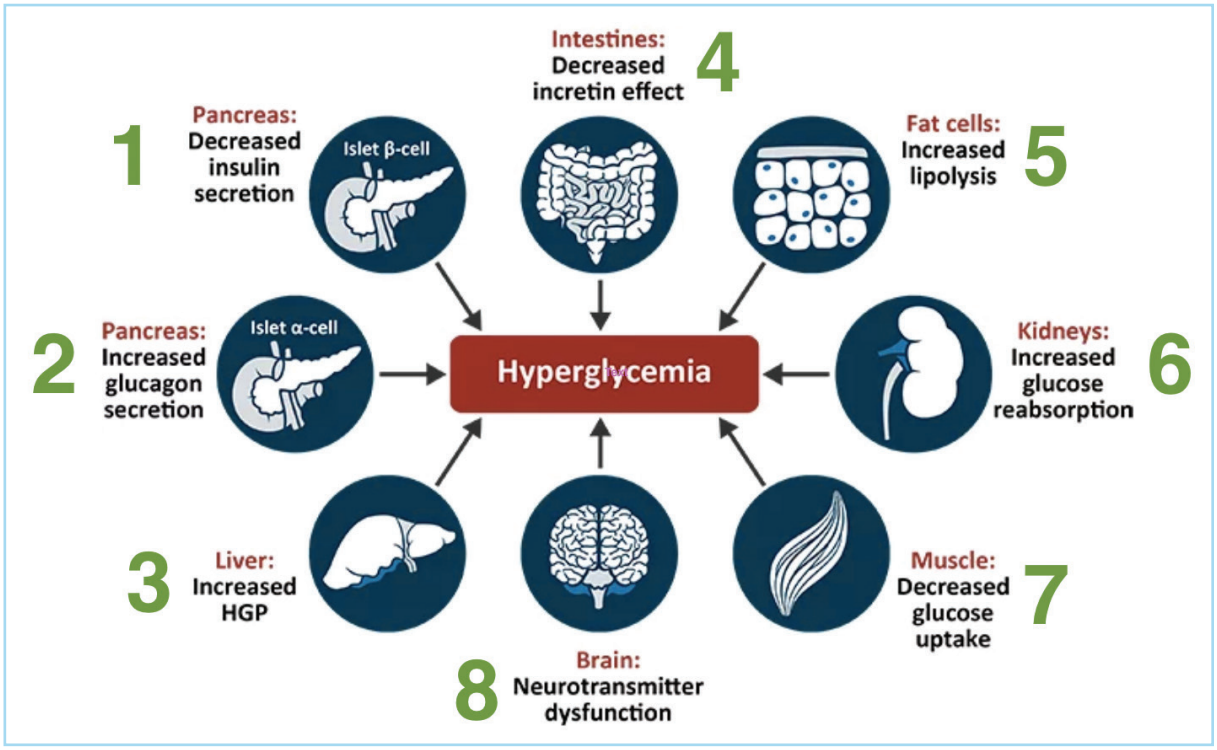


Figure 70: **Ominous Octet**

Signs and Symptoms

The clinical presentation of a patient with diabetes may range from being asymptomatic to symptomatic related to multiple organ involvement. The varied presentations can be summarized as follows:

Symptoms:

1. Known diabetes patient seeking follow-up, treatment or referral
2. Patients with symptoms of diabetes e.g. increased thirst (polydipsia), dry mouth, increased frequency of micturition (polyuria), increased hunger (Polyphagia)
3. Patients with diagnosed or undiagnosed complications of diabetes such as CVD or kidney disease
4. With non-healing foot ulcer
5. Infections E.g. infections in the genital area (vulvovaginitis, balanitis)
6. Diabetes detected in asymptomatic adults during a routine check-up

Note:

- In 50% of the cases, diabetes mellitus is asymptomatic.
- In children, Diabetic Keto-Acidosis (DKA) can be the first presentation of diabetes mellitus.
- The goal of diabetes management is to prevent complications of diabetes and uplift the feeling of well-being.

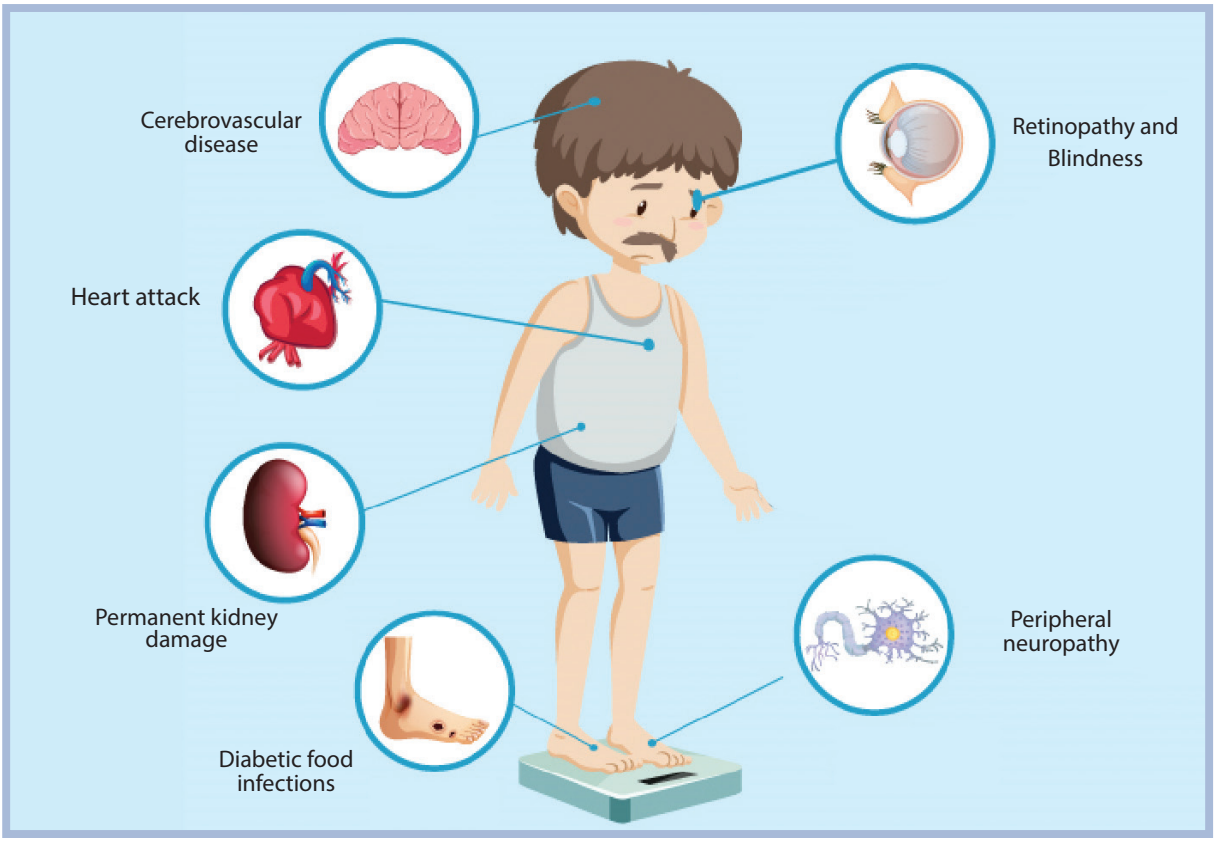


Figure 71: Complications of Diabetes Mellitus

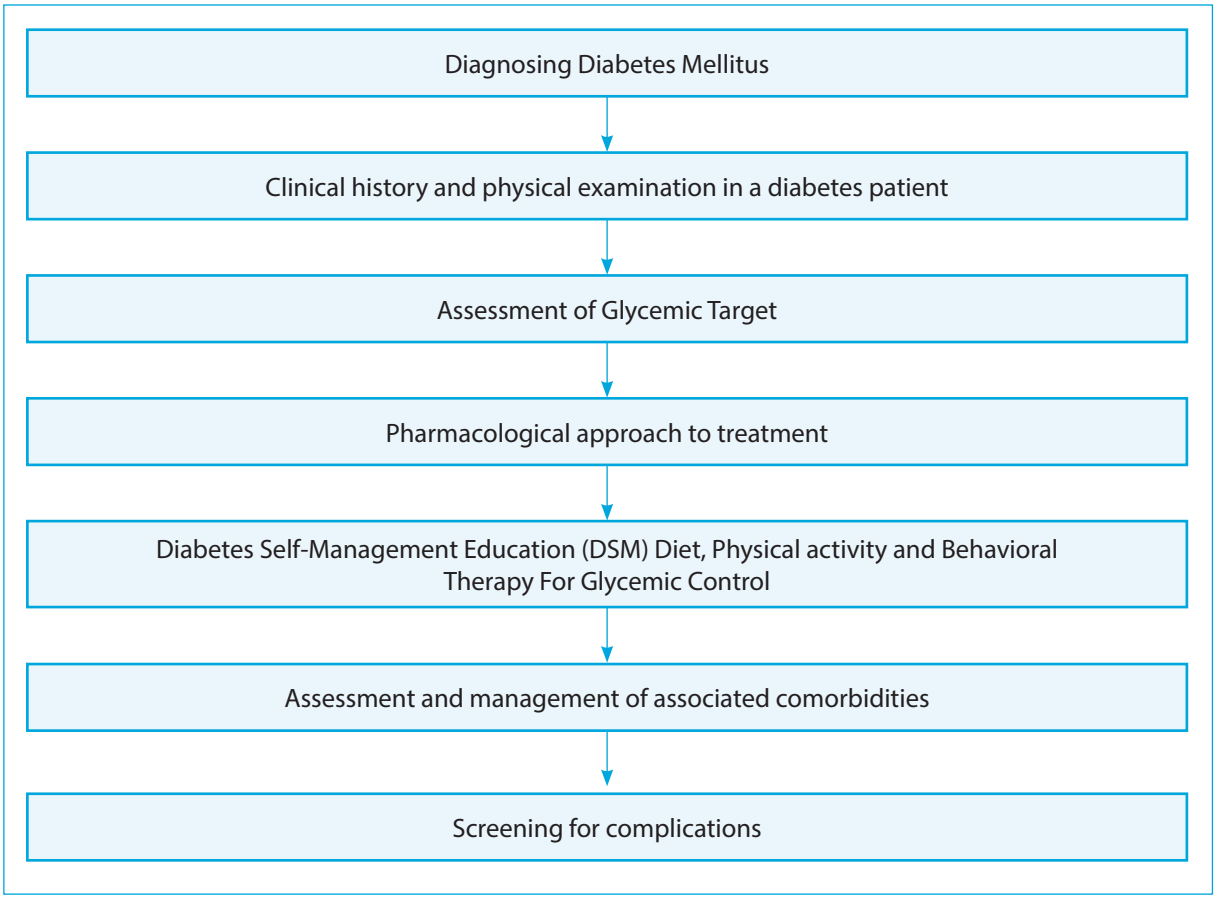


Figure 72: Flow diagram showing the overall approach to a patient with diabetes mellitus

Diabetes Self-Management Education (DSME) is an integral component of diabetes management

Diagnosis

Screening in asymptomatic adults:

Indications for screening for diabetes or pre-diabetes in asymptomatic adults:

1. Testing should begin at the age of 30 years. If results are normal, testing should be repeated at a minimum of 3 year intervals.
2. Testing should be considered in adults with overweight or obesity or who have one or more of the following risk factors:
   i. First-degree relative with diabetes
   ii. History of CVD
   iii. Hypertension (>140/90 mm Hg or on therapy for hypertension)
   iv. HDL cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL
   v. Women with polycystic ovary syndrome
   vi. Physical inactivity
3. Patients with pre-diabetes (HbA1c >5.7%, IGT, or IFG) should be tested yearly
4. Women who were diagnosed with GDM should have lifelong testing at least every 3 years
5. People with HIV

Diagnosing Pre-diabetes

Criteria defining Pre-diabetes	Threshold
Impaired Fasting Glucose	100 mg/dL to 125 mg/dL
Impaired Glucose Tolerance	140 mg/dL to 199 mg/dL
HbA1c	5.7% to 6.4%

Diagnosing diabetes mellitus and its types

Criteria defining Diabetes Mellitus	Threshold
Fasting Plasma Glucose*	>126 mg/dL
2-hour Plasma Glucose	>200 mg/dL
HbA1c	>6.5%
Random Plasma Glucose**	>200 mg/dL

* Fasting is defined as no caloric intake for at least 8 hours

** In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, random sugar of more than 200 is enough to diagnose Diabetes mellitus.

Conditions associated with an altered relationship between HbA1c and glycemia:

1. Hemoglobinopathies including sickle cell disease
2. Pregnancy (second and third trimester)
3. Post-partum period
4. G6PD deficiency
5. HIV treated with certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs)
6. Hemodialysis, or erythropoietin therapy
7. Recent blood loss or transfusion
8. Iron Deficiency Anemia

Features suggestive of Type 1 diabetes mellitus:

1. Younger age at diagnosis (<30 years)
2. Lower BMI (<25 kg/m^2)
3. Unintentional weight loss
4. Ketoacidosis
5. Glutamic Acid Decarboxylase Autoantibodies test (GAD) and very low C peptide

Table 57: Atypical forms of diabetes mellitus

Atypical forms of Diabetes Mellitus	Salient features
Maturity Onset Diabetes of Young (MODY)	▪ Onset of hyperglycemia usually before the age of 25
	▪ Positive family history (3 generations)
	▪ Negative diabetes-associated autoantibodies
	▪ Stable, mild fasting hyperglycemia ▪ (100–150 mg/dL), stable HbA1c between ▪ 5.6% and 7.6%
	▪ No obesity
	▪ Sensitive to low-dose sulfonylurea therapy
Latent Autoimmune Diabetes Of Adulthood (LADA)	▪ Typically diagnosed after 35 years of age ▪ Patients are generally thinner
	▪ Require insulin therapy more rapidly than in type 2 Diabetes Mellitus patients
Ketosis Prone Type 2 Diabetes	▪ Acute presentation with elevated glucose levels of 500–700 mg/dL, elevated ketone levels, and a HbA1c ranging from 12% to 14% in patients with type 2 DM
	▪ Negative diabetes-associated autoantibodies
Post pancreatitis diabetes	
Others	▪ Endocrinopathies (Cushing's disease, Acromegaly, Hypothyroidism) ▪ Steroid intake ▪ Post-transplant

Diagnosis of Gestational Diabetes Mellitus (GDM)

Perform a 75-g OGTT, with plasma glucose measurement at fasting (no caloric intake for at least 8 hours) and at 1 hour and 2 hours, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

Fasting: 92 mg/dL
1 hour: 180 mg/dL
2 hour: 153 mg/dL

Hyperglycemia during pregnancy is of 2 types:

1. Gestational DM: Hyperglycemia identified for the first time, anytime during that particular pregnancy is called GDM
2. Known diabetes going on to be pregnant

Note:
- All women with diabetes should be given pre-conception counseling.
- Conception with DM can lead to congenital abnormalities, thus it is very important to have good glycemic control right before conception.
- Uncontrolled hyperglycemia during pregnancy can lead to Congenital anomalies. To avoid complications, tight glycemic control during pregnancy is recommended.

Table 58: Clinical history and physical examination of a patient with Diabetes Mellitus

Review of clinical history in a patient with diabetes	
Diagnosis	• Year of diagnosis • Classical history of type 1 vs. type 2 • Family history for MODY • Family history of CAD, CVA
Control	• Home capillary blood glucose readings • Insulin or OHAs: adherence, side effects • Dietary history
Complications (Macro and Micro)	• Previous retinal screening (dilated eye examination)
	• Known kidney disease
	• Ischemic heart disease/ Peripheral artery disease/ CVA
	• Sensory loss, abdominal bloating, postural dizziness
Associated conditions	• Known autoimmune diseases, hypertension, hyperlipidemia
	• Symptoms suggestive of Obstructive Sleep Apnea (OSA)
Lifestyle	• Smoking history
	• Stressors

Table 59: Review of physical examination in a patient with diabetes

General examination	▪ Hypertension ▪ Cachexia
	▪ Orthostatic hypotension
	▪ Kussmaul breathing
	▪ Bronze skin ▪ Moon facies, Buffalo hump ▪ Macroglossia, Prognathism
	Acanthosis nigricans, Hirsuitism, Obesity
Foot examination: Vascular examination	▪ Assessment of feet for deformity, ulcers, fissuring ▪ Sensory examination of the feet and check for knee and ankle-deep tendon reflexes
	Dorsalis pedis and posterior tibial artery pulses
Skin examination	Acanthosis nigricans, Necrobiosis lipodica diabeticorum, Granuloma annulare
Fundoscopy	Visualization of the whole retina to include the optic disc, macula and vessels If hemorrhages or exudates are seen, within one disc diameter of the macula, the patient should be referred to an ophthalmologist on an urgent basis

Assessment of glycemic targets

Table 60: Timing for assessment of glycemic targets (HbA1c)

Timing for assessment of glycemic targets	
Patients who are meeting treatment goals* and who have stable glycemic control	Six monthly
Patients whose therapy has recently changed and/or who are not meeting glycemic goals	Quarterly

*Glycemic control is assessed by HbA1c measurement and blood glucose monitoring

Table 61: Glycemic target goals

Measures*	Glycemic Targets	Remarks
HbA1c	<7.0 % without significant hypoglycemia	Does not provide a measure of glycemic variability and hypoglycemia
Blood Glucose Monitoring and HbA1c	Fasting Blood Sugar (FBS): 80-130 mg/dL Post Prandial Blood Sugar (PPBS): <180 mg/dL	For patients prone to glycemic variability especially patients with Type1 diabetes or Type 2 with severe insulin deficiency Frequent monitoring is important.

*Capillary blood glucose in non-pregnant adults

Note:

The marked discrepancy between measured HbA1c and plasma glucose levels should prompt consideration that the HbA1c assay may not be reliable for that individual.

- One should consider using an HbA1c assay without interference.
- Check the standardization of the HbA1c machine.
- In newly diagnosed diabetes, good glycemic control has been proven to prevent long-term complications of diabetes.
- There is evidence of increased mortality with tight glycemic control in frail, old patients with long duration of diabetes and those with long-term complications.

