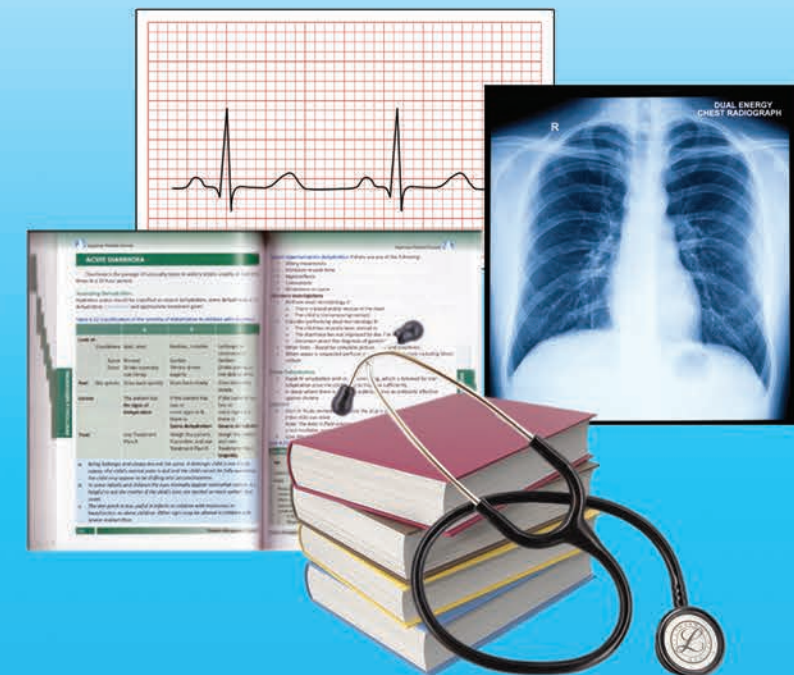




MYANMAR MEDICAL ASSOCIATION



MMA CMEBook 2019





MMA CME Book 2019

MMA CME Book 2019

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Foreword

On the occasion of the 65th Myanmar Medical Conference we are publishing the MMA CME 2019 book. This is to supplement the CME activities that we have been carrying out for our members. Mostly these activities have been in the form of conferences, lectures, seminars and workshops. We are now providing CME in another format in the print form so that this book may be read and read again and kept for reference. We have chosen topics that we believe will be of interest to the non-specialist medical practitioner. We will be publishing more books like this in the future so that our doctors can keep themselves updated.

CME can also be carried out in other formats. We have now developed an on-line CME programme in collaboration with the World Medical Association and full activity will start six months from now. We hope that all doctors will be able to join in this programme. At one point CME will become compulsory for all doctors practicing in the country and we are building a platform which everybody will be able to access wherever they are.

All this will update the practicing doctor and this will help in providing the best for the patients.

MMA is to provide the best for doctors who will provide the best to patients.



Professor Rai Mra
President
Myanmar Medical Association
January 2019

Editorial Board

- ◆ Prof. Rai Mra
- ◆ Prof. Htin Aung Saw
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Genetics in general practice

Myanmar Anatomy Society

GPs are well positioned to determine whether a patient / family might consider pursuing genetic investigation. General practitioners are potentially well placed to integrate many genetics issues into routine consultations. GPs working with families are well placed for long term follow up of genetics-based risks. GPs are also accustomed to communicating test results to patients and managing the subsequent implications of a test. Genetic counselling should be regarded as an integral part of the genetic testing process and should be offered and strongly recommended in most genetic testing situations.

WHO report on community genetics services

South-East Asia regions that can increase inherited diseases such as Down syndrome, and large family size that may increase the number of affected children in families with autosomal recessive conditions. The services required for the prevention and care of congenital disorders and genetic diseases include prevention strategies at primary, secondary and tertiary health-care levels.