Table 62: Individualization of glycemic targets*

More stringent glycemic control	Less stringent glycemic control
■ Patients with low- risk of hypoglycemia ■ Newly diagnosed patients ■ Long life expectancy ■ Absent co-morbidities ■ Absence of established vascular complications ■ Highly motivated patients ■ Excellent self-care capabilities ■ Readily available resources and support system	■ Patients with a high-risk of hypoglycemia ■ Long-standing disease duration ■ Short life expectancy ■ Severe co-morbidities ■ Severe established vascular complications ■ Preference for less burdensome therapy ■ Limited resource and support system

*Patient and disease factors are used to determine optimal glycemic targets

Table 63: Glycemic targets for glycemia and blood pressure in older adults with diabetes

Framework for considering treatment goals for glycemia and blood pressure in older adults with diabetes					
Health Status	**Rationale**	**HbA1c**	**FBS (mg/dL)**	**PPBS (mg/dL)**	**Blood pressure (mg/dL)**
Healthy	Longer life expectancy	<7.5%	90-130	90-150	<140/80
Intermediate health	Intermediate life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8%	90-150	100-180	<140/80
Poor health	Limited remaining life expectancy makes benefits uncertain	<8.5%	110-150	150-200	<150/90

Healthy: Few co-existing chronic illnesses, intact cognitive and functional status Intermediate health: Three or more co-existing chronic illnesses, two or more instrumental activities of daily living impairments, or mild to moderate cognitive impairment

Poor health: Long-term care or end-stage chronic illnesses, moderate to severe cognitive impairment, or 2+ activity of daily living dependencies

Table 64: Approach to a diabetes patient with hypoglycemia

Identification	▪ Symptoms of hypoglycemia include shakiness, irritability, confusion, palpitation, and hunger ▪ Typically described as an inconvenient and frightening feeling in patients with diabetes, confusion, altered level of consciousness, or a seizure
Diagnosis	Level 1: Glucose < 70 mg/dL and > 54 mg/dL Level 2: Glucose < 54 mg/dL Level 3: A severe event characterized by altered mental and/or physical status requiring assistance for the treatment of hypoglycemia
Treatment	▪ 15-20 g of pure glucose or any form of carbohydrate that raises glucose for the conscious patient with blood glucose <70 mg/dL ▪ Repeat treatment if blood glucose monitoring shows continued hypoglycemia after 15 minutes ▪ Intravenous administration of 25 g of glucose (25% dextrose 100 ml) followed by a glucose infusion guided by serial plasma glucose measurements in an unconscious patient

Remember hypoglycemia vulnerable groups:

1. Young children with type1 diabetes
2. Patients with impaired kidney function
3. Hypoglycemia unawareness
4. Cognitive impairment
5. Frail older adults
6. Physical disability
7. Alcohol use
8. Polypharmacy
9. Previous history of hypoglycemia

Prevention of Hypoglycemia

1. Reviewing awareness*, occurrence, frequency, causes and timing of episodes of hypoglycemia at the initial visit, every follow-up visit and the annual visit
2. Identifying vulnerable groups including young children with type 1 diabetes, patients with impaired kidney function, hypoglycemia unawareness, cognitive impairment, frail older adults, physical disability, alcohol use, polypharmacy, and previous history of hypoglycemia.
3. Understanding situations that increase the risk of hypoglycemia such as when:
   - Fasting for lab tests/ procedures
   - When meals are delayed
   - During or after intake of alcohol
   - During and after intense exercise
   - After an episode of post-meal vomiting
   - During sleep
4. Encouraging individualized glucose targets, patient education, exercise management, medication adjustment, glucose monitoring and routine clinical surveillance

* Hypoglycemia unawareness is characterized by deficient counter-regulatory hormone release, especially in older adults, and in those with diminished autonomic response. Hypoglycemia unawareness is a risk factor for hypoglycemia and can be caused as a result of hypoglycemia.

Management

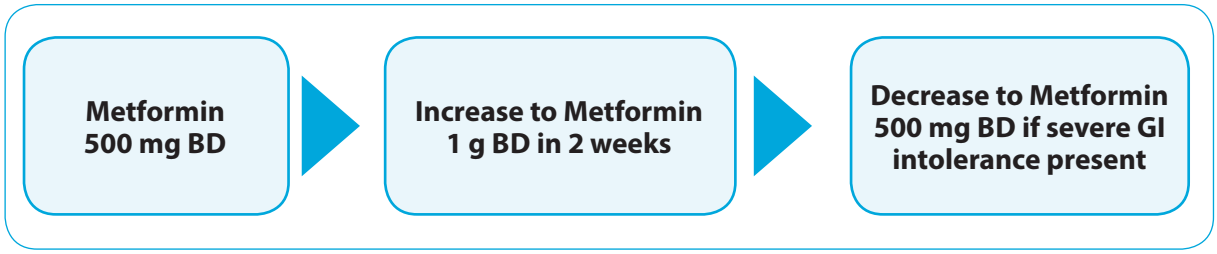
Pharmacological Approaches to Glycemic Treatment

Table 65: Pharmacological Therapy for Diabetes Mellitus: Individual uniqueness of sugar-lowering agents

Class	Drug	Weight change	CV effect	DKD progression	Side effects	Risk of hypoglycemia	Dosing considerations
Biguanides	Metformin	Modest loss	Benefit	Neutral	Diarrhea, Nausea, Flatulence, Bloating Vitamin B12 deficiency	-	eGFR<30: Contraindicated
SGLT2 inhibitors	Empagliflozin	Loss	Benefit	Benefit	Genito- urinary infections, Volume depletion, Hypotension	-	eGFR<30: Avoided
DPP4 inhibitors	Linagliptin	Neutral	Neutral	Neutral	Nasopharyngitis, Joint pain	-	No dosage adjustment
	Sitagliptin	Neutral	Neutral	Neutral		-	Dosage adjustment required
Sulphonylureas	Glimepiride	Gain	Neutral	Neutral	Hypoglycemia	++	Dosage adjustment required
	Glipizide	Gain	Neutral	Neutral		++	
	Gliclazide	Gain	Neutral	Neutral		++	
Thiazolidinediones	Pioglitazone	Gain	Risk in heart failure, Benefit in ASCVD	Neutral	Heart failure, Fluid retention, Bone fractures	-	No dosage adjustment. Discontinue with signs of heart failure

ASCVD: Atherosclerotic cardiovascular disease, SGLT2: Sodium-Glucose Transporter 2, DPP4: Dipeptidyl peptidase 4
CV effect: cardiovascular effect, DKD: Diabetic kidney disease, eGFR: estimated Glomerular Filtration Rate

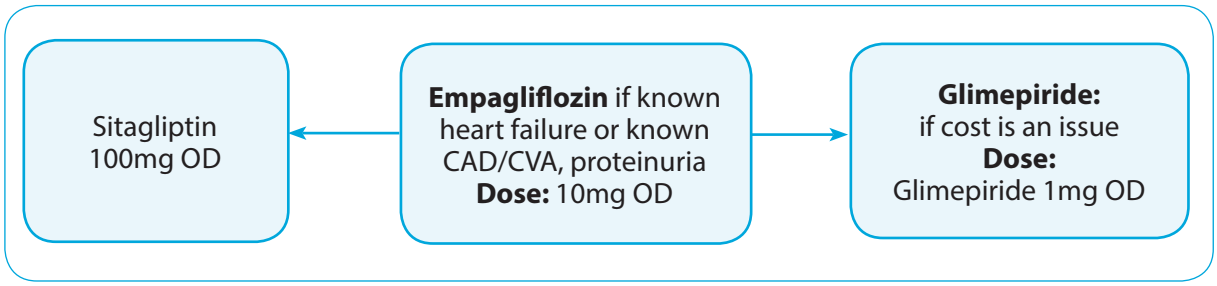
Note:
Avoid sulphonylureas in those at risk of hypoglycemia



Start insulin in patients with type 2 diabetes mellitus if:
Evidence of on-going catabolism (weight loss)

- Presence of symptoms of hyperglycemia: Concurrent infection and/or hospital admission
- HbA1c>10%
- Blood glucose level> 350mg/dL

Notes
Due to glucose toxicity, many people with type 2 diabetes with high HbA1c (>10) need upfront insulin (eg: Insulin glargine 10 IU/kg) plus Metformin 500 mg bd plus Sitagliptin 100 mg to help oral hypoglycemic agents work. Titrate by Fasting and Postprandial blood glucose.



Glimepiride: if cost is an issue

1. Aware patients on Empagliflozin that they will have glycosuria/ glucose in their urine
2. Encourage genital hygiene
3. Ensure plenty of water in-take at-least 3-4 liters per day

Metformin:

- Mild GI intolerance may be acceptable
- Do not use in critically ill patients in ICU

Salient features in the management of Children with Diabetes Mellitus:

- All children and adolescents with type 1 diabetes should be asked to monitor glucose levels multiple times daily (up to 6–10 times/day by blood glucose meter), including before meals and snacks, at bedtime, and as needed for safety in specific situations such as exercise, or the presence of symptoms of hypoglycemia.
- HbA1c goals must be individualized and reassessed over time although an HbA1c of <7% is appropriate for many children.
- Less stringent HbA1c goals (such as <7.5%) may be appropriate for patients who cannot articulate symptoms of hypoglycemia; lack access to analog insulins.
- Assess for additional autoimmune conditions soon after the diagnosis of type 1 diabetes e.g.: thyroid abnormalities
- First-line treatment of elevated blood pressure (defined as 90th to <95th percentile for age, sex, and height or, in adolescents aged ≥13 years, 120–129/<80 mm Hg) is lifestyle modification focused on healthy nutrition, physical activity, sleep (DASH).
- The goal of treatment is blood pressure <90th percentile for age, sex, and height or, in adolescents aged ≥13 years, <130/80 mm Hg.
- After the age of 10 years, the addition of a statin may be considered in patients who, despite medical nutrition therapy and lifestyle changes, continue to have LDL cholesterol >160 mg/dL or LDL cholesterol >130 mg/dL and one or more cardiovascular disease risk factors.
- The goal of therapy is an LDL cholesterol value <100 mg/dL.
- In incidentally diagnosed or metabolically stable children with type 2 diabetes (HbA1c <8.5% and asymptomatic), metformin is the initial pharmacologic treatment of choice if renal function is normal.
- Youth with marked hyperglycemia (blood glucose ≥250 mg/dL, HbA1c ≥8.5%) without acidosis at diagnosis ho are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with basal insulin while metformin is initiated and titrated.

Note:
Provide adolescents with diabetes with mental health assessment, education and counseling.

Indications for Insulin Therapy

1. Patients with type 1 diabetes mellitus
2. Early introduction of insulin in patients with type 2 diabetes mellitus should be considered in the following conditions:
   i. Evidence of on-going catabolism (weight loss)
   ii. Presence of symptoms of hyperglycemia*
   iii. HbA1C>10%
   iv. Blood glucose level>300mg/dL**

* Symptoms of hyperglycemia include polyphagia, polydipsia and polyuria
** Random blood glucose measurement

Note:
All insulin are effective in blood sugar control. However, only some may be available in government/ peripheral settings.

Table 66: Types of Insulin and Insulin regimen

Types of Insulin	Preparations of Insulin	Onset of Action	Peak action	Duration of action	Timing of giving Insulin
Rapid-acting	Aspart, Glulisine, Lispro	15-30 minutes	1-2 hours	3-5 hours	Immediately before meal
Short-acting	Human Regular	30-60 minutes	2-4 hours	5-8 hours	30 minutes before meal
Intermediate-acting	Neutral Protamine Hagedorn (NPH)	2-4 hours	4-10 hours	12-24 hours	30 minutes before meal
Long-acting (1st gen)	Detemir	1-2 hours	6-12 hours	20-24 hours	Once or twice daily
	Glargine 100	2-4 hours	Peak less	<24 hours	Once or twice daily
Ultra-long acting (2nd gen)	Degludec	1-2 hours	Peak less	>40 hours	Once daily
	Glargine 300	4-6 hours	Peak less	28- 36 hours	Once daily

Glargine 100: 100 U per ml of Glargine, Glargine 300: 300 U per ml of Glargine

Table 67: Insulin regimen

Insulin Regimens	Formulation	Salient features
Basal bolus regimen	▪ Multiple daily injections (1–2 injections of basal insulin* and 3 injections of prandial insulin** per day)	• Basal insulin analogues exhibit better efficacy compared with human NPH insulin. • Rapid-acting prandial insulin analogues have a lower hypoglycemia risk than regular human insulin.
Pre-mixed insulin	▪ Two daily injections (NPH + prandial insulin)	• Less costly than basal-bolus regimen • Useful during postprandial excursion***
		• Higher risk of hypoglycemia than basal-bolus regimen
		• Less flexibility than basal-bolus regimen in terms of meal timing and content

* Basal insulin: Long-acting insulin (basal insulin analogues) or Neutral Protamine Hagedorn (NPH)
** Prandial insulin: Rapid-acting insulin (insulin analogue) or Short-acting (regular insulin)
*** Post prandial excursion: Defined as the change in glucose concentration from before to after a meal

Table 68: Neutral Protamine Hagedorn (NPH) regimen

Insulin Regimens	Formulation	Salient features
Basal bolus regimen	▪ Multiple daily injections (1–2 injections of basal insulin and 3 injections of prandial insulin per day)	▪ Basal insulin analogues exhibit better efficacy compared with human NPH insulin. ▪ Rapid-acting prandial insulin analogues have a lower hypoglycemia risk than regular human insulin.
Pre-mixed insulin	▪ Two daily injections (NPH + prandial insulin)	▪ Less costly than basal-bolus regimen ▪ Useful during postprandial excursion
		▪ Higher risk of hypoglycemia than basal bolus regimen
		▪ Less flexibility than basal bolus regimen in terms of meal timing and content

Intensification of type 2 diabetes mellitus treatment

If diabetes is uncontrolled on oral hypoglycemic agents, and if both fasting and post-prandial blood sugar levels are high

Add flat-acting basal insulin-like glargine

Start with 10U and titrate according to blood sugar levels

- Titrate every 5 days according to fasting, postprandial level/ self-glucose monitoring by glucometer
- Do not stop metformin/ dipeptidyl peptidase (DPP)-4 inhibitor/ SGLT2 inhibitor when adding Insulin
- Decrease the dose of sulphonylurea (If planning to continue sulphonylurea: Give only once daily morning dose)

If glargine is not available, give premixed insulin (Regular/ NPH): 50/50 or 30/70

- Give 2/3rd of the dose in the morning (30 minutes before the biggest meal in the morning/9:30 a.m. brunch) and 1/3rd dose in the evening (30 minutes before the evening meal)
- Continue Metformin with Insulin (if serum creatinine is normal)

- SGLT2 inhibitor and DPPIV inhibitor can be continued if a patient is already on these drugs
- Dosing: Start with 10U morning dose and 6U evening dose
- Do not overlap sulfonylurea with short-acting insulin or pre-mixed insulin to avoid hypoglycemia risk.

Intensification of Type 1 diabetes

Basal bolus insulin regimen best mimics physiological insulin secretion, thus is the first choice in type 1 diabetes

If not available, can be managed with NPH and a Regular insulin regimen

1. **Basal bolus regimen**
   - Glargine insulin 12 U once a day at 7 a.m. (Note: Need not be given before meal) plus
     Short-acting analogue before food
     Regular insulin three times a day, e.g.: 8U pre-lunch, 4U pre-snack, 6U pre-dinner (before each major meal)

2. NPH with regular insulin regimen (Premixed regimen)
   - Calculate daily insulin requirement (0.5U/kg per day)
   - Give 2/3rd of the dose in the morning (30 minutes before the biggest meal in the morning/ 9:30 a.m. brunch) and 1/3rd dose in the evening (30 minutes before the evening meal)
   - 50 percent of the total dose should be NPH and 50 percent regular insulin

For example:

In the morning, give 6U regular insulin and 10U NPH 30 minutes pre-brunch, 5U regular insulin pre-dinner, 8U NPH at bed time

Note:
Insulin Dosing is not fixed and titration is done based on self-monitoring of blood glucose levels.

Table 69: Insulin delivery technique

Patient Education on Insulin Use	
Insulin Injection Sites	■ Insulin should be administered in the subcutaneous tissue, or the fatty layer under the skin. ■ Avoidance of intra-muscular delivery* ■ Common areas include the back of the arm, abdomen, upper buttocks, and outer part of the thighs. ■ It is important to choose a different site each time.
Insulin Injection Technique	■ Always wash hands and pick a clean injection site ■ Insulin injection site needs to be rotated
Assessment of Insulin Use	■ Assessment of injection device use, technique and proper injection site rotation ■ Presence of lipohypertrophy** or injection site infection***

* Intramuscular injection can lead to unpredictable insulin absorption and variable effects on glucose, with intramuscular injections being associated with frequent and unexplained hypoglycemia
** Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth
*** Re-use of needles or continued injection in the same location can lead to skin infection

Storage of Insulin in rural where fridge is not available:

- Insulin can be stored in a mud pot with wet sand covered with a lid or put a paper on top of the wet sand, away from direct sunlight
- Keep the insulin on top of the sand and put a cool wet cloth around the insulin
- Use a small clay pot or earthenware pitcher storage utensil which reduces the external temperature

Glucometer use

Steps of Glucometer use

- Wash and dry hands (or wipe with an alcohol swab and let dry)
- Take the test strip out and place in a glucometer, wait for the blood drop to show
- Prick finger. Use the side, not the center
- Rotate fingers and squeeze a drop of blood, wipe away with cotton, then hold the second drop of blood to the side of the test strip
- Wait for the glucometer to finish reading and display the results

Diet, Physical activity and Behavioural therapy for Glycaemic Control

Medical Nutrition Therapy

- Advise overweight patients to reduce weight by reducing their food intake.
- For individuals with type-1 diabetes, it is recommended to count carbohydrate and match it at the meal time insulin.
- In Zimbabwean hand jive model (Figure 73),
  1. Starches or carbohydrate containing food to be taken in one meal is the amount that can be held in 2 fists.
  2. The amount covering the palm of one hand is for protein-containing foods.
  3. Green non starch vegetables, will be as much as can be held by 2 hands.
  4. Oil is to be taken less than equivalent to tip of the thumb.
- Teach patient about "carb consistency" in every meal.
- Make sure patient is taking enough protein.

- Palm = 1 portion of protein (meat/fish/poultry)
- Closed fist = 1 portion of carbohydrates (grains & starches)
- Thumb = 1 portion (tablespoon) of fat-heavy foods (peanut butter
- Cupped hands = 1 portion of fruit or vegetables

Figure 73: Zimbabwean hand jive model for food Proportion calculation

Table 70: Nutrition, Physical activity and Behavioural therapy for Glycemic Control

Medical Nutrition Therapy (MNT)	▪ Nutrient dense carbohydrate sources high in fiber at least 14 g fiber per 1000 kcal and minimally processed. ▪ Non-starchy vegetables, fruits, whole grains, as well as dairy products, with minimal added sugars. ▪ Replace sugar-sweetened beverages, including fruit juices, with water. ▪ Eating food rich in long-chain n3 fatty acids such as fatty fish, nuts and seeds ▪ Need a balance of macro and micronutrients
Physical activity	▪ Should engage in 60 minutes per day or 150 minutes per week or more of moderate to vigorous-intensity aerobic activity, spread over at least 3 days in a week ▪ 2-3 sessions per week of resistance exercise on nonconsecutive days had proven benefits of improving insulin resistance. ▪ Flexibility and balance training for older adults with diabetes
Behavioral therapy	▪ Smoking cessation and abstinence from tobacco products ▪ Assess for symptoms of depression, anxiety, distress, disordered eating, and cognitive capacity
Weight loss	▪ Loss of at-least 7% of initial body weight in obese diabetic patients with the help of MNT, physical exercise and behavioural therapy

Table 71: Exercise prescription

Children and Adolescents	60 minutes per day or more of moderate or vigorous-intensity aerobic activity, with vigorous muscle strengthening activities at least 3 days/ week
Adults	150 minutes or more of moderate to vigorous-intensity aerobic activity per week, with no more than 2 consecutive days without activity
	2-3 sessions/ week of resistance exercise on non-consecutive days
Older adults	Interrupt prolonged sitting every 30 minutes
	Flexibility and balance training 2-3 times per week

Assessment and Management of Associated Co-morbidities

Table 72: Treatment targets for common co-morbidities associated with diabetes

Blood pressure	• <130 mm Hg (systolic) • <80 (diastolic)
LDL	<70 mg/dL
Triglycerides	<150 mg/dL
HDL	>40 mg/dL for men >50 mg/dL for women

Note:

• Give a statin to all patients with type 2 diabetes aged >40 years

• Consider risk vs. benefit of statins in patients more than or equal to 75 years of age on starting statin.

Table 73: Management of associated co-morbidities associated with diabetes

Associated co-morbidities and complications	Management
Hypertension with Albuminuria* or CAD**	• ACEI or ARB • Low salt intake (<5g/dL)
Dyslipidemia	• Moderate to high intensity statin therapy • Adults > 75 years: Discussion of potential benefit and risks of statin initiation
Atherosclerotic cardiovascular disease	Aspirin therapy (75-162 mg/day) for secondary prevention
	Statin therapy
Diabetic neuropathy	Optimize glucose control
	Pregabalin or Duloxetine or Gabapentineas initial pharmacologic treatment Amitriptyline or Selective Serotonin Reuptake Inhibitors (SSRI)

* Albuminuria: urine albumin to creatinine ratio 30-299 mg/g creatinine

** Coronary artery disease

WHO chart for cardiovascular risk evaluation

How to use the charts to assess cardiovascular risk?

- First make sure that you select the appropriate charts using information
- If blood cholesterol cannot be measured due to resource limitations, mean cholesterol value for the population can be used.
- Before applying the chart to estimate the 10 year cardiovascular risk of an individual, the following information is necessary:
  - Presence or absence of diabetes
  - Gender
  - Smoker or non-smoker
  - Age
  - Systolic blood pressure (SBP)
  - Total blood cholesterol (if in mg/dL divide by 38 to convert to mmol/l).

Once the above information is available proceed to estimate the 10-year cardiovascular risk as follows:

- Step 1: Select the appropriate chart depending on the presence or absence of diabetes
- Step 2: Select male or female tables
- Step 3: Select smoker or non-smoker boxes
- Step 4: Select age group box (if age is 50-59 years select 50, if 60-69 years select 60 etc)
- Step 5: Within this box find the nearest cell where the individual's systolic blood pressure (mm Hg) and total blood cholesterol level (mmol/l) cross. The color of this cell determines the 10 year cardiovascular risk.

WHO/ISH Risk Prediction Chart:

10-year risk of a fatal or non-fatal cardiovascular event by gender, age, systolic blood pressure, total blood cholesterol, smoking status and presence or absence of diabetes mellitus.

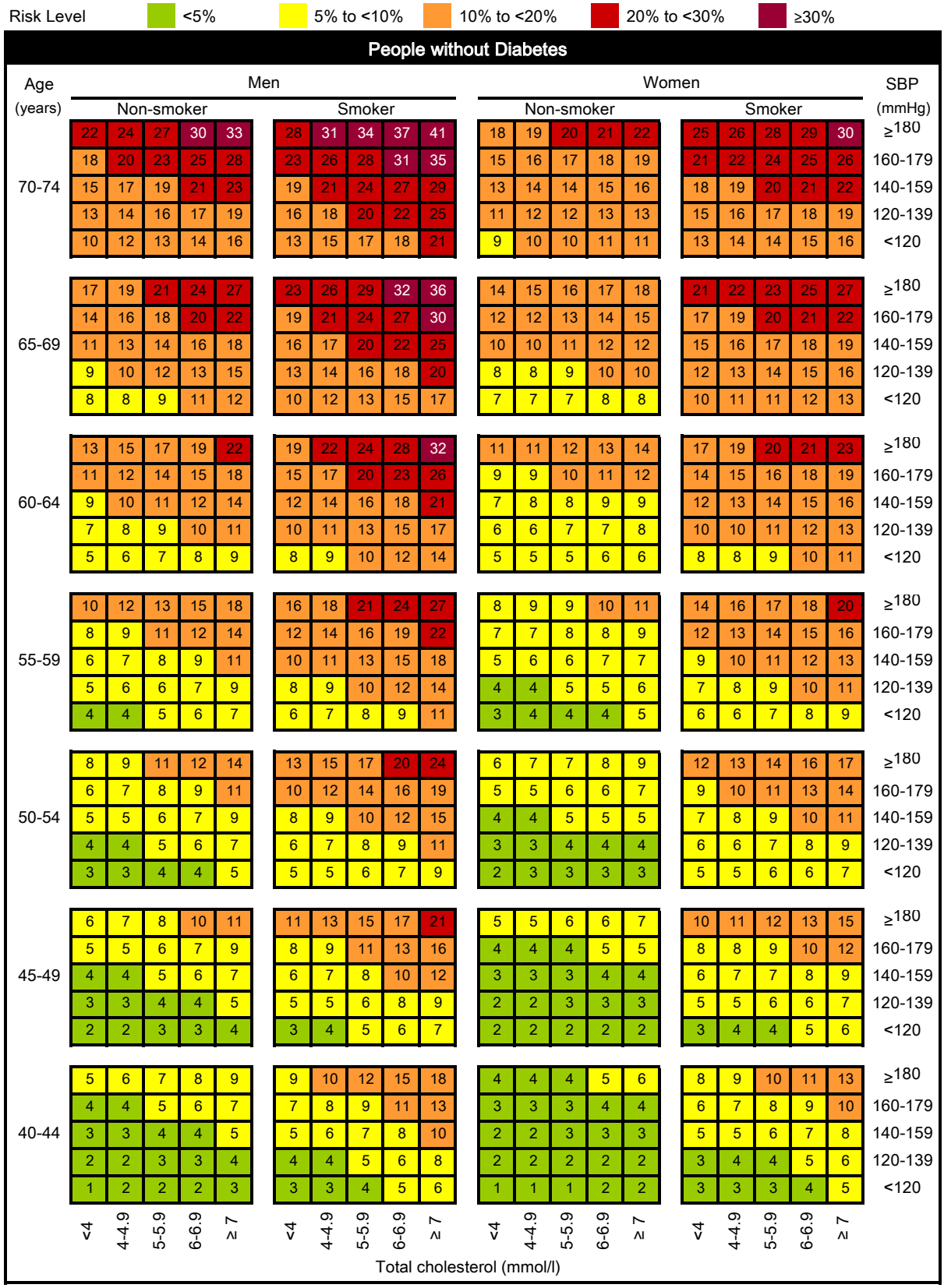


Figure 74(a): WHO cardiovascular laboratory based risk prediction chart without diabetes

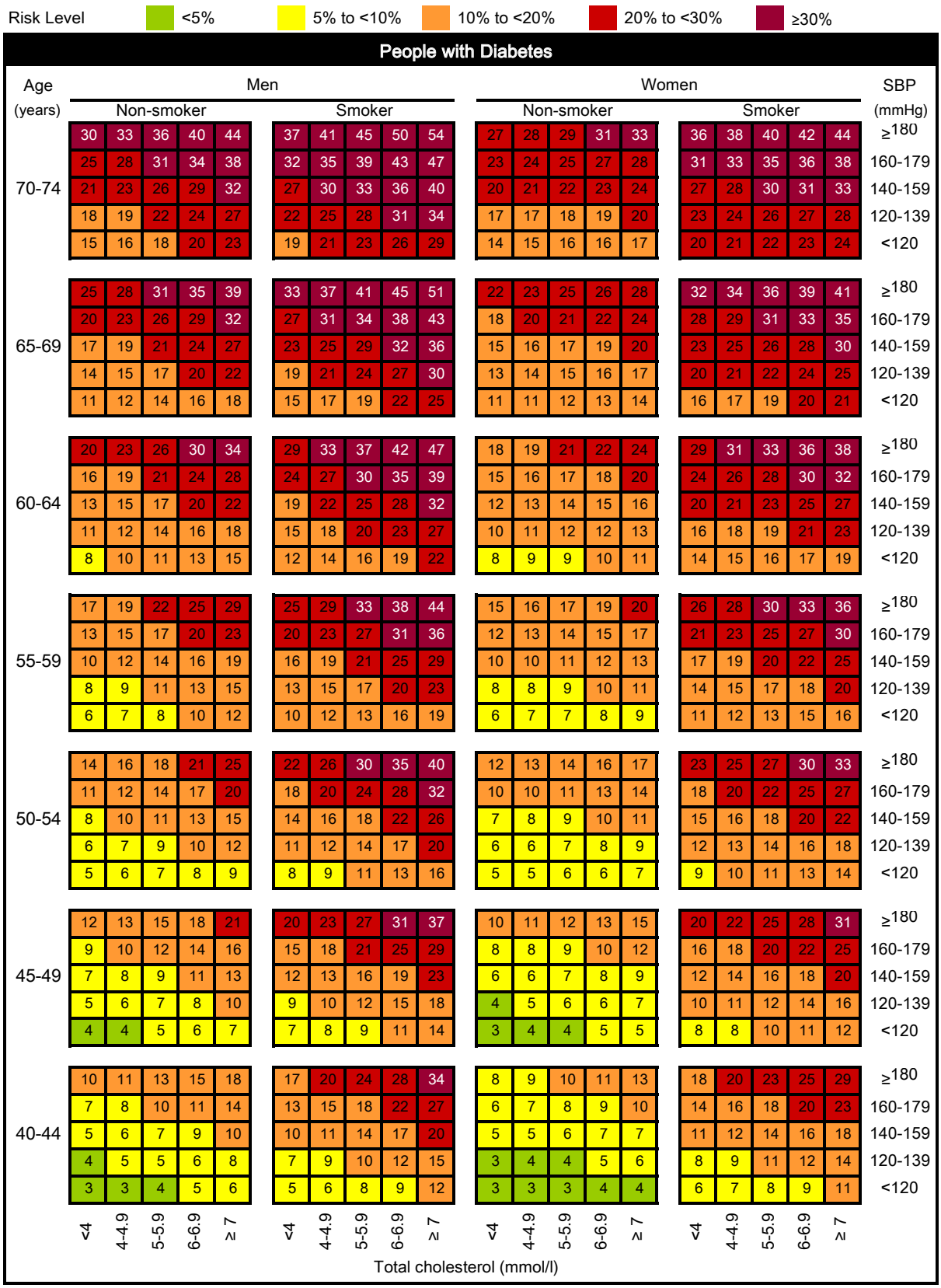


Figure 74(b): WHO cardiovascular laboratory based risk prediction chart with diabetes

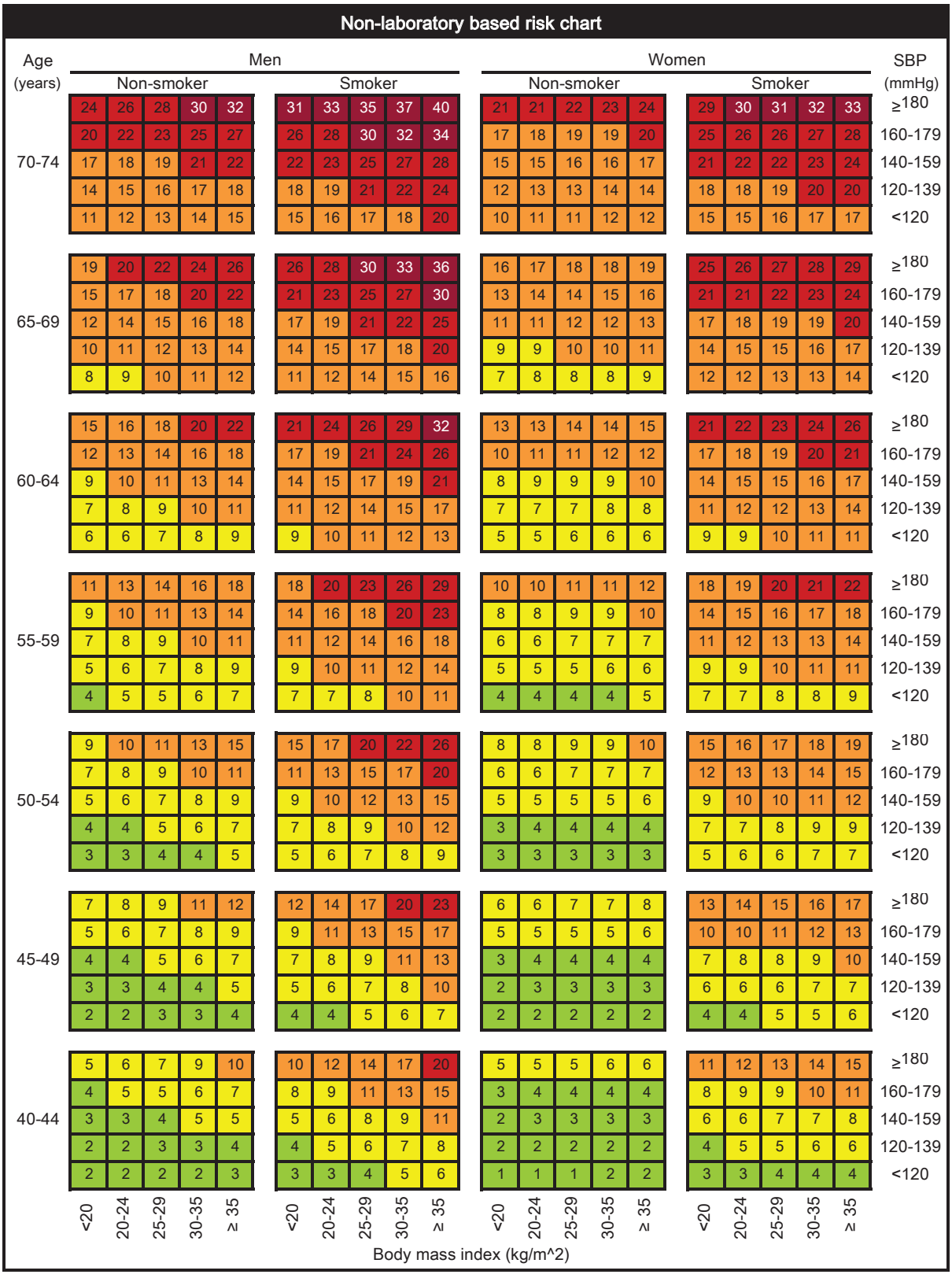


Figure 75: WHO cardiovascular non-laboratory based risk prediction chart

Screening for Complications

When to screen for complications and what is the timing for follow-up screening?

Table 74: Screening for complications in a patient with diabetes

	Screening	Follow-up
Diabetic Retinopathy	▪ Within 5 years after the onset of Type 1 diabetes ▪ At the time of diagnosis of Type 2 diabetes	▪ Screening every 1-2 years if there is no evidence of retinopathy for >1 annual eye exams ▪ Atleast annually if any level of diabetic retinopathy is present ▪ More frequently if retinopathy is progressing or sight threatening
Diabetic Neuropathy	▪ Within 5 years after the onset of Type 1 diabetes ▪ At the time of diagnosis of Type 2 diabetes	▪ Annual examination after the first screening
Diabetic Foot	▪ Atleast annually	
Diabetic Kidney Disease	▪ Atleast annually urinary albumin and estimated GFR should be assessed in patients with Type 1 diabetes with duration >5 years and in all patients with Type 2 diabetes regardless of treatment	▪ Patients with urinary albumin >300 mg/g creatinine and/or an estimated glomerular filtration rate 30-60 mL/min/1.73 m2 should be monitored twice annually to guide therapy

Management of Diabetes with pregnancy and Gestational Diabetes Mellitus:

1. Patient education is of utmost importance.
2. Medical Nutritional Therapy is the 1st line treatment.
3. Among the pharmacological treatment, Insulin is the preferred therapy.
4. Women with pre-existing type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy
5. In women of child-bearing age pre-conception counseling should be done. Tight glycemic control pre-conception should be advised to prevent congenital abnormalities

Hyperglycemic Emergencies

Table 75: Emergency management of Diabetic ketoacidosis

History	History of diabetes and a history of altered insulin dose, infection, significant medical "stress". Abdominal pain and tachypnea are often present.
Physical Examination	Kussmaul breathing, Odor of acetone in breath, dehydration
Lab tests	The diagnostic criteria for DKA include blood glucose above 250 mg/dL, arterial pH < 7.30, serum bicarbonate < 18 mEq/l and moderate degree of ketonemia and/or ketonuria
Management (acidosis should be resolved first)	▪ Fluid: Estimated fluid deficit is 5–7 liters. Correct with normal saline, 2L in the first 2 hours, the remainder over the next 22 hours. ▪ Insulin: Intravenous infusion of 0.1 U/kg/h insulin. Reduce plasma glucose by 50–75 mg/dL/h. Initial target plasma glucose is 200–250 mg/dL.
	▪ Once achieved, reduce insulin rate and provide dextrose to 'clamp' the plasma glucose until acidosis/anion gap is resolved.
	▪ Acid/base: pH will climb with plasma expansion and insulin administration. Use 50meq sodium bicarbonate only for severe academia (pH <6.9).
	▪ Electrolytes: Close monitoring and correction of serum potassium is critical. (If serum potassium <5, correct hypokalemia before any insulin is given.)
	▪ Search for cause: Seek to determine underlying precipitant, such as treatment non-adherence, infection, myocardial infarction etc

Table 76: Emergency management of Hyperglycemic Hyperosmolar State

History	History of diabetes and a history of altered insulin dose, infection, significant medical "stress". Abdominal pain and tachypnea are often present.
Physical Examination	Kussmaul breathing, Odor of acetone in breath, dehydration
Lab tests	The diagnostic criteria for DKA include blood glucose above 250 mg/dL, arterial pH < 7.30, serum bicarbonate < 18 mEq/l and moderate degree of ketonemia and/or ketonuria
Management	▪ Fluid: Estimated fluid deficits (7–9 liters). Correct rate depends on blood pressure, other signs of volume contraction and any history of underlying cardiovascular disease, especially heart failure. ▪ Insulin: Should be initiated after initial saline plasma expansion. Intravenous infusion of 0.1 U/kg/h. ▪ Goal is to reduce plasma glucose by 50– 75 mg/dL/h. Target plasma glucose is 250–300 mg/dL.
	▪ Monitor electrolytes
	▪ Search for cause: Seek to determine underlying precipitant, such as treatment non-adherence, infection, myocardial infarction etc.

Advocacy

All health-care workers are recommended to push for policy changes to prevent onset of diabetes and obesity, as following:

1. Applying sugar tax in sugary beverages
2. Restricting sugary drinks and factory food in school premises
3. Encouraging local farmers and fiber- food and vegetables
4. Discouraging factory made ultra-processed foods (noodles, breads, biscuits) especially in school premises

Pediatric diabetes

Clinical subtypes of diabetes in children according to age at diagnosis:

- < 6 months – Monogenic Neonatal Diabetes
- 6 months to < 10 years – Type 1 Diabetes
- 10 to < 25 years
  - Type 1 Diabetes
  - Type 2 Diabetes

Features favoring a diagnosis of T2DM rather than T1DM at diagnosis include:

- Overweight or obesity
- Age above 10 years
- Strong family history of T2DM
- Acanthosis nigricans (evidence of insulin resistance)
- Undetectable islet autoantibodies (if measured)
- Elevated or normal C-peptide (if assessed)

Diagnosis of diabetes mellitus

The clinical signs of type 1 diabetes in children and young people include:

- Hyperglycemia (random plasma glucose more than 11 mmol/litre)
- Polyuria
- Polydipsia
- Weight loss
- Excessive tiredness

Laboratory diagnostic criteria for diabetes:

- Fasting plasma glucose ≥ 7.0 mmol/L or
- 2-hour post-load plasma glucose ≥ 11.1 mmol/L or
- HbA1c ≥ 48 mmol/mol (> 6.5%)

Diabetic ketoacidosis in children and young people

Diabetic ketoacidosis (DKA) is a preventable but serious complication of type 1 diabetes and carries a mortality rate of 0.3–0.5% in developed economies and about 10% in developing economies. It occurs due to an interplay between insulin (deficiency) and counter-regulatory hormones (excess). The former leads to hyperglycemia and ketosis, while the latter (epinephrine, cortisol and growth hormone) released in response to stress, aggravates hyperglycemia by blocking the action of insulin and enhancing glycogenolysis in the liver. When blood glucose levels exceed the renal threshold (180mg/dL), glycosuria occurs. The resultant osmotic diuresis leads to volume depletion and dehydration, which activates the renin-angiotensin-aldosterone axis and also triggers the release of counter-regulatory hormones. These hormones act towards preserving the intravascular volume. Vomiting, due to stimulation of chemoreceptor trigger zone by hydrogen ions and ketones, further aggravates volume loss and dehydration leading to a vicious cycle.