Types of genetic testing

- Diagnostic testing: genetic testing performed in a symptomatic individual to confirm or exclude a genetic condition.
- Predictive testing: genetic testing in a healthy high-risk relative for a specific later-onset monogenic disorder.
- Susceptibility testing (risk profiling): a genetic test of a marker or several genetic markers with the aim to detect an increased or decreased risk for a multifactorial condition in a healthy individual.
- Pharmacogenetic testing: testing for a genetic susceptibility for adverse drug reactions or for the efficacy of a drug treatment in an individual with a given genotype.
- Carrier testing: a genetic test that detects a gene mutation that will generally have limited or no consequence to the health of that individual.
- Prenatal testing: a genetic test performed during a pregnancy, where there is increased risk for a certain condition in the fetus.
- Pre-implantation genetic diagnosis: testing the presence of a mutation, linked haplotype or chromosomal change in one or two cells of an embryo in a family with a previously known risk for a Mendelian or chromosomal disorder, in order to select the unaffected embryos to be implanted.
- Genetic screening: testing where the target is not high-risk individuals or families, but where the test is systematically offered to the general population or a specific group (eg. newborns, young adults, ethnic group).

Guidelines for genetic counselling

- Genetic counselling has to be provided or supervised by a healthcare professional appropriately trained for genetic counselling.
- Healthcare professionals should not agree to testing without pre-test counselling in circumstances where doing so would go against their professional judgement.
- Predictive tests for future severe illnesses with no options for treatment or prevention should not be performed without pre- and post-test genetic counselling, psychosocial evaluation and follow-up.
- Before actual testing takes place, there should be free and informed consent.
- In situations where testing children or other persons who are not able to give informed consent is considered, those individuals should be involved in genetic counselling and in the decision-making process, according to their capacities.
- Testing for adult-onset conditions in children should only be considered when treatment or surveillance would begin in childhood.

Pre-test genetic counselling

Individuals are informed about the purpose of the test, including:

- Up-to-date, reliable description about symptoms and natural history of the disease.
- Prospects of prevention or early diagnosis and treatment.
- Inheritance pattern.
- The risk of disease, available reproductive choices, reliability and limitations of the test concerned, and possible psychological impact and other consequences of the test result to the person and their relatives.
- Privacy and confidentiality of the results, as well as possible consequences related to its disclosure to third parties, such as insurance companies and employers, are discussed, when appropriate.
- Pre-test counselling includes discussion about the rights to know and to decide including the right not to know.
- Possible uncertainties due to present lack of knowledge are declared.
- Discussion about the need to inform relatives about the test result, as well as the best ways to do this, are initiated, especially in conditions where early diagnosis may improve the prognosis.
- Written materials and/or reliable internet addresses related to the subject should be offered when available.
- A written summary of the discussion should be offered.

Post-test genetic counselling

- After disclosure of test results, the first focus is on the emotional impact on the person and others involved.
- If necessary, follow-up contacts with the genetic counselling unit should be offered, and / or a consultation with a psychologist.
- The possibility to contact a social worker and patient support organizations should also be offered.
- A written summary of the test result and issues discussed should be given.
- Implications to the individual (including a follow-up plan, when relevant) and their near relatives should be discussed
- A strategy to inform relatives should also be discussed. Written material to help the counsellor to spread the information in the family should also be offered.

Role of primary care in genetic counselling

GPs are now frequently asked about inherited diseases in the context of both:

- The possibility of an individual patient having an increased risk of a condition which already affects a close member of their family.
- The risks of a couple having a child affected by a particularly disorder that may or may not appear in the family.