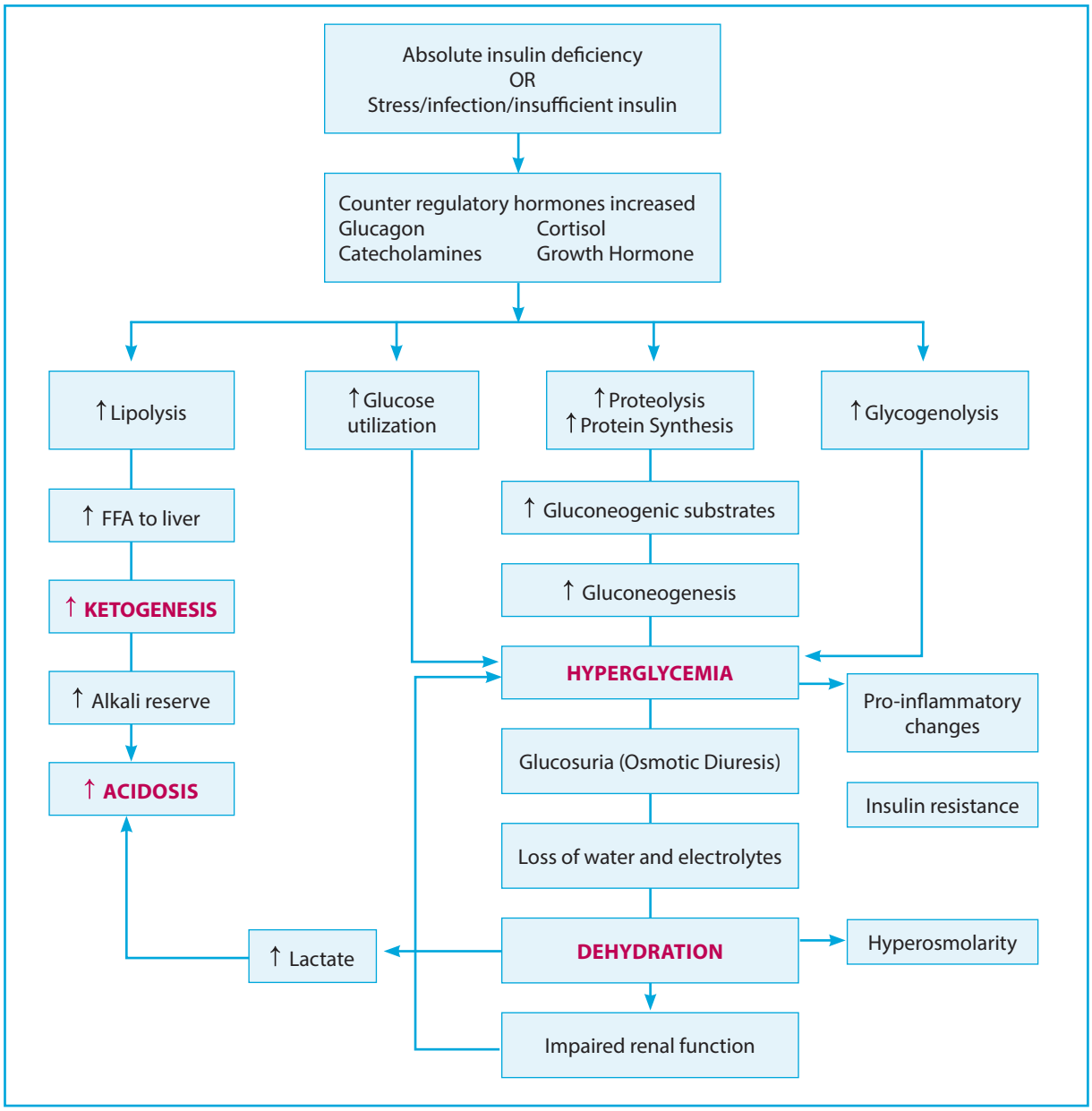


Figure 76: Management of DKA in children and young adults

Table 77: Risk factors of DKA

Newly diagnosed cases	Established diabetes
• Age < 2 years • Delay in diagnosis	• Insulin omission • Poor metabolic control • Previous episodes of DKA • Gastroenteritis with persistent vomiting • Stressful situations like infections, surgery • Limited access to medical services

In diabetes diagnosed before the age of 20 years, DKA as the initial presentation occurs in approximately 25% but this may vary within and across populations. The prevalence decreases with increasing age from 37% in children aged 0 to 4 years to 15% among those aged 15 to 19 years. Diabetic ketoacidosis prevalence is significantly higher in people with T1DM (about 30%) compared with T2DM (about 10%)

Diagnosis of DKA

Clinical manifestations of Diabetic ketoacidosis:

- Dehydration
- Tachypnea; deep, sighing (Kussmaul) respiration
- Nausea, vomiting, and abdominal pain that may mimic an acute abdominal condition
- Confusion, drowsiness

Diagnosis of DKA requires presence of ALL three biochemical criteria:

- Hyperglycemia (blood glucose >11 mmol/L [200 mg/dl])*
- Venous pH < 7.3 or serum bicarbonate <18 mmol/L (or mEq/L)
- Ketonemia** or ketonuria

* *Children and young people with known diabetes may develop DKA with normal blood glucose levels.*

** *If facilities for blood ketone (beta-hydroxybutyrate) level are not available, use urinary ketone levels to make the diagnosis, but they are not useful for monitoring. Urinary ketones of more than ketones++ on standard dipsticks are typically equivalent to near patient blood ketones of >3.0 mmol/l.*
(Urinary ketones must be read 15 seconds after stick is dipped)

Table 78: Classification of severity of DKA

Category	Venous pH	Plasma bicarbonate mmol/L
Mild	<7.3	10 – 15
Moderate	<7.2	5 – 10
Severe	<7.1	<5

Management of DKA

Emergency management/initial resuscitation:

1. General Resuscitation

Airway: Ensure that the airway is patent and if the child is comatose, insert an airway.
If consciousness reduced or child has recurrent vomiting, consider inserting N/G tube, aspirate and leave on open drainage.

Breathing: Give 100% oxygen by face-mask.

Circulation: Insert IV cannula and take blood samples (see below). Cardiac monitor for T waves (peaked in hyperkalemia) Measure blood pressure and heart rate

2. Initial fluid bolus:

- All children and young people with mild, moderate or severe DKA who are not in shock and are felt to require IV fluids should receive a 10 ml – 20 ml/kg 0.9% sodium chloride bolus over 30 minutes.
- Patients with shock, defined by the presence of tachycardia, prolonged central capillary refill, poor peripheral pulses, and hypotension require appropriate restoration of their circulation and circulatory volume. Patients with shock should receive a 20 ml/kg bolus over 15 minutes.
- Following the initial 20 ml/kg bolus, in patients in shock should be reassessed and further boluses of 10 ml/kg may be given if required to restore adequate circulation up to a total of 40 ml/kg at which stage inotropes should be considered.
- Shocked patients will require high dependency care and should be discussed with the most senior pediatrician or intensivist available at the earliest opportunity.
- Whilst excessive fluid should be avoided because of the risk of cerebral oedema it is important to ensure that the circulation is adequate and fluid should be given to support this. Cerebral perfusion is dependent on both perfusion pressure and intracranial pressure and hypotension will exacerbate the risk of brain injury.

3. Initial Investigations:

- Blood glucose
- FBC, Urea and electrolytes (electrolytes on blood gas machine give a guide until accurate results available) and CRP
- Blood gases (venous)
- Ketones – Blood/urine

Other investigations should be done only if indicated e.g. CXR, CSF, throat swab, blood cultures, urinalysis, culture and sensitivity etc. (A raised white blood cell count is common in DKA and does not necessarily indicate sepsis).

DKA may be precipitated by sepsis or intercurrent infection, and fever is not part of DKA. Infection may co-exist with DKA. Suspect sepsis if there is fever or hypothermia, hypotension, refractory acidosis or lactic acidosis. A high lactate should increase concern about possible infection or sepsis.

Assess and document the following:

1. Conscious Level: Perform hourly neurological observations including Glasgow Coma Score and note whether or not drowsy on admission.
   If reduced conscious level on admission, or there is any subsequent deterioration:
   - Seek urgent anesthetic review if the airway cannot be protected
   - Discuss with the responsible senior pediatrician or critical care specialist to decide the appropriate care setting (pediatric HDU or PICU)
2. Full Examination - looking particularly for evidence of:
   - Cerebral oedema - headache, irritability, slowing pulse, rising blood pressure, reducing conscious level.
     Conscious level is directly related to the degree of acidosis, but signs of raised intracranial pressure suggest cerebral oedema.
   - Infection
   - Ileus (which is common in DKA)
3. WEIGHT OF THE CHILD. If this is not possible because of the clinical condition, use the most recent clinic weight as a guideline, or an estimated weight from centile charts.

Where PICU or HDU do not exist within the admitting hospital, transfer to another hospital for care. ALL children with DKA are high-dependency patients and require a high level of nursing care, even if on general pediatric wards.

Indications for PICU admission

- Severe DKA (especially if long duration of symptoms, compromised circulation, or depressed level of consciousness)
- Children at increased risk for cerebral injury
  - <5 years of age
  - pCO2 < 21 mm Hg,
  - blood urea nitrogen > 20 mg/dL

Subsequent management of DKA:

1. Fluids:

It is essential that all fluids given are documented carefully, particularly the fluid which is given in the accident and emergency department and on the way to the ward, as this is where most mistakes occur.

a) Volume of fluid

Once circulating blood volume has been restored and the child adequately resuscitated, calculate fluid requirements as follows:

Requirement = Deficit + Maintenance

Fluid Deficit

It is not possible to accurately clinically assess the degree of dehydration to work out the deficit.

Traditionally, children with DKA are assumed to be severely dehydrated, with fluid deficits ranging from 10% to 15%, with a conservative estimate assumed at 10%, but even this was discovered to be an overestimate.

Therefore, deficit volume for replacement is calculated at 6.5% to 8.5% which is equivalent to ([65–85] mL × body weight).

Maintenance Fluid (calculated using the Holliday – Segar formula)

- 100 ml/kg/day for the first 10 kg of body weight
- 50 ml/kg/day for the next 10 to 20 kg
- 20 ml/kg/day for each additional kilogram above 20 kg

Fluid Calculation: Calculate the fluid deficit, subtract the initial 10ml/kg bolus (unless given for Shock) then divide this over 48 hours and add to the hourly rate of maintenance fluid volume, giving the total volume evenly over the next 48 hours.

NB. Do not give additional intravenous fluid to replace urinary losses. Urinary catheterization should be avoided but may be useful in the child with impaired consciousness.

b) Type of fluid

Use 0.9% sodium chloride with 20 mmol potassium chloride in 500 ml (40 mmol per litre) until blood glucose levels are less than 14 mmol/l

c) Oral Fluids

- Do not give oral fluids to a child or young person who is receiving intravenous fluids for DKA until ketosis is resolving and there is no nausea of vomiting.
- A nasogastric tube may be necessary in the case of gastric paresis.
- If oral fluids are given before the 48hr rehydration period is completed, the IV infusion needs to be reduced to take account of the oral intake.

d) Fluid Losses

If a massive diuresis continues for several hours fluid input may need to be increased; this should be isotonic to the urine. However urinary losses should not be routinely replaced. If large volumes of gastric aspirate continue, these will need to be replaced with 0.45% saline with Potassium Chloride.

2. Potassium replacement

Ensure that all fluids (except any initial boluses given) contain 40 mmol/l potassium chloride. Hypokalaemia can occur up to 48 hours after starting DKA treatment.

Where Potassium is above the upper limit of the normal range at presentation, add when:

- Patient has passed urine.
- There is history of having recently passed urine,
- Potassium has fallen to within the upper limit of the normal range (less than 5.5mmol/l)
- If Potassium is low at presentation (<3.0 mmol/l) then insulin administration should be deferred until Potassium is >3.0mmol/l.

If the child or young person with DKA develops hypokalaemia (potassium below 3.0 mmol/litre):

- Consider temporarily stopping the insulin infusion.

3. Insulin therapy

Timing

Start insulin 1 – 2 hours after initiation of IV fluid replacement

Type and dose, preparation and route of administration

- Regular (soluble) insulin 0.05–0.1 U/kg/h given intravenously (IV). The lower dosage (0.05 U/kg/h) can be considered for children with pH > 7.15.
- Add 50 units of soluble insulin to 49.5ml 0.9% sodium chloride solution
- For priming, flush infusion tubing with insulin solution prior to administration
- Do not give bolus doses of intravenous insulin (can precipitate development of cerebral edema due to rapid fall in osmotic pressure and hypokalemia due to transcellular shift of potassium)

Duration of therapy

- Continue insulin infusion at 0.05–0.1 unit/kg/h at least until resolution of DKA [pH > 7.30, serum bicarbonate >18 mmol/L, (betahydroxybutyrate <1 mmol/L, if available)], which invariably takes longer than normalization of blood glucose concentrations.
- Monitor venous pH every 2 h to ensure steady improvement.

Dose adjustment

- Add 5% dextrose to the IV fluid when the plasma glucose falls to approximately 14–17 mmol/L (250–300 mg/dL) to prevent an unduly rapid decrease in plasma glucose concentration and hypoglycemia.

  It may be necessary to increase concentration of dextrose to 10% or even 12.5% while continuing to infuse insulin to correct the metabolic acidosis.

If infusion pump is not available

- In children with uncomplicated mild to moderate DKA, hourly or 2-hourly subcutaneous (SC) rapid-acting insulin analog (insulin lispro or insulin aspart) may be as effective as IV regular insulin infusion.

  This method should not be used in children whose peripheral circulation is impaired.

Dose SC: 0.15 units/kg every 2 h (initiated 1 h after the start of fluid replacement). The dose can be reduced to 0.1 unit/kg every 2 h if plasma glucose continues to decrease by >5 mmol/L (90 mg/dL) even after adding dextrose.

- *Subcutaneous administration of regular insulin every 4 hours is another alternative in mild DKA when IV infusion or rapid acting insulin analogs are not available. A suggested starting dose is 0.13–0.17 units/kg/dose of regular insulin every 4 h (0.8–1unit/kg/day in divided doses). Doses are increased or decreased by 10%–20% based on the blood glucose level before the next insulin injection.178 Dosing frequency may be increased to every 2 or 3 h if acidosis is not improving.*

Insulin management once ketoacidosis is resolved

- Consider stopping intravenous fluid therapy when ketosis is resolving and oral fluids are tolerated without nausea or vomiting.
- Do not change from intravenous insulin to subcutaneous insulin until ketosis is resolving
- Start subcutaneous insulin at least 30 minutes before stopping intravenous insulin.

4. Bicarbonate

Do not give intravenous sodium bicarbonate to children and young people with DKA.

Only consider bicarbonate if there is life threatening hyperkalaemia or in severe acidosis with impaired myocardial contractility. It is anticipated that this would only ever be done following discussion with an Intensivist.

5. Monitoring

a) Nursing Observations

Ensure full instructions are given to the senior nursing staff emphasizing the need for flow chart of hour-by-hour clinical observations, medications, fluids, and laboratory test results.

b) Monitoring during the initial treatment of DKA should include the following:

Hourly (or more frequently as indicated)

- Vital signs (heart rate, respiratory rate, blood pressure)
- Neurological assessment (Glasgow coma scale score or similar assessments for warning signs and symptoms of cerebral injury
- Amount of administered insulin
- Accurate fluid input (including all oral fluid) and output.
- Capillary blood glucose concentration (must be crosschecked against laboratory venous glucose)

At admission and every 2–4 h, or more frequently, as clinically indicated

- Serum electrolytes, glucose, blood urea nitrogen, calcium, magnesium, phosphate, and blood gases
- Blood beta-hydoxybutyrate concentrations, if available

c) Medical reviews

A physician should carry out a patient review at the start of treatment and then at least every 4 hours, and more frequently if:

- children are aged under 2 years
- they have severe DKA (blood pH below 7.1)
- there are any other reasons for special concern.

At each review assess the following:

- clinical status, including vital signs and neurological status
- results of blood investigations
- ECG trace
- cumulative fluid balance record.

Diagnosis and management of complications of DKA

Cerebral oedema:

Immediately assess a child or young person with DKA for suspected cerebral oedema if they have any of these early manifestations:

- Headache
- Agitation or irritability
- Unexpected fall in heart rate
- Increased blood pressure.

If cerebral oedema is suspected in these children or young people, treat immediately with the most readily available of

- Hypertonic saline (2.7% or 3% 2.5-5 ml/kg over 10-15 minutes) or
- Mannitol (20% 0.5-1 g/kg over 10-15 minutes)

If a child or young person develops any of these signs:

- Deterioration in level of consciousness
- Abnormalities of breathing pattern, for example respiratory pauses &/or drop in SaO2.
- Oculomotor palsies
- Abnormal posturing
- Pupillary inequality or dilatation.

  treat them Immediately for cerebral oedema using the most readily available of
- Hypertonic saline (2.7% or 3% 2.5-5 ml/kg over 10-15 minutes) or
- Mannitol (20% 0.5-1 g/kg over 10-15 minutes)

In addition, fluids should be restricted to ½ maintenance rates and inform senior staff immediately.

After starting treatment for cerebral oedema with mannitol or hypertonic saline immediately seek specialist advice on further management, including which care setting would be best for the child or young person.

- Do not intubate and ventilate until an experienced doctor is available
- Once the child is stable, exclude other diagnoses by CT scan - other intracerebral events may occur (thrombosis, haemorrhage or infarction) and present similarly. Treatment of suspected cerebral oedema should not be delayed through pending imaging.
- The effect of mannitol should be apparent within 15 minutes and typically lasts for 120 minutes. If there is no improvement with mannitol within 30 minutes a repeated dose of mannitol may be given (or hypertonic saline may be preferred). Mannitol may promote a brisk diuresis due to its osmotic effect and renal excretion.
- If mannitol was given initially and there is no response to mannitol treatment within 15-30 minutes then hypertonic saline may also be given and there is some suggestion that the effect of mannitol and hypertonic saline may be additive.

Other complications:

- Hypoglycemia and hypokalemia – avoid by careful monitoring and adjustment of infusion rates. Consideration should be given to adding more glucose if BG falling quickly even if still above 4 mmol/l.
- Systemic Infections – Antibiotics are not given as a routine unless a severe bacterial infection is suspected. Fever, raised lactate and raised inflammatory markers may all indicate possible concomitant infection.
- Aspiration pneumonia – avoid by nasogastric tube in vomiting child with impaired consciousness

Other associations with DKA require specific management:

Continuing abdominal pain is common and may be due to liver swelling, gastritis, bladder retention, ileus. However, beware of appendicitis and ask for a surgical opinion once DKA is stable. A raised amylase is common in DKA.

Education and follow-up

After a child or young person with known diabetes has recovered from an episode of DKA, discuss with them and their family members or caregivers (if appropriate) the factors that may have led to the episode.

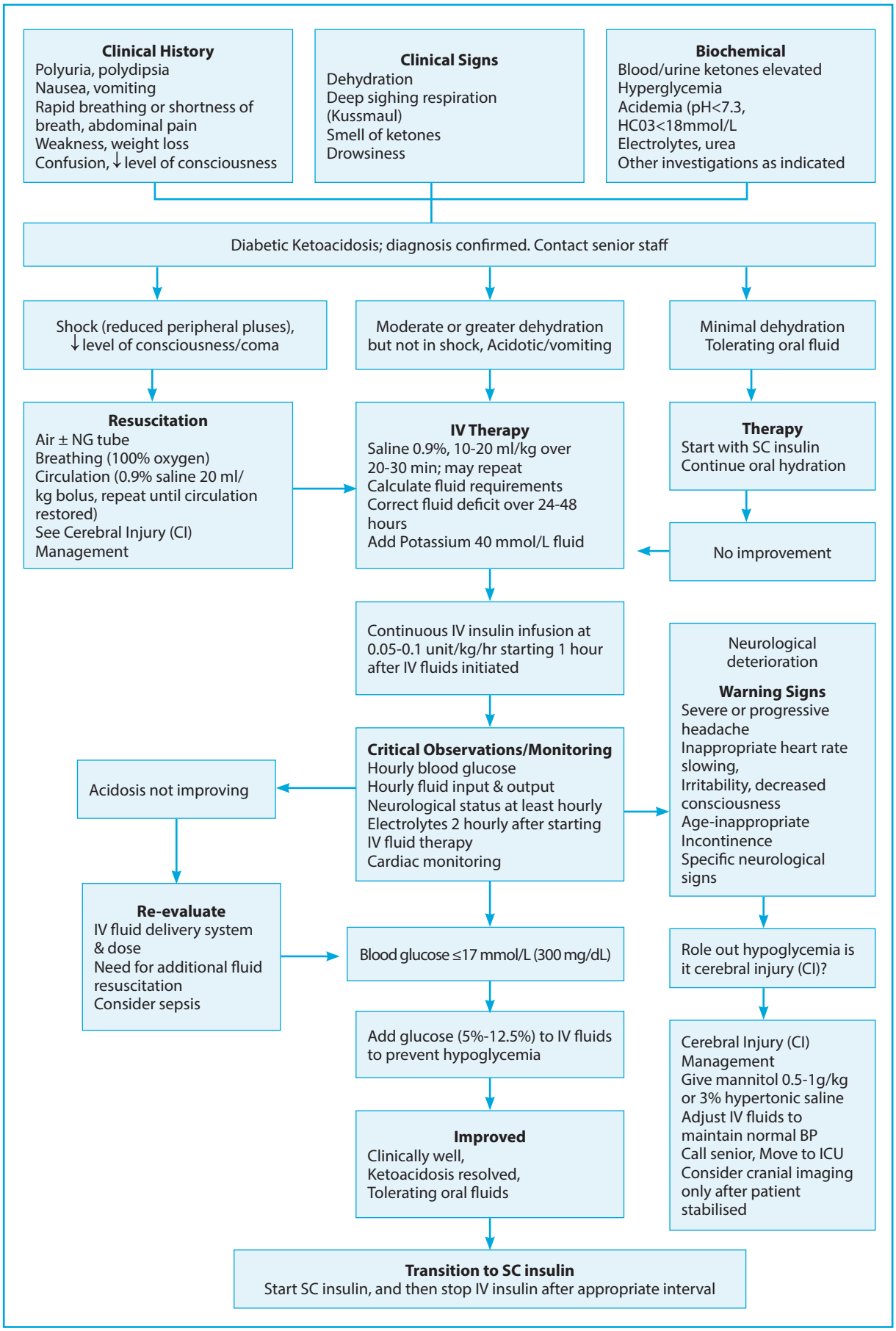


Figure 77: Algorithm for management of Diabetic Ketoacidosis

Outpatient care after diagnosis of type 1 diabetes

An outpatient clinic review should occur every 3 months OR more often if difficulties in managing diabetes are recognized, or the child is very young.

An outpatient visit should include an assessment of the following:

- Diabetes management review
  - Self-management skills - eating a healthy diet, engaging in exercise, taking appropriate amounts of insulin, adequacy of storage and transport of insulin, injection technique and self-monitoring of blood glucose
  - History of any hypoglycemia episodes, awareness, and method of treating hypoglycemia
- General Health and well being
  - History of intercurrent health problems such as infections, enuresis/nocturia, diabetes-related emergency and hospital/emergency department visits
  - Review of all current medications and supplements including medications from alternative medicine sources, and herbal preparations.
- Physical Examination
  - Height, weight, body mass index (BMI) and pubertal status
  - Blood pressure with reference to age-appropriate normal levels.
  - Oral mucosa and dentition (for dental caries, gingivitis)
  - Thyroid gland, cardiac, and abdominal (for hepatomegaly) examinations,feet examination (for corns, ingrown toenails and other lesions) as well as neurological function test (e.g., light touch, vibration sense).
  - Skin, particularly at the insulin administration and glucose monitoring sites, for evidence of lipohypertrophy, lipoatrophy and infection
- Laboratory Assessment – HbA1c every 3 months

Monitoring for complications and associated conditions of type 1 diabetes

- Advise children and young people with type 1 diabetes monitoring for:
  - Thyroid disease, at diagnosis and then annually until transfer to adult services
  - Moderately increased albuminuria (albumin:creatinine ratio [ACR] 3 to 30 mg/mmol) to detect diabetic kidney disease, annually from 12 years
  - Hypertension, annually from 12 years.
- Refer children and young people with type 1 diabetes for diabetic retinopathy screening from 12 years,
- Explain to children and young people with type 1 diabetes and their families or caregivers the importance of annual monitoring from 12 years for diabetic kidney disease.

Management of type 2 diabetes

Management goals include education for diabetes self-management, normalization of glycemia while minimizing hypoglycemia, weight management, dietary changes, increase in physical activity and exercise capacity and control of comorbidities and complications, including hypertension, dyslipidemia, nephropathy, sleep disorders, and hepatic steatosis.

At each clinic visit for children and young people with type 2 diabetes:

- measure height and weight and plot on an appropriate growth chart
- calculate body mass index (BMI). Check for normal growth or significant changes in weight, because these may reflect changes in blood glucose levels.

Education

- Diabetes education – in a culturally sensitive and age-appropriate manner that should include the pathophysiology and treatment as well as self-management specific for type 2 diabetes
- Diet modification with focus on:
  - Eliminating sugar-sweetened soft drinks and juices.
  - Reducing the intake of foods made from refined, simple sugars
  - Limiting intake of high-fat and/or calorie dense foods.
  - Reducing the intake of processed, prepackaged, and convenience foods.
  - Limiting portion sizes.
  - Reducing meals eaten away from home.
  - Increasing vegetable intake and limited use of fruit as a substitute for high-calorie and low nutrient foods.
  - Changing staple foods from enriched white rice and white flour to unpolished rice and whole grains with lower glycemic index to promote gradual absorption of glucose with meals.
- Diet education that targets the family
  - Teaching families to interpret nutrition fact labels.
  - Emphasizing healthy parenting practices related to diet and activity by promoting parental modeling of healthy eating habits,
  - Encouraging positive reinforcement of all goals achieved (e.g., no, or minimal weight gain, reduction in high caloric drinks).
  - Promoting meals eaten on schedule, in one place, preferably as a family unit, and with no other activity (television, computer, studying), and minimizing frequent snacking.
- Exercise education
  - Encourage youth to participate in at least 60 min of moderate to vigorous physical activity daily with muscle and bone strength training at least 3 days a week.
  - Reduce sedentary time, including watching TV, computer-related activities, texting, and video games to less than 2 h a day.
  - Promote physical activity as a family event, including daily efforts to be physically more active, such as using stairs instead of elevators, walking or bicycling to school and to shop, and doing household chores
- Sleep recommendations
  - Discuss sleep timing, duration, and quality.
  - Promote adequate quality sleep of 8–11 h a night according to age (9–11 h for children 5–13 years of age and 8–10 h for adolescents 14–17 years)

Glycemic monitoring and targets

- Fasting blood glucose targets are 70–110 mg/dL (4–6 mmol/L)
- Postprandial blood glucose targets are 70–140 mg/dL (4–8 mmol/L)
- HbA1c target is <7% and in most cases can be <6.5%
- During acute illness or when symptoms of hyper- or hypoglycemia occur, youth should perform more frequent testing and contact their diabetes care team for advice
- HbA1c concentration should be measured every 3 months, if possible.

Pharmacotherapy

Medications for youth-onset T2D should be initiated, preferably in collaboration with a pediatric endocrine subspecialist or pediatrician. At each visit regular medication use should be assessed, especially before adding additional medications.

- Initial therapy
  - If HbA1c <8.5% (69 mmol/mol) – metformin is the treatment of choice together with healthy lifestyle changes.
  - In youth with ketosis/ketonuria/ketoacidosis or HbA1c ≥8.5% (69 mmol/mol), insulin is required initially with once-a-day intermediate-acting or long-acting basal insulin (starting dose 0.25–0.5 units/kg).
  - Transition to metformin only can usually be achieved over 2–6weeks by decreasing the insulin dose by 30%–50% each time the dose of metformin is increased, with a goal of eliminating insulin therapy if this can be achieved with optimal glycemic management.
- Subsequent therapy
  - The goal of initial treatment should be to attain an HbA1c of <7.0% (53 mmol/mol)
  - If a HbA1c of <7.0% (53 mmol/mol) is not attained, consider addition of a second agent
  - If HbA1c >10%, initiation or re-initiation of basal insulin is the preferred option

Psychotherapy:

Most of the children need mental health support. Parents should be encouraged to talk to school teachers about support to the children.

Table 79: Recommendation for monitoring for complications and associated conditions of type 2 diabetes

Comorbidity/ Complication	Intervals for Screening	Screening Test
Hypertension	Starting at diabetes onset and at every diabetes related clinical encounter	BP measurement using appropriately sized cuff
Dyslipidemia	Yearly starting at diabetes onset (ideally after glycemic control achieved or within 3 months of diagnosis)	Fasting lipids
Nephropathy	Yearly starting at diabetes onset	Albumin to creatinine ratio
NAFLD (Non-Alcoholic Fatty Liver Disease)	Yearly starting at diabetes onset	ALT, AST
OSA (Obstructive Sleep Apnea)	Yearly starting at diabetes onset	Symptoms: snoring, sleep quality, apnea, morning headaches, daytime sleepiness
PCOS (Polycystic Ovary Syndrome)	Yearly (unless there is menstrual irregularity) starting at diabetes onset in pubertal females	Menstrual cycle history and evidence of hyperandrogenism
Retinopathy	Yearly starting at diabetes onset	Comprehensive eye examination with dilated pupils or retinal photography
Neuropathy	Yearly starting at diabetes onset	Symptoms of numbness, pain, cramps and paresthesia and tests of vibration sense, light touch, and ankle reflexes
Psychosocial health	Starting at diabetes onset and then every diabetes related clinical encounter	Symptoms of depression and disorder eating; and use validated screening questionnaires or referral for further evaluation
Social determinants of health	Starting at diabetes onset and then every diabetes related clinical encounter	Assess food security, financial concerns, social/school and community support
Smoking, vaping, drugs and alcohol use	Starting at diabetes onset and then every diabetes related clinical encounter	Clinical assessment on history
Pre-conception counseling	Starting at diabetes onset and then every diabetes related clinical encounter	History of sexual activity

CHAPTER-8

NEURODEVELOPMENTAL DISORDERS

NEURODEVELOPMENTAL DISORDERS

Introduction

Neurodevelopmental disorders (NDDs) is an umbrella term covering disorders related to the maturation of the CNS. In this module we will discuss Intellectual Disability, Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder (ADHD), and Epilepsy under neurodevelopmental disorders in children and adolescents. These disorders usually have a childhood onset, impairment or delay in functions related to central nervous system maturation, and a steady course rather than the remissions and relapses that tend to characterize many other mental health disorders.

Children and adolescents often present with symptoms of more than one condition and sometimes the symptoms overlap. The quality of home and social-educational environments influence children's and adolescents' wellbeing and functioning. Exploring and addressing psychosocial stressors along with opportunities to activate supports are critical elements of the assessment and management plan.

Quick Overview

- Assess for problems with development
- Assess for presence of other neurodevelopmental disorders.
- Management protocols
- Psychosocial Interventions

8.1. INTELLECTUAL DISABILITY

Intellectual Disability (ID) is defined as a condition of impairment of skills manifested during the developmental period, which contribute to the overall level of intelligence, i.e., cognitive, language, motor, and social abilities. The American Association on Intellectual and Developmental Disabilities (AAIDD) describes ID as characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. This disability originates before age 18.

Before the age of 5 years, a child with delay in motor and other milestones of development is considered to have Global Developmental Delay.

Table 80: Normal Developmental Milestones in Children

Age	Gross Motor	Fine Motor	Speech	Social
3 months	Neck holding	Follows moving objects, reaches for toys	Turns towards sound, babbling	Recognizes mother, social smile
6 months	Sits without support	Begins to pass things from one hand to the other	Monosyllables	Smiles at mirror image, knows if someone is a stranger
9 months	Stands with support	Moves things smoothly from one hand to the other, begins picking things up using finger and thumb (pincer grasp begins)	Bisyllables	May be afraid of strangers, stays around familiar adults
12 months	Stands without support, walks with support	Easily picks up things with finger and thumb (Mature pincer grasp)	Starts saying words	Cries when parents leave, Plays simple game like peek-a-boo
18 months	Walks without support, may walk up stairs holding and run	Scribbles	Says several single words	Simple pretend play like feeding a doll
2 years	Kicks ball, walks up and down stairs with two feet on each step, runs	Copies straight lines, builds tower of more than 4 blocks	2-4 words short sentences	Plays beside other children but starts including them in the games.
3 years	Rides tricycle, walks up and down steps with one foot on each step, runs easily	Copies circle, Builds tower of more than 6 blocks	Uses 2-3 sentences at a time	Takes turns in games, dresses and undresses self
4 years	Hops, stands on one foot for up to 2 seconds	Starts copying some capital letters	Tells stories, sings songs from memory	Make believe play, prefers to play with other children than alone. Can't tell between real and make believe.
5 years	Hops, may skip, swings and climbs	Copies triangle, and other geometric shapes	Tells simple stories using full sentences.	Sings, dances, acts. Is aware of gender. Can tell what's real and what's making believe.

Etiopathogenesis

Average prevalence of intellectual disability is 1%. Prevalence is higher in males in both adults and C&As.

Etiology and Risk Factors

Etiology of ID is heterogeneous. Injury, infections and toxins have become less prevalent causes because of improved antenatal care, while genetic factors have become more prominent. No specific etiology can be found in up to 40% of cases, particularly in mild ID. Environmental influences (e.g., malnutrition, emotional and social deprivation experienced, for example, in poorly run orphanages) can also cause or aggravate ID. These factors, which influence the development and function of the child's brain prenatally, perinatally or postnatally, can be divided into three groups: organic, genetic and socio-cultural.

Table 81: Common causes of Intellectual Disability

Prenatal	**Chromosomal Disorders** - Down's syndrome, Fragile X syndrome, etc **Inborn errors of metabolism** - Galactosemia, Phenylketonuria, Mucopolysaccharidoses, etc **Hypothyroidism, and endocrine disorders** Brain malformations such as genetic microcephaly, hydrocephalus, and myelomeningocele. **Adverse environmental influences** - Deficiencies such as iodine deficiency and folic acid deficiency - Severe malnutrition in pregnancy - Substances use such as alcohol (fetal alcohol syndrome), nicotine and cocaine during early pregnancy - Exposure to other harmful chemicals such as pollutants, heavy metals, and harmful medications such as thalidomide, phenytoin and warfarin in early pregnancy - Maternal infections such as rubella, syphilis, toxoplasmosis, cytomegalovirus and HIV - Others: such as excessive exposure to radiation and Rh incompatibility
Natal	**Complications of pregnancy** - Diseases in the mothers, such as heart and kidney disease, diabetes - Placental dysfunction - Severe prematurity, very low birth weight, birth asphyxia - Difficult or complicated delivery - Birth trauma - Neonatal: Septicemia, severe jaundice, hypoglycemia
Postnatal (During infancy and childhood)	- Brain infections such as tuberculosis, Japanese encephalitis, and bacterial meningitis - Head injury - Chronic lead exposure - Severe and prolonged malnutrition - Gross under stimulation

Manifestations and Subtypes

The manifestations of intellectual disability are mainly developmental delay in intellectual functioning and deficits in social adaptive functioning. According to the severity of the delay in intellectual functioning, deficits in social adaptive function and Intelligence Quotient (IQ), the psychiatric classifications describe four levels of severity:

Common Presentations of Child & Adolescent Developmental Disorders by Age Group

May be reported by the carers, self-reported or observed during the assessment process.

Table 82: Common Presentations of Child & Adolescent Developmental Disorders by Age Group

Age	Developmental Disorders
Infants and Young Children (age <5)	Poor feeding, failure to thrive, poor motor tone, delay in meeting expected developmental milestones for appropriate age (e.g. smiling, sitting, interacting with others, sharing attention, walking, talking and toilet training), • Delay in speech, poor communication, • Poor socialization, • Restrictive interest, repetitive and stereotypic behaviors, • Echolalia, • Solitary play, • Poor eye contact, • Poor pointing, etc.
Middle Childhood (age 6-12)	• Delay in reading and writing, • Delay in self-care such as eating, dressing, bathing, brushing teeth, clothing, and toileting. • Poor concept of time, money and space.
Adolescents (age 13-19)	• Poor school performance, • Difficulty understanding instructions, • Difficulty in social interaction and adjusting to changes.
All Ages	• Difficulty carrying out daily activities, or following instructions; • Difficulty in social interactions and adjusting, to changes; • Difficulties or oddities in communication, • Restrictive/repetitive patterns of behaviours, interests, and activities

Table 83: Adult attainment according to the degree of intellectual disability

Degree	IQ Range	Adult Attainment
Mild	50-70	Literacy + Self Help Skills ++ Good Speech ++ Semi-Skilled Work +
Moderate	35-50	Literacy +/- Self-Help Skills + Domestic Speech + Unskilled Work with or without supervision +
Severe	20-35	Assisted Self-Help Skills + Minimum Speech + Assisted with Household Chores +
Profound	Less than 20	Speech +/- Self Help Skills +/-
Note: +/- Sometimes Attainable, + Attainable, ++ Definitely Attainable		

Profound

IQ is usually below 20; profound intellectual disability accounts for 1% to 2% of all cases. These individuals cannot take care of themselves and have no language. Their capacity to express emotions is limited and poorly understood. Seizures, physical disabilities, and reduced life expectancy are common.

Severe

IQ is usually between 20 and 34; severe intellectual disability accounts for 3% to 4% of all cases. Every aspect of their development in the early years is distinctively delayed; they have difficulty pronouncing words and have a very limited vocabulary. Through considerable practice and time, they may gain basic self-help skills but still need support at school, home and in the community.

Moderate

IQ is usually between 35 and 49, accounting for about 12% of all cases. They are slow in meeting intellectual developmental milestones; their ability to learn and think logically is impaired but can communicate and look after themselves with some support. With supervision, they can perform unskilled or semiskilled work.

Mild

IQ is usually between 50 and 69 and accounts for about 80% of all cases. Development during their early life is slower than in normal children and developmental milestones are delayed. However, they can communicate and learn basic skills. Their ability to use abstract concepts, analyze and synthesize is impaired but can achieve reading and computing skills to grade three to six level. They can perform house-work, look after themselves and do unskilled or semiskilled work. They usually require some support.

Clinical Features

Speech

Children with intellectual disability (ID) usually have delayed language development and difficulties speaking and expressing themselves. The degree of severity varies with the level of impairment of intellectual ability. Mild cases can achieve language skills that are only a little poorer than children in the normal range of development. Severe or profound cases can't communicate at all or speak only a few words.

Perception

Children with ID are slow in reacting and perceiving environmental stimuli. They have difficulties distinguishing small differences in shape, size and color.

Cognition

The capacity to analyze, reason, comprehend and calculate, and for abstract thinking is often impaired to a greater or lesser extent according to severity. Children with mild ID are capable of achieving reading and mathematics skills to approximately the level of a typical child aged 9 to 12. Individuals with severe or profound IDs lack the capacity to comprehend, calculate or even understand what others say.

Concentration and memory

The ability to concentrate is low and narrow. By and large, memory is poor and they are slow at remembering although there are exceptions (e.g., savants). They have difficulties recalling and their memories are often inaccurate.

Emotion

Emotions are often naive and immature but may improve with age. Capacity for self-control is poor, impulsive and aggressive behavior is not uncommon. Some are timid, withdrawn and shy.

Movement and behavior

Children with ID often lack coordination, may be clumsy or show excessive movement. Meaningless or stereotyped movements (e.g., rocking, head-banging, teeth-biting, shouting, tearing clothes, pulling hair, playing with the genitals) are frequent in severe ID. Destructive, aggressive or violent behavior can also be observed. Self-injurious behavior (e.g. self-slapping or biting) may occur in moderate and severe ID.

Health problems associated with intellectual disability

Compared with normal children, children with ID are at a higher risk of having other health problems. The most prevalent health conditions are: epilepsy, cerebral palsy, anxiety disorders, oppositional defiant disorder, and autistic disorder.

Behavior problems

Symptoms like restlessness (continuously moving around, unable to sit in one place), poor concentration, impulsiveness, temper tantrums, irritability and crying are common. Other disturbing behavior, like aggression, self-injurious behavior (such as head banging) and repetitive rocking may also be seen (see the section on challenging behaviors below).

Sensory impairment

Visual and hearing problems are present in about 5%-10% of persons with ID. Other developmental disabilities, such as cerebral palsy, speech problems and autism can occur along with ID. Persons with multiple disabilities pose a big challenge in terms of providing care.