The GP may need to:

- Explain mechanism of inheritance of a disease to patients.
- Dispel unnecessary fears in patients without significantly increased risk of disease.
- Advise on lifestyle changes for patients who may have inherited an increased susceptibility to a disease - eg. coronary heart disease.
- Provide advice and support to people
- Ethnic groups at special risk
- People with a clear family history of high levels of certain forms of cancer occurring at an early age - eg. breast, colorectal, ovarian and endometrial cancers, familial adenomatous polyposis.
- Help people come to terms with a diagnosis or a high risk in themselves, their baby or a family member. Explain conditions and their inheritance to them when a relative has informed them they need testing.
- Advise on antenatal screening for disorders where there is a strong family history such as muscular dystrophy, cleft lip, spina bifida, congenital heart defect. There is a need to ensure that parents are aware of the alternatives for the pregnancy when screening is positive.
- Advise on the alternatives to normal conception - eg. in vitro fertilization with embryo selection, adoption, sperm or egg donation.

**Counselling the person, couple or family**

- Counselling should be carried out in a relaxed atmosphere with sufficient time to absorb the initial shock of diagnosis or bereavement.
- Advice should include the clinical presentations of the disease, treatment, natural history, prognosis, complications and a clear explanation of the genetics. The risk to the individual of developing symptoms, the risk to future offspring, and the way in which the disease is transmitted.
- All information must be given in simple, easy to understand language.
- Carefully assess the understanding of the couple about the problem: establish whether they have any misconceptions which need rectifying, or any misplaced guilt.
- The reproductive options of the couple must be discussed in an unbiased manner. If required, contraceptive measures should be arranged and the possibility of in vitro fertilization or adoption investigated.

As a GP, good communication is key in all consultations. The added issues involved in communicating genetic information include:

- Impact on others (and subsequent confidentiality issues, and guilt feelings that may arise if a person feels they have passed on a genetic condition to a relative).
- Language of genetics, which may not be understood. Terms such as "risk", "mutant", "disease" are better avoided and replaced with more neutral words such as "chance", "variant" and "condition" respectively. Terms such as "carrier" may be misinterpreted as "infectious". Numbers and percentages may not be understood.
- Cultural or ethical differences.
- Uncertainty.

**Benefits of Exercise****Physiology & Biochemistry Society**

According to Global Health Risks data of the World Health Organization (2004), next to high blood pressure, tobacco use and high blood glucose, physical inactivity stands as 4th leading cause of death globally, with about 3.3 million attributable deaths per year. Physical activity represents a corner stone in the primary prevention of at least 35 chronic conditions (Booth et al., 2012). Over the past two decades, considerable knowledge has accumulated concerning the significance of exercise as the first-line treatment of several chronic diseases. There is evidence-based basis for prescribing exercise as medicine in the treatment of 26 different diseases. These are psychiatric diseases (depression, anxiety, stress, schizophrenia); neurological diseases (dementia, Parkinson's disease, multiple sclerosis); metabolic diseases (adiposity, hyperlipidemia, metabolic syndrome, polycystic ovarian syndrome, type 2 diabetes, type 1 diabetes); cardiovascular diseases (hypertension, coronary heart disease, heart failure, cerebral apoplexy, and intermittent claudication); pulmonary diseases (chronic obstructive pulmonary disease, asthma, cystic fibrosis); musculoskeletal disorders (osteoarthritis, osteoporosis, back pain, rheumatoid arthritis); and cancer (Pedersen and Saltin 2015).

Exercise is physical activity that is planned, structured and designed needs to be repetitive in order to improve or maintain physical fitness, physical performance, or health. Physical activity is bodily movement produced by skeletal muscles that results in energy expenditure. Exercise is a form of physical stress and when challenged with exercise, the human body responds through a series of integrated changes in function that involve most of its physiologic systems. When the body engages in exercise training several times a week or more frequently, each of these physiologic systems undergoes specific adaptations that increase the body's efficiency and capacity.

These integrated physiological changes in the body are improved body composition (through increased energy expenditure, induced lipolysis, increased the ability of muscles to burn fat instead of glycogen which in turn is achieved by activation of a number of enzymes in the skeletal muscle necessary for lipid turnover, reduced abdominal adiposity and improved weight control), enhanced lipid lipoprotein profiles (through reduced triglyceride levels, increased high-density lipoprotein cholesterol levels and decreased low-density lipoprotein to high-density lipoprotein ratios), improved glucose homeostasis and insulin sensitivity (through enhanced skeletal muscle insulin sensitivity of glucose transport system, the up-regulation of GLUT-4 protein expression in skeletal muscle, reduced hormonal stimulation of hepatic glucose production), improved autonomic tone, reduced blood pressure, improved coronary blood flow, augmented cardiac function (through increased heart rate variability, attenuated the age-related decline in baroreflex function and improved the impaired cardiovagal baro reflex function, beneficial effects



on indices of arterial stiffness and enhanced endothelial function). The molecular mechanisms by which exercise exerts its beneficial effects on the cardiovascular system are not fully understood, they primarily involve: reduction of oxidative stress, namely by enhancement of superoxide dismutase (SOD) enzymes activity, increased endothelial nitric-oxide synthase (NOS3) expression and NO-mediated signaling, increased prostacyclin and cystathionine- γ -lyase and decreased thromboxane, ATP, and endothelin-1 levels. The physiological changes to exercise also include reduced systemic inflammation as marked reductions in C-reactive protein levels, increased levels of Interleukin-6, Interleukin-1ra, and Interleukin-10 (through muscle-derived IL-6 inhibiting TNF production and stimulated the production of the anti-inflammatory cytokines IL-1ra and IL-10 and a variety of myokines), decreased blood coagulation, increased bone mineral and mass, improved psychological well-being (through reduced stress, anxiety and depression, increased Brain-derived neurotrophic factor (BDNF) resulting in increased hippocampal volume and reduced deterioration in physiological function normally associated with aging.

These integrated physiological changes can bring about the exercise-related health benefits for the general population and selected populations. The 2018 Physical Activity Guidelines Advisory Committee documented physical activity-related health benefits as follow:

In children ages 3 through 5 years, a reduced risk of excessive weight gain and favorable indicators of bone health was found and whereas in children of 6 to 17 years of age improved cognitive function, improved cardio respiratory and muscular fitness, improved bone health, improved cardiovascular risk factor status, improved weight status or adiposity and fewer symptoms of depression were evident.

In adults of all ages, exercise resulted in lower risk of all-cause mortality, lower cardiovascular incidence and mortality (including heart disease and stroke), lower incidence of hypertension, lower incidence of type 2 diabetes, lower incidence of bladder, breast, colon, endometrium, esophagus, kidney, stomach, and lung cancers. In addition, there was reduced risk of dementia, improved cognitive function, improved quality of life, improved sleep, reduced feelings of anxiety and incidence of depression in healthy people and in people with existing clinical syndromes. When a sufficient dose of moderate-to-vigorous physical activity was attained, there was reduced risk of excessive weight gain, weight loss and the prevention of weight regain following initial weight loss and an additive effect on weight loss when combined with moderate dietary restriction.

In older adults (65 years old and above), there was reduced incidence of falls, reduced incidence of fall-related injuries, improved physical function with and without frailty and improved quality of life.

In women who were pregnant or postpartum, there was reduced risk of excessive weight gain and reduced risk of gestational diabetes. No risk to fetus from moderate-intensity physical activity was found. There was also reduced risk of postpartum depression.



In general population and children 5 to 13 years of age, habitual exercise brought improved cognition, improved performance on academic achievement tests, improved neuropsychological performance (executive function, processing speed, memory) and reduced risk of dementia. Even acute episodes of exercise brought improved cognition (executive function, attention, academic performance, memory, crystallized intelligence, processing speed).