Diagnosis

Three basic criteria should be met for a diagnosis of intellectual disability:

- Significantly sub average intellectual functioning (IQ of 70 or below)
- Concurrent deficits or impairments in adaptive functioning in at least two of the following areas: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety
- Onset is before age 18 years.

8.2. AUTISM SPECTRUM DISORDER

Autism was initially described in 1948 by Leo Kanner as a syndrome of social communication deficits combined with repetitive and stereotyped behaviors in children. Autism Spectrum Disorder (ASD) refers to a neurodevelopmental condition defined by some behavioral features. Core clinical characteristics of ASD include impairments in two areas of functioning-social communication and social interaction, as well as restricted, repetitive patterns of behavior, interests or activities. These symptoms are present in the early developmental period, but may not be fully manifest until social demands exceed the child's limited capacities, or may be masked by learned strategies in later life.

Despite its early unfolding, this condition is not diagnosed until a few years later. The increased identification of this disorder, its emotional impact on families and the challenging financial demands associated with its treatment and support currently make ASD an important illness at the scientific, clinic and public health levels. The treatments now available can achieve a far better quality of life for sufferers. But it must be recognized that ASD cannot be cured yet.

Epidemiology

ASD is thought to affect about 1% of the general population, but severe cases are probably much less common. Autism is more common in boys than in girls, with a ratio of about 4:1.

Course

The onset of autism spectrum disorder occurs in early childhood, and problems are typically noted during the first or second year of life. For most, the disorder is chronic and lifelong. Some severely affected children show improvement as they mature, although others may worsen. Very few of these individuals are able to progress normally through school or to live independently. Nearly all of the defining features of the disorder, including social aloofness, language abnormalities, and rigid and ritualistic behavior, tend to persist into adulthood.

Clinical features

- Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following:
  - Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
  - Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
  - Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
- Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history
  - Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

  - Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take the same route or eat the same food every day).
  - Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
  - Hyper- or hypo reactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/ temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
- Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
- Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
- These disturbances are not better explained by intellectual disability or global developmental delay.

Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Assessment of Intellectual Disability and Autism Spectrum Disorder

The assessment of intellectual disability and autism spectrum disorder has been combined into a single assessment flowchart, with the aim to identify C&A with symptoms of ID or ASD. This helps in increasing sensitivity of detection and prevents missing out of cases, also it prevents the need of specialized human resource for initial evaluation. This can help in early identification and referral of the C&A for further evaluation at a higher center.

Assessment

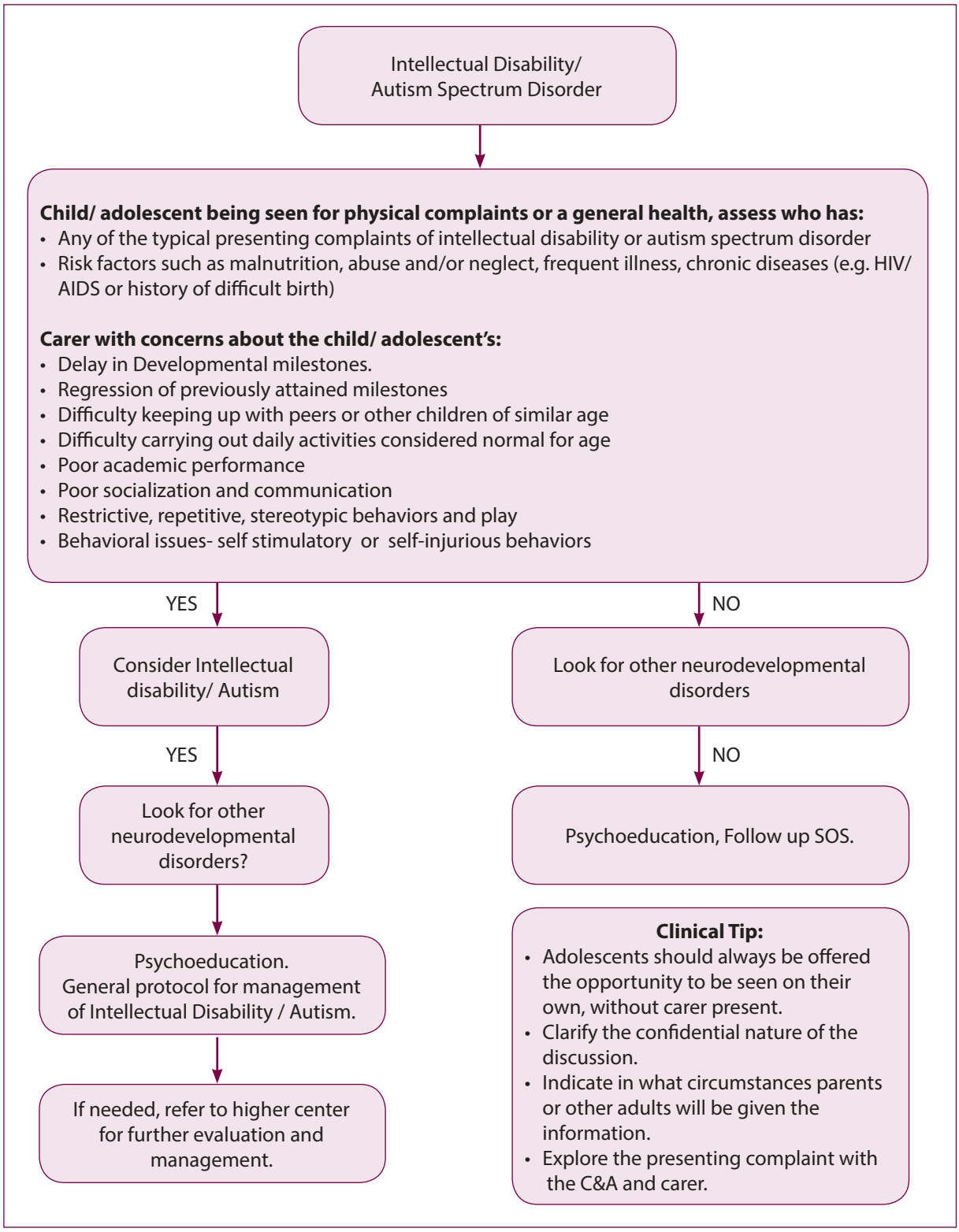


Figure 78: Intellectual Disability/ Autism Spectrum Disorder

General Protocol for Management of Intellectual Disability/ Autism Spectrum Disorder.

- Provide guidance on child/ adolescent well-being.
- Provide psychoeducation to the person and carer and parenting advice guidance on developmental disorders.
- Provide carer support.
- Liaise with teachers and other school staff
- Link with other available resources in the community such as Community-Based Rehabilitation.
- Offer Parent Skills Training, when available
- Refer children with developmental delays to healthcare facilities for further assessment, advice on management plans and family planning.
- Refer for Speech Therapy, Occupational Therapy
- Home based training for carers on socialization and communication.
- Extensive engagement and stimulation
- Ensure appropriate follow-up.

Psychoeducation for Intellectual Disability/ Autism Spectrum Disorder

Encourage the carer to:

- Learn what the child's strengths and weaknesses are and how they learn best, what is stressful to the child and what makes him/her happy, and what causes problem behaviours and what prevents them.
- Learn how the child communicates and responds (using words, gestures, non-verbal expressions, and behaviors).
- Help the child develop by engaging with her/ him in everyday activities and play. Children learn best during activities that are fun and positive.
- Involve them in everyday life, starting with simple tasks, one at a time. Break complex activities down into simple steps so that the child can learn and be rewarded one step at a time.
- Make predictable daily routines by scheduling regular times for eating, playing, learning, and sleeping.
- Keep their environment stimulating: avoid leaving the child alone for hours without someone to talk to and limit time spent watching TV and playing electronic games.
- Keep them in a school setting for as long as possible, attending mainstream schools even if only part-time.
- Use balanced discipline. When the child/adolescent does something good, offer a reward. Distract the child/adolescent from things they should not do.
- DO NOT use threats or physical punishments when the behaviour is problematic
- Persons with developmental disorders may often have associated behavioural problems that are difficult for the carer to manage. See guidance for improving behaviours.
- Promote and protect the human rights of the C&A and family and be vigilant about maintaining human rights and dignity.
  - Educate carer to avoid institutionalization.
  - Promote access to health information and services.
  - Promote access to schooling and other forms of education.
  - Promote access to occupations.
  - Promote participation in family and community life.

Clinical Tip:
If exposure to one or more types of maltreatment was identified in the assessment, assess ongoing exposure and risks to the child/ adolescent.

Follow up:

- If the C&A is improving, continue the same management plan.
  Offer Regular Follow up.
- If no improvement, provide psychoeducation, advice on parenting as appropriate and advice regular follow-up to a higher center for further assessment and management.

Recommended on Frequency of Contact

- Schedule the second appointment within 1 week.
- Initially maintain regular contact via telephone, home visits, letters or contact cards more frequently, eg monthly for the first 3 months.

Clinical Tip:

- Adolescents should always be offered the opportunity to be seen on their own, without carers present.
- Clarify the confidential nature of the discussion.
- Indicate in what circumstances parents or other adults will be given the information.
- Explore the presenting complaint with the C&A and carer.

At every visit:

- For children under 5 years, monitor child development.
  - Assess for the presence of any new problem or symptom related to mood, behaviour or development/ learning. For adolescents, assess for the presence of worsening mood (irritable, easily annoyed or frustrated, down or sad) or suicidal thoughts.
  - Assess for other neurodevelopmental conditions or other CAMH problems, refer to the appropriate module for assessment.
  - Explore and address psychosocial stressors in the home, school or work environment, including exposure to violence or other forms of maltreatment.
  - Assess opportunities for the C&A to participate in family and social life.
  - Assess the carer's needs and support available to the family.
  - Monitor attendance at school.
  - Review management plan and monitor adherence to psychosocial interventions.

8.3. ATTENTION DEFICIT HYPERACTIVITY DISORDER

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neuro-developmental disorder seen in children and adolescent, although phenomenologically it has a behavioral presentation. This disorder begins before the age of 12 years and is characterized by difficulty paying attention (inattention), excessive activity (hyperactivity) and acting without regard to consequences (impulsivity), which are otherwise not appropriate for an individual's age. Some individuals with ADHD also display difficulty regulating emotions. In C&A, problems in paying attention may result in poor school performance. Only C&A with a moderate to severe degree of psychological, social, or educational impairment in multiple settings should be diagnosed as having ADHD.

Many children with ADHD in childhood have co-morbid behavioral disorders in their later years. There are significant comorbidities among these disorders and also with other Child and Adolescent Mental Health (CAMH) conditions.

Quick Overview

- Assess for problems with attention or overactivity
- Assess for the presence of other CAMH conditions.
- Management Protocols for Attention Deficit Hyperactivity Disorder (ADHD)
- Psychosocial Interventions

Epidemiology

ADHD is one of the most common mental disorders among children and adolescents, with approximately 5% of children under 18 years affected worldwide with boys out-numbering girls by three to one.

Course

ADHD is a chronic disorder and symptoms often persist into adult life. The persistence of symptoms seems to be associated with severity. Patients with more severe symptoms and combined type ADHD are at higher risk for persistence. The durability of symptoms is also associated with negative outcomes such as lower academic achievement, marital problems and marriage dissatisfaction, divorce, difficulty dealing with offspring, lower job performance, unemployment, maintaining job positions below the individual's potential, involvement in traffic accidents and increased risk for other psychiatric disorder.

Comorbidity

Children with ADHD often suffer from other psychiatric conditions. Systematic screening for the presence of other mental disorders is essential. Children and adolescents with ADHD are more likely to have features of oppositional defiant disorder, anxiety disorders, conduct disorders and depression.

Causes and Risk Factors

The etiology of ADHD is considered to be multi-factorial, that is, multiple environmental, genetic and biological factors play a role in increasing the risk for the disorder.

- Genetics
- Brain development – studies have shown that areas of the brain that control attention appear to be less active in children with ADHD.
- Intellectual disabilities – children with intellectual disabilities are twice as likely to have behavioural disorders.
- Learning difficulties –problems with reading and writing are often associated with behaviour problems.
- Gestation and birth – difficult pregnancies, Intra-uterus exposure to tobacco, prematurity and low birth weight may contribute in some cases to the child's problem behaviour later in life.
- Temperament – children who are difficult to manage, temperamental or aggressive from an early age are more likely to develop behavioural disorders later in life.
- Family life – behavioural disorders are more likely in dysfunctional families where harsh disciplining practices, physical abuse, neglect etc are present.

However, each risk factor explains only a small proportion of the risk of developing the disorder. None of the risk factors identified are necessary for the development of ADHD, they are nonspecific and related to other mental disorders and neuro-developmental abnormalities as well.

Clinical Features

For a diagnosis of ADHD, the symptoms should appear before a person is twelve years old, be present for more than six months, and cause problems in at least two settings (such as school, home, or recreational activities). ADHD is divided into three subtypes- inattentive, hyperactive and mixed type.

ADHD- Inattentive type

A child or adolescent who has most or all of the following symptoms;

- Be easily distracted, miss details, forget things, and frequently switch from one activity to another
- Have difficulty maintaining focus on one task
- Become bored with a task after only a few minutes, unless doing something they find enjoyable
- Have difficulty focusing attention on organizing or completing a task
- Have trouble completing or turning in homework assignments, often losing things (e.g., pencils, toys, assignments) needed to complete tasks or activities
- Appear not to be listening when spoken to
- Daydream, become easily confused and move slowly
- Have difficulty processing the information as quickly and accurately as others
- Struggle to follow instructions
- Have trouble understanding details; overlooks details

ADHD- Hyperactive/impulsive type

A child or adolescent may have most or all of the following symptoms;

- Fidget or squirm a great deal
- Talk nonstop
- Dash around, touching or playing with anything and everything in sight
- Have trouble sitting still during dinner, school, and while doing homework
- Be constantly in motion
- Have difficulty performing quiet tasks or activities
- Be impatient

- Blurt out inappropriate comments, show their emotions without restraint, and act without regard for consequences
- Have difficulty waiting for things they want or waiting their turn in games
- Often interrupt conversations or others' activities

ADHD -Mixed type

Features of inattention and hyperactivity are present.

Table 84: Changes in ADHD symptoms from childhood to adolescence

Symptoms	Pre-school years	Primary school years	Adolescence
Inattention	• Short Play Sequences (less than 3 minutes) • Leaving Activities Incomplete • Not Listening	• Brief Activities (less than 10 years) • Premature changes of activities • Forgetful, disorganized, distracted	Less persistence than peers (less than 30 minutes)
Overactivity	"Whirlwind"	Restless when calm expected	Fidgety
Impulsivity	Does not listen • No sense of danger (hard to distinguish from oppositionality)	Acting out of turn, interrupting others children and blurting out answers • Thoughtless rule breaking • Intrusions on peers, accidents	Poor self- control • Reckless risk-taking behaviors

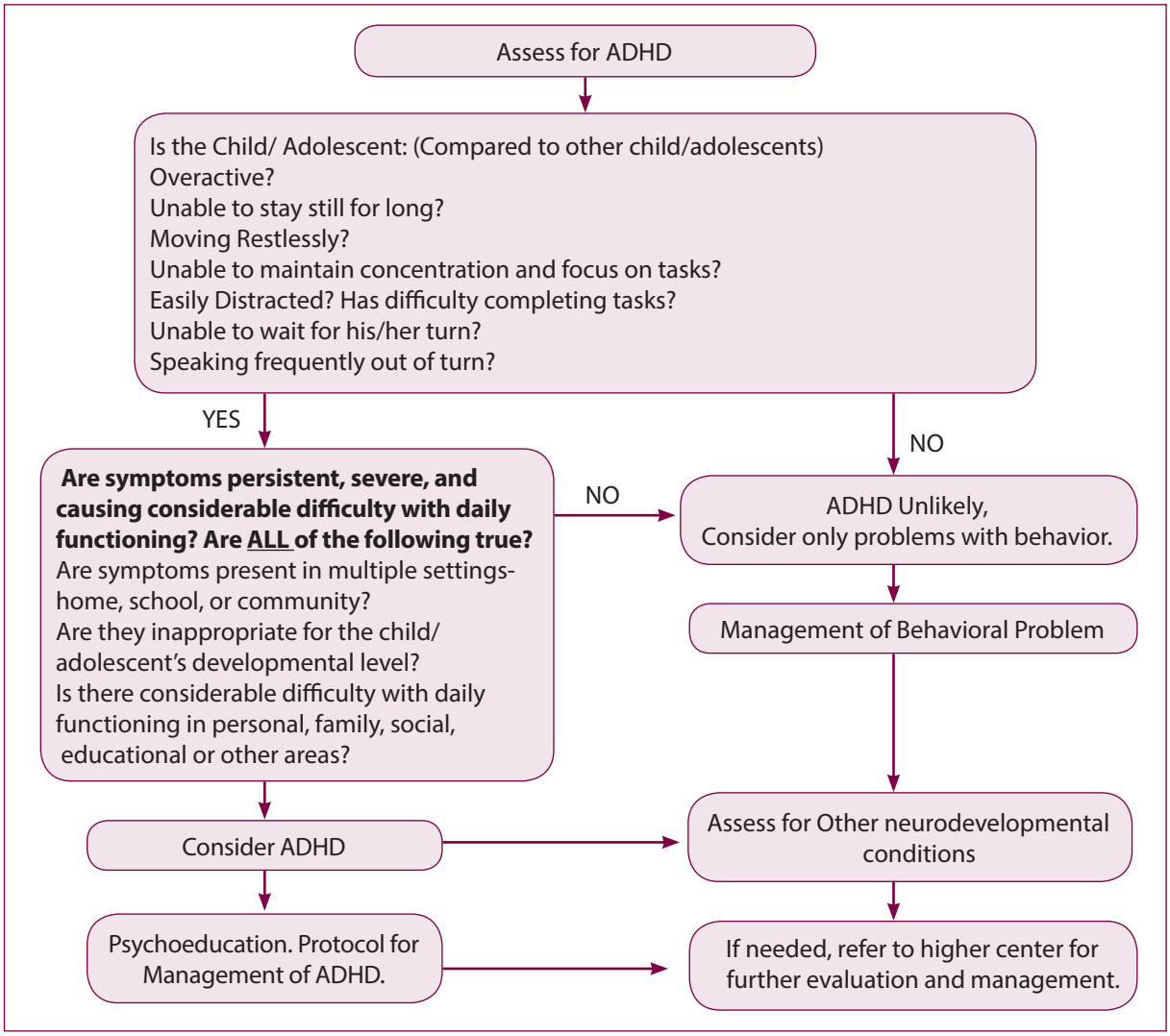


Figure 79: Assessment of ADHD

Management

- Provide guidance on child/ adolescent well-being.
- Provide psychoeducation to persons and carers and parenting advice.
- Guidance on improving behaviour.
- Assess for and manage stressors, reduce stress and strengthen social supports.
- Liaise with teachers and other school staff.
- Link with other available resources in the community
- Offer follow-up

Psychoeducation to C&A and carers and parenting advice

- Psychoeducate the C&A and Carer about ADHD.
- Explain the difficulty to the carer and the C&A as appropriate and help them identify strengths and resources.
- Praise the carer and the child/adolescents for their efforts.
- Explain to the carer that parenting a C&A with ADHD can be rewarding but also very challenging.
- Explain that C&A with ADHD should not be blamed for having the disorder. Encourage carers to be kind and supportive and show love and affection.