In individuals with pre-existing medical conditions, exercise caused reduced risk of all-cause and cancer mortality in breast and colorectal cancer, reduced risk of prostate cancer mortality. In Osteoarthritis cases, there was decreased pain and improved function and quality of life. There was also reduced risk of progression of cardiovascular disease, reduced risk of increased blood pressure overtime in hypertension cases. In type 2 diabetes, reduced risk of cardiovascular mortality, reduced progression of disease indicators: hemoglobin A1c, blood pressure, blood lipids, and body mass index occurred. In Multiple sclerosis cases, exercise improved walking and improved physical fitness. In Dementia and some conditions with impaired executive function (attention deficit hyperactivity disorder, schizophrenia, multiple sclerosis, Parkinson's disease, and stroke), improved cognition occurred. Individuals with schizophrenia got improved quality of life. Fewer depressive symptoms occurred in individuals with and without major depression and reduced trait anxiety for individuals with and without anxiety disorders.

Regarding the exercise-related health benefits, there is a definite dose-response relationship. Physical activity is better than physical inactivity, exercise is better than daily physical activity and more total exercise volume equals more health benefits. However, inappropriate exercise can do more harm than good. The magnitude of exercise-related health benefits depend largely on the types of exercise, intensity and duration of the training sessions, the force or load used in training, and the body's initial level of fitness.

Types of exercise are:

1. Endurance or aerobic exercise - It involve major muscle groups and is continuous and rhythmic in nature e.g., Brisk walking outside or inside on a tread mill, Bicycling/ Stationary cycling indoors, Dancing, Low-impact aerobics, Swimming or water aerobics, Playing tennis, Stair climbing, Jogging / Running, Hiking, Rowing, Ice-skating or roller-skating). Aerobic activity leads to improved cardiorespiratory fitness (VO_2 max) with an increase in the capacity and efficiency of the cardiorespiratory system in order to transport oxygen to skeletal muscles as well as for muscles to utilize this oxygen. Cardiorespiratory fitness also is associated with improvements in biomarkers (e.g., atherogenic lipoprotein profile, blood pressure, insulin sensitivity) for CVD and type 2 diabetes of adults and older adults with and without these diseases. Aerobic activity also leads to improved strength and endurance of the major muscle groups used to perform the chosen behavior, such as running or swimming. The high impact of some aerobic activities such as running or playing tennis, and the strong muscular forces of others, such as rowing or wrestling, improve bone health.



2. Strength exercises - make the muscles stronger. The activities chosen should work all the major muscle groups of the body (legs, hips, back, chest, abdomen, shoulders, and arms) e.g., Lifting light weights or objects like canned goods or water bottles at home or using weight machines / free weights at the gym (dumbbells and barbells), working with resistance bands - elastic bands, Calisthenics or exercises that use own body weight to work muscles (e.g., pushups, sit ups, squats, lunges, wall-sits and planks), other activities that build and keep muscle like heavy gardening (digging, shoveling). Greater muscular strength is associated with greater ease performing daily tasks for people of all ages, and provides reductions in blood pressure equivalent to aerobic activities. For older adults, muscle-strengthening activities (often in combination with balance training) are associated with improved physical function as well as reduced risk of falls and reduced risk of injury due to falls. It can help to maintain lean body mass during a program of weight loss and even itself can cause little weight loss.

3. Bone-strengthening exercises - It involves significant impact or muscular forces, both of which apply stress to bone, which adapts by increasing its strength. Bone-strengthening activities include hopping, jumping, skipping, running dancing, stair climbing, or push-ups, standing on one's toes and suddenly dropping to one's heels. These activities provide significant impact forces. It reduces the risk of osteoporosis and fractures.

4. Balance-exercises - It helps maintain a steady posture against anticipated or unanticipated perturbations while walking or standing. Balance-exercises include standing on one foot, then the other (if you can, don't hold on to anything for support), get up from a chair without using your hands or arms, walking heel-to-toe, Tai Chi, Use of a Swiss Ball or a wobble board. It can prevent falls and fall injuries among older adults.

5. Flexibility exercises (Stretching) - Dynamic and static stretching improved the range and ease of movement around joints. If joint flexibility is limited, it impedes the performance of daily activities. However, one should not stretch so far that it hurts.