Guidance For Improving Behavior

Encourage the Carer to:

- Give loving attention, including playing with the child every day
- Provide opportunities for the adolescents to talk to you.
- Be consistent about what your C&A is allowed and not allowed to do. Give clear, simple, and short instructions on what the child should and should not do.
- Give the child/adolescent simple daily household tasks to do that match their ability level and praise them immediately after they do the task.
- Praise or reward the C&A when you observe good behaviour and give no reward when behaviour is problematic.
- Find ways to avoid severe confrontations or foreseeable difficult situations.
- Respond only to the most important problem behaviours and make punishment mild (e.g. withholding rewards and fun activities) and infrequent compared to the amount of praise.
- Put off discussions with the child/adolescent until you are calm. Avoid using criticism, yelling, and name-calling.
- DO NOT use threats or physical punishment, and never physically abuse the C&A. Physical punishment can harm the child-carer relationship; it does not work as well as other methods and can make behaviour problems worse.
- Encourage age-appropriate play (e.g. sports, drawing or other hobbies) for adolescents and offer age-appropriate support in practical ways (e.g. with homework or other life skills).

Practical tips that can be applied in Schools to support C&A with CAMH problems:

- Provide opportunities for the child/adolescent to use their skills and strengths.
- For C&A who get distracted easily,
- Ask them to sit at the front of the class.
- Give the student extra time to understand and complete assignments.
- Divide long assignments into smaller pieces and assign one piece at a time.
- Provide extra praise for effort and rewards for achievements.
- DO NOT use threats or physical punishments or excessive criticism.

- For students with significant difficulties in the classroom,
- Recruit a volunteer to come to class to provide one-on-one attention or pair the student with a peer who can provide support or help with learning.
- If the child/adolescent has been out of school,
- Help them return as soon as possible by creating a gradually increasing reintegration schedule.
- During the reintegration period, the student should be excused from quizzes and exams.
- For C&A with behavioral problems,
  - Refer to the guidance for improving behavior.
  - DO NOT use threats or physical punishments or excessive criticism.
  - Use alternative disciplinary methods, such as time-out, taking away privileges, detention periods, etc.

Brief psychological treatments

This guide does not provide specific protocols to implement brief psychological interventions. When needed, the C&A and the carer can be referred for appropriate psychological treatment such as parent skills training, interpersonal therapy and behavioural therapy.

Table 85: Pharmacological Intervention for ADHD

(To be initiated after consultation with a specialist/ consultant)

Medication	Dosing	Side effects	Caution/ Contraindication
Methylphe-nidate (Not available in Nepal)	Safety and efficacy not established for children bellow 6 years. **Children greater than 6 years:** (immediate release tablets) **Initial:** 0.3mg/kg/dose PO before breakfast and before lunch, may increase by 0.1mg/kg/dose weekly. **Maintenance:** 0.3-1mg/kg PO before breakfast and before lunch. Not to exceed 2mg/kg/day PO in divided doses.	**Common:** Insomnia, decreased appetite. **Rare:** Can affect on growth hormone, height should be monitored. Can worsen psychotic/manic symptoms	Use with caution in any child and adolescent with a cardiac disease (ECG monitoring is advised before prescribing medication). Can decrease the seizure threshold. Can exacerbate tic disorders. Potential for abuse of medication, strict monitoring required.
Atomoxetine (Available in Nepal)	Safety and efficacy are not established for children below 6 years of age. **Children above 6 years:** **Initial:** 0.5mg/kg per day once morning or divided dose, then after a week increase to 1.2mg/kg per day **Maintenance:** Maximum dose in children up to 70 kg is 1.4mg/kg per day or 100mg/day whichever is less.	**Common:** Dry mouth, Sedation, insomnia, fatigue, decreased appetite, nausea. **Rare:** Priapism	Use with caution in C&A with cardiac diseases. Can cause the induction of hypomania/ mania. Reports of an increase in suicidal ideations (monitor for same)

Follow up:

- If the C&A is improving, continue the same management plan. Offer regular follow-up.
- If no improvement, provide psychoeducation, advice on parenting as appropriate and advice regular follow-up to a healthcare facility for further assessment and management.

Clinical Tip:

- Adolescents should always be offered the opportunity to be seen on their own, without carers present.
- Clarify the confidential nature of the discussion.
- Indicate in what circumstances parents or other adults will be given the information.

Clinical Tip:

- If exposure to one or more types of maltreatment was identified in the assessment, assess ongoing exposure and risks to the child/ adolescent.

Recommended on Frequency of Contact

- Schedule the second appointment within 1 week.
- Initially maintain regular contact via telephone, home visits, letters or contact cards more frequently, eg monthly for first 3 months.

At every visit:

- For children under 5 years, monitor child development.
  - Assess for the presence of any new problem or symptom related to mood, behaviour or development/learning. For adolescents, assess for the presence of worsening mood (irritable, easily annoyed or frustrated, down or sad) or suicidal thoughts.
  - Assess for other neurodevelopmental disorders, refer to the appropriate module for assessment.
  - Explore and address psychosocial stressors in the home, school or work environment, including exposure to violence or other forms of maltreatment.
  - Assess opportunities for the C&A to participate in family and social life.
  - Assess the carer's needs and support available to the family.
  - Monitor attendance at school.
  - Review management plan and monitor adherence to psychosocial interventions.

8.4. EPILEPSY

Introduction

Epilepsy is a chronic non-communicable disorder of the brain, characterized by recurrent unprovoked seizures. Epilepsy is one of the most common neurological disorders and with proper treatment, can be well controlled in the majority of C&A.

Epilepsy has many causes. It may be genetic. Epilepsy may occur in C&A who have a history of birth trauma, brain injury (including head trauma), or brain infections. In some C&A, no cause may be identified.

Seizures are caused by abnormal electrical activity in the brain and are of two types: convulsive and non-convulsive. Non-convulsive epilepsy has features such as change in mental status while convulsive epilepsy has features such as sudden abnormal movements, including stiffening and shaking of the body. The latter is associated with greater stigma and higher morbidity and mortality. This module covers only convulsive epilepsy.

Quick Overview

- Emergency Assessment and Management of Acute Convulsions (Seizures)
- Asses for Epilepsy
- Assess for other priority CAMH conditions
- Management protocol for Epilepsy
- Psychosocial Intervention
- Follow-up

Epidemiology

- Prevalence: It occurs in 0.8-1.2% of the general population.
- Age of Onset: In many cases, the onset is during childhood or adolescence.
- Male/ Female preponderance: No significant difference in prevalence between males or females
- Course: If left untreated, it is a chronic recurrent condition, with significant morbidity, mortality, stigma, and associated mental health issues.
- Outcome: When treated early, most cases can achieve seizure-free status after 2- 5 years of regular medication. Even if long term medication is needed, the patients can lead a normal life if seizure is managed adequately.

Etiology/ Risk Factors for Seizures:

- Genetic
- Complications during childbirth
- Head injury
- Tumours
- Brain infections: Meningitis, encephalitis, cerebral malaria
- Neurocysticercosis
- Metabolic Disorders
- Endocrine Disorders

- Electrolyte Imbalance
- Stroke
- Some seizures have no known cause

Note: People with epilepsy only rarely have children with epilepsy

Types of Seizures:

- Generalized Tonic-Clonic Seizure
- Partial Seizure
- Complex partial Seizure
- Absence Seizure
- Febrile Seizure

Clinical Features of Generalized Tonic Clonic Seizure

- Each episode very closely resembles the other episodes of seizures
- Pre-ictal Stage: can have headaches, flashes of light, confusion or alteration of consciousness
- Loss of consciousness is usually total in the case of GTCS
- Tonic-clonic contraction of the whole body- jerky rhythmic involuntary body movements
- Uprolling of eyes- eyes roll upwards, with white sclera visible
- Clinching of teeth/ tongue bite- may cause bleeding, blood mixed frothing
- Frothing from mouth
- Loss of bowel/ bladder- urine or stool may be passed during the episode of seizure
- Injury- can sustain cut injuries, bruises, hematomas, dislocation of joints, burns due to falling on fire, etc.
- Post-ictal stage- may appear as confusion or alteration of consciousness, headaches, body aches, the patient may fall asleep
- Seizure episodes can be life-threatening

Pseudoseizures

These may looks like seizure but are not seizures. Conversion disorders may present as pseudoseizures. The following characteristics can differentiate it from seizures:

- Atypical presentation- different presentation at different episodes
- No total loss of consciousness
- Usually caused by stress- the episodes may follow a stressful event or in the presence of an ongoing stressful situation
- No associated injury- no bodily injury like cuts, hematoma, bruises, etc
- No frothing/clinching of teeth/tongue bite
- No loss of bowel/bladder control
- Eyes usually closed, if not, no uprolling like mentioned in the seizure
- No pre-ictal or post-ictal-like symptoms- the patient usually has normal conscious states before and after the episodes.
- Pseudoseizures are not life-threatening conditions

Table 86: Differences between Seizures and Pseudoseizures/ Conversion Disorder

Features	Convulsive Seizures	Pseudoseizure/ conversion disorder
Duration	Few minutes	Minutes to hours
Abnormal movement	Synchronous, rhythmic	Non- rhythmic, Non- synchronous, variable
Eyes	Uprolling	No uprolling/ closed
Tongue	Bitten/ bruised	No injury
Incontinence	Possible urine/ stool incontinence	No incontinence
Post episode	Confusion, body aches, vomiting, headache, drowsiness	No such features, back to usual self
Injury	Bodily injuries possible due to fall	No significant injury sustained

Management of Epilepsy

The management of Epilepsy can be approached under two headings:

- Emergency management of seizures and
- General management of epilepsy.

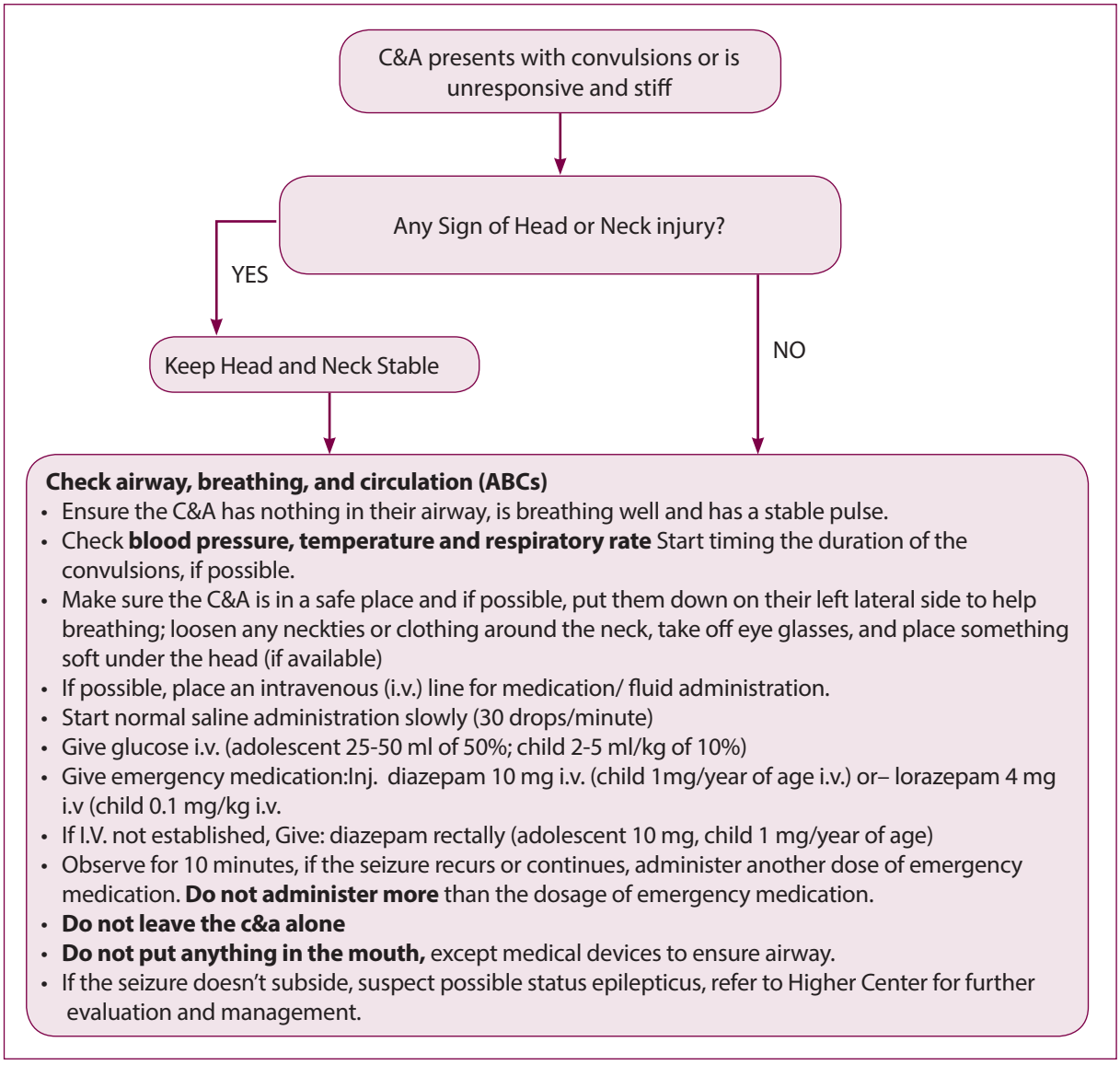


Figure 80: Emergency Presentation of Acute Seizure

If Status Epilepticus is suspected, if possible:

- Give one of the following medications intravenously:
  - Valproic acid:
- 20 mg/kg i.v. once up to a maximum dose of 1 g, over 30 min
  - Phenobarbital:
- 15-20 mg/kg i.v. up to a maximum dose of 1 g, over 100 mg/min
- If no i.v. access can use the same dose of i.m. Phenobarbital.
  - Phenytoin:
- 15-20 mg/kg i.v. up to a max dose of 1 g, over 60 min
- use the second i.v. line (Different from diazepam)
- Phenytoin causes significant damage if extravasates, must have good i.v. Line!
- If Seizures subside, assess for epilepsy. If seizures don't subside, refer to a higher centre.

Note: If seizure occurs in a pregnant adolescent girl, suspect eclampsia and refer to a higher centre immediately.

Assessment

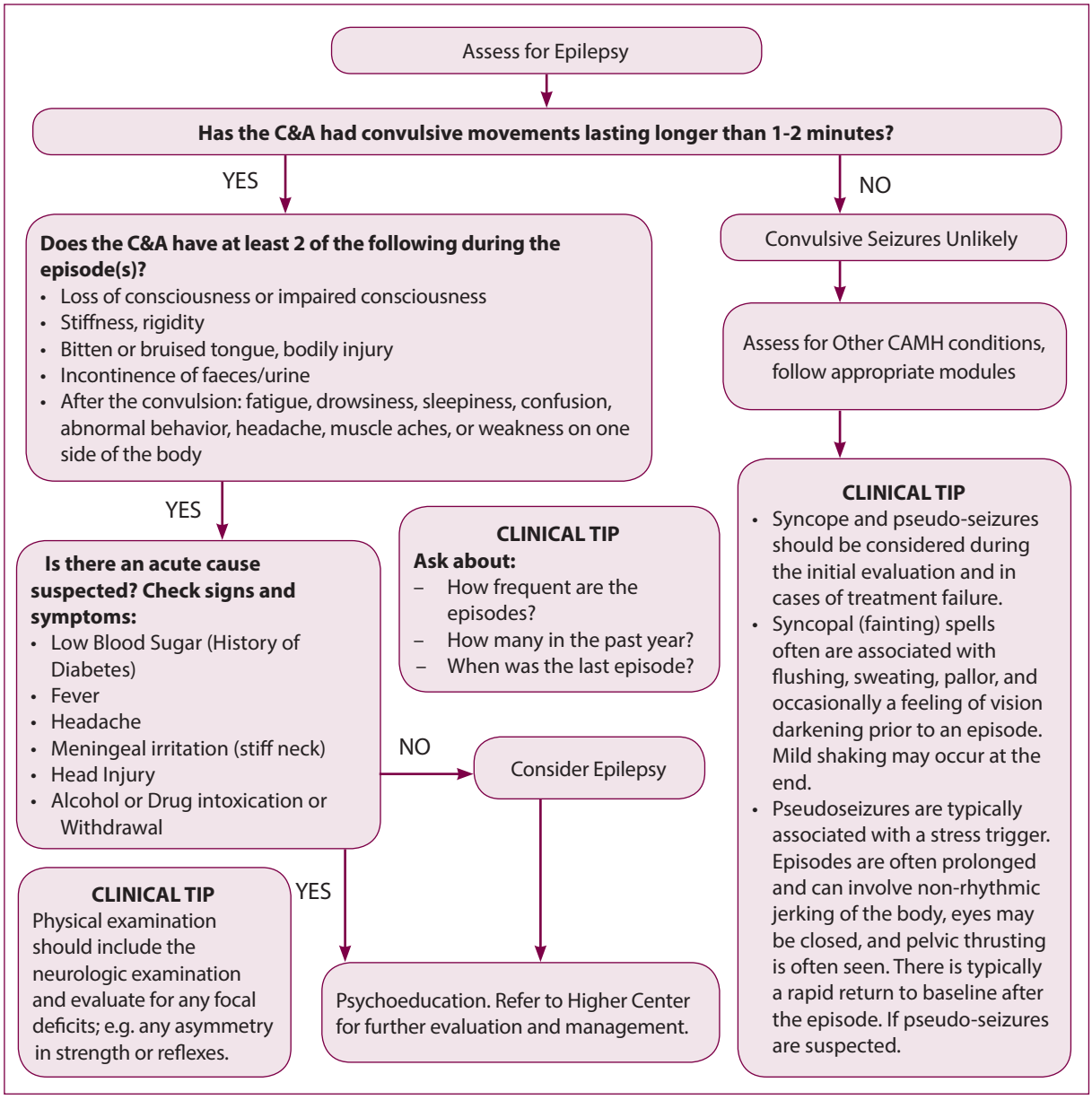


Figure 81: Assessment of epilepsy

Management

Psychosocial Interventions

Psychoeducation

- Provide information on: "What is a convulsion/epilepsy" and the importance of medication
  - "A convulsion is caused by excess electrical activity in the brain – it is not caused by witchcraft or spirits."
  - Epilepsy is the recurrent tendency for convulsions."
  - "It is a chronic condition, but if you take your medicine as prescribed, in the majority of C&A it can be fully controlled."
  - The C&A may have several people helping them take care of their convulsions. Discuss this with the C&A.
  - Ask the C&A and carers to let you know if they are seeing a traditional or a faith healer, showing respect for this, but emphasizing the need for being seen at a healthcare facility. The C&A and carers should also be informed that medicines and herbal products can sometimes have adverse interactions, so the health care providers must know about everything they take.

Clinical tip:

- Seizures lasting greater than 5 minutes are a medical emergency – one should seek help immediately.
- Most C&A with epilepsy can have normal lives with good adherence to treatment.

- Provide information on: How carers and school staff can manage convulsion at home and school
  - Lay C&A down, on their side, head turned to help to breathe.
  - Do not put anything in their mouth or restrain the C&A.
  - Ensure the C&A is breathing properly.
  - Stay with C&A until the convulsion stops and they wake up.
  - Sometimes C&A with epilepsy knows that a convulsion is imminent. They should lie down somewhere safe if they have that feeling.
  - Epilepsy is not contagious. You cannot catch the disorder by assisting the C&A experiencing convulsions.
- Provide information on: When to get medical help.
  - When a C&A with epilepsy appears to have trouble breathing during a convulsion, they need immediate medical help.
  - When a C&A with epilepsy has a convulsion lasting longer than 5 minutes outside of a health facility, they need to be taken to one.
  - When a C&A with epilepsy is not waking up after a convulsion, they need to be taken to a health facility.
- Promote functioning in daily activities and community life
  - Refer to Essential Care and Practice (ECP) for interventions that promote functioning in daily living and community life
  - In addition, inform carers and C&A with epilepsy that
- C&A with epilepsy can lead normal lives. They can, in the future, marry and have children.
- Parents should not remove children with epilepsy from school.
- C&A with epilepsy can, in the future, work in most jobs. However, they should avoid jobs with a high risk of injury to themselves or others (e.g. working with heavy machinery).

- C&A with epilepsy should avoid cooking on open fires and swimming alone.
- C&A with epilepsy should avoid alcohol and recreational substances, sleeping too little, or going to places with flashing lights.
- Local driving laws related to epilepsy should be observed.
- C&A with epilepsy may qualify for disability benefits.
- Community programs for C&A with epilepsy can assist in schools and community, and support for both the C&A and family.

Pharmacological Interventions

- Choose a medication that will be consistently available.
- Start with only one medication at the lowest starting dose.
- Increase the dose slowly until convulsions are controlled.
- Considering monitoring blood count, blood chemistry, and liver function tests if available.

Note:

- Check for drug-drug interactions. When used together, anti-epileptics may increase or reduce the effect of other anti-epileptics. Anti-epileptics may also reduce the effect of hormonal birth control, immunosuppressants, antipsychotics, methadone, and some anti-retrovirals.
- Rarely, can cause severe bone marrow depression, hypersensitivity reactions including Stevens - Johnson syndrome, altered Vitamin D metabolism and Vitamin K-deficient hemorrhagic disease in newborns.
- When possible, avoid the use of sodium valproate in pregnant adolescents due to the risk of neural tube defects.
- All anticonvulsant medications should be discontinued slowly as stopping them abruptly can cause a seizure breakthrough.

Table 87: Anti-epileptic Medications

Medication	Oral Dosing	Side Effects	Contraindications/ Cautions
Carbamazepine	**Adolescents:** Start 100-200mg daily in 2-3 divided doses, increase by 200mg each week (Maximum 1400mg daily) **Children:** Start 5mg/kg daily in 2-3 divided doses, increase by 5mg/kg each week (Maximum (40mg/kg daily or 1400mg daily)	**Common:** Dizziness, drowsiness, nausea, vomiting, ataxia, dry mouth. **Rare/ Serious:** Steven-Johnson's syndrome, Liver failure, Syndrome of Inappropriate Diuretic Hormone secretion (SIADH)	Documented hypersensitivity, History of bone marrow suppression, jaundice, hepatitis, pregnancy/ lactation
Phenobarbital	**Adolescents:** Start 60mg daily in 1-2 divided doses, increase weekly by 2.5-5mg/kg depending on tolerance (Maximum 180mg daily) **Children:** Start 2-3mg/kg daily in 2 divided doses, increase weekly by 1-2 mg/kg depending on tolerance (Maximum 6mg/ kg daily)	**Common:** Sedation, hyperactivity in children, ataxia, nystagmus, sexual dysfunction, depression. **Rare/ Serious:** Liver Failure, Decrease bone density, Steven-Johnson's Syndrome.	Documented hypersensitivity, porphyria, liver disease, kidney disease, pregnancy/ lactation.

Medication	Oral Dosing	Side Effects	Contraindications/ Cautions
Phenytoin	**Adolescents:** Start 150-200mg daily in two divided doses, increase by 50 mg every 3-4 weeks (Maximum 400mg daily) **Children:** Start 3-4mg/kg daily in 2 divided doses, increase by 5 mg/kg every 3-4 weeks (Maximum 300mg daily)	**Common:** Sedation, confusion, dizziness, tremor, motor twitching, ataxia, double vision, nystagmus, slurred speech, nausea, vomiting, constipation. Rare/ Serious: Hematologic abnormalities, hepatitis, polyneuropathy, gum hypertrophy, acne, lymphadenopathy, increase in suicidal ideation	Hypersensitivity, cardiovascular disease, liver and kidney disease.
Sodium Valproate	**Adolescents:** Start 400mg daily in 2 divided doses, increase by 500 mg each week (Maximum 3000mg daily) **Children:** Start 15-20mg/kg daily in 2-3 divided doses, increase each week by 15mg/kg (Maximum 40mg/kg daily)	**Common:** Sedation, headache, tremor, ataxia, nausea, vomiting, diarrhea, weight gain, transient hair loss. **Rare/ Serious:** Impaired hepatic function, thrombocytopenia, leucopenia, drowsiness/ confusion (valproate-induced hyperammonemic encephalopathy, a sign of toxicity), liver failure, hemorrhagic pancreatitis	Liver disease, drug interactions.

Follow-up

If the C&A is not improving on the current dose of medication

- Review adherence to medications.
- Consider increasing medication dose as needed to the maximal dose if no adverse side effects.
- If response is still poor,
  - Consider switching medication. The new medication should be at optimum dose before slowly discontinuing the first.
- If response is still poor, review the diagnosis, and refer to a specialist.
- Follow- up more frequently.

Recommended frequency of contact
Follow-up should occur every 3-6 months.

If the C&A is showing improvement

At every contact,

- Evaluate side-effects of medication including adverse effects and idiosyncratic reactions (clinically and with appropriate laboratory tests when available).
- Provide psychoeducation and review psychosocial interventions.
- Is the patient an adolescent girl who is pregnant? If so, consult a specialist.
- Does the patient have any new symptoms of concern? Review for any new symptoms of depression and anxiety given high risk of co-morbidity with epilepsy.
- Is the patient on any new medications that may have interactions? (Many anti-convulsants have interactions with other medications). If so, consult a specialist.

Consider medication discontinuation when appropriate

If the C&A has been convulsion free for several years (>2 years at least),

- Discuss the risk of seizure occurrence with C&A/ carer (if epilepsy is due to head injury, or neuroinfection, there is a higher risk of seizure recurrence off medication), and the risks and benefits of discontinuing medications.

If in agreement, gradually take the C&A off medication by reducing the doses over 2 months and monitoring closely for seizure recurrence.

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ANNEXES

Annex 1: PEN-Plus Steering Committee

Designation	Name	Affiliated Institution
Committee Chair	Dr. Roshan Pokhrel	Secretary, Ministry of Health and Population (MoHP)
Co-Chair	Prof. Dr. Bhagawan Koirala	Co-Chair, Nepal NCDI Poverty Commission
Member	Dr. Dipendra Raman Singh	Director-General, Department of Health Services (DoHS)
Member	Dr. Chuman Lal Das	Director, Epidemiology and Disease Control Division (EDCD), DoHS (till Jestha 21, 2080)
Member	Dr. Rudra Prasad Marasini	Director, Epidemiology and Disease Control Division (EDCD), DoHS
Member	Dr. Pradip Gyanwali	Member Secretary, Nepal Health Research Council (NHRC)
Member	Dr. Phanindra Prasad Baral	Chief, NCD and Mental Health Section, EDCD
Member	Dr. Biraj Man Karmacharya	Representative, NCDI Poverty Network
Member	Dr. Rajesh Sambhajirao Pandav	Representative, WHO-Nepal
Member Secretary	Ms. Yeshoda Aryal	Chief, Health Coordination Division, MoHP

Annex 2: PEN-Plus Coordination Committee

Designation	Name	Affiliated Institution
Committee Chair	Dr. Dipendra Raman Singh	Director General, Department of Health Services (DoHS)
Co-Chair	Dr. Chuman Lal Das	Director, Epidemiology and Disease Control Division (EDCD), DoHS (till Jestha 21, 2080)
Member	Dr. Rudra Prasad Marasini	Director, Epidemiology and Disease Control Division (EDCD), DoHS
Member	Ms. Yeshoda Aryal	Division Chief, Health Coordination Division, Ministry of Health and Population (MoHP)
Member	Dr. Sarbesh Sharma	Director, Management Division, DoHS
Member	Dr. Bibek Kumar Lal	Director, Family Welfare Division (FWD), DoHS
Member	Dr. Yadu Chandra Ghimire	Director, National Health Training Center (NHTC) (till Jestha 28, 2080)
Member	Dr. Anup Bhattachan	Director, National Health Training Center (NHTC)
Member	Mr. Sunil Raj Sharma	Director, National Health Education Information and Communication Center (NHEICC)
Member	Dr. Anup Bastola	Director, Curative Service Division
Member	Dr. Pradip Gyanwali	Director, Nepal Health Research Council (NHRC)
Member	Dr. Biraj Man Karmacharya	Representative, NCDI Poverty Network
Member Secretary	Dr. Phanindra Prasad Baral	Chief, NCD and Mental Health Section, EDCD

Annex 3: PEN-Plus Technical Working Committee

Designation	Name	Affiliated Institution
Committee chair	Dr. Phanindra Prasad Baral	Chief, NCD and Mental Health Section, EDCD
Member	Dr. Meghnath Dhimal	Representative, Nepal Health Research Council
Member	Mr. Chetan Nidhi Wagle	Representative, Nepal Health Training Center
Member	Dr. Lonim Prasai Dixit	Representative, World Health Organization Nepal
Member	Dr. Abha Shrestha	Coordinator, Nepal NCDI Poverty Commission
Member	Dr. Archana Shrestha	Coordinator, Nepal NCDI Poverty Commission
Member	Dr. Shiva Raj Adhikari	Coordinator, Nepal NCDI Poverty Commission
Member	Dr. Krishna Aryal	Coordinator, Nepal NCDI Poverty Commission
Member	Dr. SP Kalaunee	Coordinator, Nepal NCDI Poverty Commission
Member	Prof. Dr. Abhinav Vaidya	Coordinator, Nepal NCDI Poverty Commission
Member	Ms. Abhilasha Gurung	Health Specialist, Health Section, UNICEF, Nepal Country Office
Member Secretary	Dr. Biraj Man Karmacharya	Representative, NCDI Poverty Network

Annex 4: PEN- Plus Team

S.N.	Name	Designation
1	Prof. Dr. Bhagawan Koirala	Lead, PEN-Plus
2	Dr. Phanindra Prasad Baral	Co-Lead, PEN-Plus
3	Dr. Biraj Man Karmacharya	Co-Lead, PEN-Plus
4	Dr. Abha Shrestha	Coordinator, Nepal NCDI-Poverty Commission
5	Dr. Shristi Singh	PEN-Plus Project Coordinator
6	Dr. Sulav Regmi	PEN-Plus Program Officer (Clinical)
7	Dr. Shruti Shah	PEN-Plus Program Officer (Clinical)
8	Mr. Bishwash Maharjan	PEN-Plus Program Officer (Programmatic)
9	Ms. Anu Gomanju	Voices of NCDI Poverty Advocacy Fellow, KIOCH
10	Dr. Sandeepa Karki	NCD Specialist
11	Dr. Alisha Manandhar	Monitoring and Evaluation Coordinator
12	Mr. Dhurba Khatri	Sr. Social Behavior Change Officer
13	Dr. Biraj Gautam	Medical Officer, Bardiya
14	Mr. Suraj Sujan Bohara	PEN-Plus Field Officer, Bardiya
15	Dr. Roshika Budathoki	Medical officer, Damak
16	Ms. Samikshya Aryal	PEN-Plus Field Officer, Damak
17	Ms. Elina Khadka	Staff Nurse, Bardiya
18	Ms. Sabina Kumari Gamuwa	Health Assistant, Bardiya
19	Mr. Niraj Katuwal	Health Assistant, Damak
20	Ms. Seerina Basnet	Staff Nurse, Damak
21	Ms. Shraddha Parajuli	Program officer (Dailekh)
22	Ms. Neha Khatun	Program officer (Siraha)
23	Ms. Renuka Thami	Program officer (Gulmi)
24	Ms. Rakshya Bohara	Program officer (Bajhang)

Annex 5: List of National-Level Consultants for the Development of the Protocol

S.N.	Speciality	Name	Organization
1	National Lead Consultant for PEN-Plus Protocol Development	Prof. Dr. Sanjib Kumar Sharma	B.P. Koirala Institute of Health Sciences (BPKIHS)
2	PEN-Plus Manual Development Consultant	Dr. Ishwor Prasad Upadhyaya	National Health Training Center
3	Cardiology	Dr. Kunjang Sherpa	National Academy for Medical Sciences (NAMS)
		Dr. Urmila Shakya	Shahid Gangalal National Heart Center (SGNHC)
		Dr. Pankaj Ray	Kanti Children's Hospital
4	Hemoglobinopathies	Dr. Rajan Pandey	Bheri Hospital
		Dr. Sudhir Sapkota	Kanti Children's Hospital
5	Cancer	Dr. Sandhya Chapagain	National Academy for Medical Sciences (NAMS)
		Dr. Saugat Poudel	National Academy for Medical Sciences (NAMS)
		Dr. Sucharita Tuladhar	Patan Academy of Health Sciences (PAHS)
6	Respiratory Disease	Prof. Dr. Ganesh Rai	Nepal Paediatrics Society (NEPAS)
		Dr. Sangita Basnet	Patan Academy of Health Sciences (PAHS)
		Dr. Bhupendra Shah	B.P. Koirala Institute of Health Sciences (BPKIHS)
7	Diabetes	Prof. Dr. Sudha Basnet	Institute of Medicine (IOM)
		Dr. Jyoti Bhattarai	Metro Kathmandu Hospital
		Dr. Urza Bhattarai	B.P. Koirala Institute of Health Sciences (BPKIHS)
8	Neuro-Developmental Disorder	Dr. Arun Raj Kunwar	Kanti Children's Hospital
		Dr. Gunjan Dhonju	Kanti Children's Hospital

Annex 6: Special Contributors

S.N.	Name	Designation
1	Reference materials, technical sessions, and guidance for the overall PEN-Plus planning and implementation	NCDI Poverty Network Secretariat at the Center for Integration Science, Brigham & Women's Hospital, Boston, USA.
2	Dr. Budhi Setiawan	Chief Health Section, UNICEF, Nepal Country Office, Kathmandu
3	Dr. Samikshya Neupane Dulal	Child and adolescent consultant, UNICEF, Nepal Country Office, Kathmandu

Annex 7: List of participants of the PEN-Plus Clinical Protocol Review Workshop held on 14-15 September, 2022

SN	Participants	Institution/ Affiliation	PEN-Plus diseases group
1	Prof. Dr. Bhagawan Koirala	Lead, PEN-Plus	
2	Prof. Dr. Sanjib Kumar Sharma	BPKIHS	National Lead Consultant
3	Dr. Sangeeta Kaushal Mishra	MoHP	
4	Dr. Phanindra Prasad Baral	Co-lead, PEN-Plus	
5	Prof. Dr. Jitendra Pariyar	Civil Service Hospital	Cancer
6	Prof. Dr. Sudha Basnet	Institute of Medicine	Pediatrics
7	Dr. Biraj Man Karmacharya	Co-lead, PEN-Plus	
8	Dr. Abha Shrestha	Coordinator, Nepal NCDI- PC	
9	Dr. Rajan Pande	Bheri Hospital	Hematology
10	Dr. Rupesh Mishra	Civil Service Hospital	Hematology
11	Dr. Sandhya Chapagain	NAMS	Cancer
12	Dr. Saugat Poudel	NAMS	Cancer
13	Dr. Bishnu Rath Giri	Kanti Children's Hospital	Cancer
14	Dr. Prajwol Shrestha	NAMS	Pulmonology
15	Dr. Bhupendra Shah	BPKIHS	Pulmonology
16	Prof. Dr. Rajendra Koju	KUSMS	Cardiology
17	Prof. Dr. Deewakar Sharma	HAMS	Cardiology
18	Dr. Kunjang Sherpa	NAMS	Cardiology
19	Dr. Jyoti Bhattarai	Metro Kathmandu Hospital	Endocrinology
20	Dr. Urza Bhattarai	BPKIHS	Endocrinology
21	Dr. Rashmina Manandhar	Nepal NCDI-PC, KIOCH	
22	Dr. Shristi Singh	Nepal NCDI-PC, KIOCH	
23	Ms. Anu Gomanju	Nepal NCDI-PC, KIOCH	
24	Mr. Bishwash Maharjan	Nepal NCDI-PC, KIOCH	
25	Mr. Mahananda Prakash Paudyal	KIOCH	
26	Ms. Praja Pokhrel	KUSMS	

Annex 8: List of participants of the PEN-Plus Clinical Protocol Review Workshop held on 9th and 10th December 2022

SN	Participants	Institution/ Affiliation	PEN-Plus diseases group
1	Dr. Dipendra Raman Singh	Director General, DoHS	
2	Dr. Chuman Lal Das	Director, EDCD	
3	Prof. Dr. Bhagawan Koirala	Lead, PEN-Plus	
4	Prof. Dr. Sanjib Kumar Sharma	Acting Vice-Chancellor, BPKIHS	National Lead Consultant
5	Dr. Phanindra Prasad Baral	Co-lead, PEN-Plus	
6	Prof. Dr. Rajendra Koju	KUSMS	Cardiology
7	Dr. Biraj Man Karmacharya	Co-lead, PEN-Plus	
8	Dr. Ishwor Prasad Upadhyaya	NHTC	
9	Mr. Kunj Prasad Joshi	NHTC	
10	Dr. Madhav Prasad Lamsal	NHTC	
11	Dr. Abha Shrestha	Coordinator, Nepal NCDI-PC	
12	Dr. Rajan Pande	Bheri Hospital	Hemoglobinopathies
13	Dr. Nabin Simkhada	KUSMS	Hemoglobinopathies
14	Dr. Sandhya Chapagain	NAMS	Cancer
15	Dr. Saugat Poudel	NAMS	Cancer
16	Dr. Soniya Dulal	BPKIHS, Dharan	Cancer
17	Dr. Kritipal Subedi	Bheri Hospital	Cancer
18	Dr. Rajani K.C Shah	Bheri Hospital	Pulmonology
19	Dr. Puru Koirala	BPKIHS	Pulmonology
20	Dr. Bhupendra Shah	BPKIHS	Pulmonology
21	Dr. Anamika Mahato	Dhulikhel, Hospital	Pulmonology
22	Dr. Krishna Prasad Adhikari	Bheri Hospital	Cardiology
23	Dr. Kunjang Sherpa	NAMS	Cardiology
24	Dr. Jyoti Bhattarai	Metro Hospital	Diabetes
25	Dr. Urza Bhattarai	BPKIHS	Diabetes
26	Dr. Robin Maskey	BPKIHS	Diabetes
27	Dr. Rajesh Kumar Mandal	Bheri Hospital	Diabetes
28	Dr. Sandeepa Karki	KIOCH	
29	Dr. Alisha Manandhar	KIOCH	
30	Mr. Bishwash Maharjan	Nepal NCDI-PC, KIOCH	
31	Mr. Mahananda Prakash Paudyal	KIOCH	
32	Dr. Pabindra Tamang	DM Cadiologist, KUSMS	
33	Dr. Nishan Bhattarai	DM Cardiologist, KUSMS	
34	Dr. Animesh Kunwar	Resident, KUSMS	
35	Dr. Merina Shrestha	Resident, KUSMS	
36	Ms. Pragya Sharma	KUSMS	
37	Ms. Praja Pokhrel	KUSMS	

Annex 9: List of participants for the PEN-Plus clinical protocol finalization workshop held on 7th and 8th February 2023

SN	Participants	Institution/ Affiliation	PEN-Plus diseases group
1	Prof. Dr. Bhagawan Koirala	Lead-PEN Plus	
2	Dr. Ishwor Prasad Upadhyaya	NHTC	
3	Prof. Dr. Ganesh Rai	Nepal Pediatric Society (NEPAS)	Pulmonology
4	Prof. Dr. Sudha Basnet	IOM, TUTH	Endocrinology
5	Dr. Urmila Shakya	Sahid Gangalal National Heart Centre (SGNHC)	Cardiology
6	Dr. Sucharita Tuladhar	Patan Academy of Health Sciences (PAHS)	Oncology
7	Dr. Pankaj Ray	Kanti Children's Hospital	Cardiology
8	Dr. Gunjan Dhonju	Kanti Children's Hospital	Neuropsychiatry
9	Dr. Sudhir Sapkota	Kanti Children's Hospital	Hematology
10	Dr. Shristi Singh	Nepal NCDI -PC,KIOCH	
11	Dr. Sulav Regmi	Nepal NCDI -PC,KIOCH	
12	Dr. Sandeepa Karki	KIOCH	
13	Dr. Alisha Manandhar	KIOCH	
14	Mr. Bishwash Maharjan	Nepal NCDI -PC,KIOCH	
15	Mr. Dhurba Khatri	KIOCH	
16	Ms. Anu Gomanju	Nepal NCDI -PC,KIOCH	
17	Mr. Mahananda Prakash Paudyal	KIOCH	

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