Recommended exercise for health in general:

For Adult and Elderly (65 years old or older)

- moderate-intensity aerobic activity (i.e., brisk walking) 150 minutes every week, muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders, and arms) (or) vigorous-intensity aerobic activity (i.e., jogging or running) 75 minutes every week, muscle-strengthening activities on 2 or more days a week that work all major muscle groups (or) an equivalent mix of moderate- and vigorous-intensity aerobic activity and muscle-strengthening activities on 2 or more days a week that work all major muscle groups.



For children and adolescents

- 60 minutes or more of either moderate-intensity aerobic activity, such as brisk walking, or vigorous-intensity activity, such as running each day. Be sure to include vigorous-intensity aerobic activity on at least 3 days per week, include muscle strengthening activities, such as gymnastics or push-ups and bone strengthening activities, such as jumping rope or running, at least 3 days per week as part of the child's 60 or more minutes.

For pregnant women

- Healthy women who are not already highly active or doing vigorous-intensity activity should get at least 150 minutes of moderate-intensity aerobic activity a week during pregnancy and the postpartum period. Preferably, this activity should be spread throughout the week. If the women begin physical activity during this pregnancy, start slowly and increase amount of exercise gradually over time
- Pregnant women who habitually engage in vigorous-intensity aerobic activity or who are highly active can continue physical activity during pregnancy and the postpartum period, provided that they remain healthy and discuss with their health-care provider how and when activity should be adjusted over time.
- While pregnant, one should avoid doing any activity that involves lying on the back or that puts pregnancy at risk of falling or abdominal injury, such as horseback riding, soccer, or basketball.

More time equals more health benefits - If exercise go beyond 300 minutes a week of moderate-intensity activity, or 150 minutes a week of vigorous-intensity activity, even more health benefits could be obtained. However, total volume of physical activity is more important target than the specific intensity, specific duration or specific frequency.

Regarding intensity of exercise:

It is described in terms of absolute or relative intensity. Absolute intensity is the rate of energy expenditure required to perform any physical activity. It can be measured in METs, kilocalories, joules, or oxygen consumption. One MET is the rate of energy expenditure while sitting at rest, which, for most people approximates an oxygen uptake of 3.5 milliliters per kilogram per minute. The Relative intensity refers to the ease or difficulty with which an individual performs any given physical activity. It has a physiologic basis and can be described using physiologic parameters, such as percent of aerobic capacity (VO_2 max) or percent of maximal heart rate (HR_{max}). Relative intensity can also be measured with tools that assess an individual's perception about how difficult it is to perform an activity.

For health benefits, exercise intensity is moderate or vigorous activities. Moderate-intensity activity means 3 to < 6 METs, 40 - < 60% VO_2 max, 55 - < 70% HR_{max} , Borg's

Perceived Exertion Rate of 11 - 13 and Talk Test (a simple way to measure relative intensity) - can talk, but cannot sing during exercise.

Vigorous activity means 6 to < 9 METs, 60 - < 85% VO₂ max, 70 - < 90% HRmax, Borg's Perceived Exertion Rate of 14 - 16 and Talk Test - Cannot be able to say more than a few words without pausing for a breath during exercise.

If the person has a chronic diseased condition, an evaluation of exercise capacity should be done in order to create an individual exercise program. The recommended method for evaluating exercise capacity is a symptom-limited exercise test. Trained personnel (physiotherapist, nurse, laboratory assistant) under a doctor's supervision can carry this out. For exercise recommendation, the patient's disease condition, concomitant treatment, interaction of exercise with drug treatment and temporary or specific contra-indication to exercise must be considered. The program should be adapted to suit the individual patient in terms of motivation, practical feasibility and slotting the program into daily life.

Exercise is a vaccine to prevent chronic diseases and extend life. It is a prescription that could treat chronic non-communicable diseases including mental and psychological illnesses with low cost. It is also useful in rehabilitation of many diseases. In addition, there is a linear relation between exercise activity and health status, such that a further increase in exercise activity and fitness will lead to additional improvements in health status. So it should be concluded that exercise plays a critical role in promotive, preventive, curative and rehabilitative aspects of health care system, **EXERCISE IS MEDICINE**.

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Acute Abdomen

Surgical Society (Myanmar)

The acute abdomen is a very common clinical entity. It has been estimated that at least 50% of general surgical admissions are emergencies and, of these, 50% present with acute abdominal pain and it also has significant morbidity and mortality. The mortality rate varies with age, being highest at the extreme of age. The highest mortality rate is associated with laparotomy for unresectable cancer, ruptured abdominal aortic aneurysm and perforated bowel. The acute abdomen can be defined as the sudden onset of abdominal pain which needs repeated examination and constant observation; but immediate operation may or may not be required.

Aetiology and Classification

The causes of the acute abdomen may be subdivided into abdominal causes and extra-abdominal (medical) causes that can mimic the surgical condition. Abdominal causes can be in term subdivided into site from which the pain comes according to anatomy (eg. Pain from true abdomen, thoracic abdomen, pelvic and retroperitoneum). Again, it can be classified according to organ system (eg. Gastrointestinal, hepatobiliary and pancreatic, urinary, vascular, gynaecological and pain comes from abdominal wall). It can also be classified according to pathology like inflammation (eg. Acute appendicitis, diverticulitis), Perforation (eg. Peptic ulcer perforation), obstruction (eg. Intestinal obstruction, biliary colic), hemorrhage (eg. ruptured abdominal artery aneurysm) and ischaemia (eg. Mesenteric ischaemia).

Although extra-abdominal causes are not very common in surgical practice, it is needed to exclude urgently as it can be life-threatening. These are the followings.

- Myocardial infarct, atypical angina
- Pericarditis, congestive cardiac failure
- Basal Pneumonia
- Diabetic Ketoacidosis
- Uremia
- Sick cell anaemia crisis
- Herpetic neuralgia
- Pulmonary embolus

Common causes of acute abdomen in surgical practice

There are several numbers of usual common causes frequently admitted to surgical units. These include as follow by order of decreasing frequency.

1. Acute appendicitis

2. Perforated peptic ulcer
3. Acute gastritis / exacerbation of peptic ulcer
4. Acute Cholecystitis
5. Hepatitis, Cholangiohepatitis
6. Acute pancreatitis
7. Colic (intestinal, ureteric, biliary)
8. Gynaecological causes (ruptured ectopic pregnancy, etc)

Clinical features of acute abdomen

Symptoms

The main symptom of acute abdomen is abdominal pain. It is necessary to take the detail history of abdominal pain as it can indicate the origin, pathology and severity of the acute abdomen. For example, site of the pain (according to nine region of abdomen) can indicate that that pain arise from which organ and system. And the nature and character of the pain can detect the underlying pathology of the condition. For example, pain in acute appendicitis can start with dull aching visceral pain around the umbilicus then shift to right iliac fossa as constant sharp somatic pain.

The other important symptoms to ask thoroughly are vomiting, abdominal distension, diarrhea and constipation. Vomiting may be due to inflammation, obstruction and reflex. Vomiting is less pronounced in acute appendicitis but it can markedly occur in acute pancreatitis and intestinal obstruction. The onset, content involved, in relation to pain and food are important to be noted. Abdominal distension is a feature suggestive of intestinal obstruction. Adhesion either postoperative or inflammatory causes (eg. tuberculosis abdomen), hernia that is obstructive one and intra-abdominal malignancy are three common causes of mechanical intestinal obstruction in surgical practice.

The bowel habit of the patient is very important to note as constipation that can be absolute or relative is a very mark symptom in intestinal obstruction but it can also occur in generalized peritonitis. Diarrhea, although not common in acute abdomen, it can be come across in any causes of pelvic irritation or abscess, colitis and distal large gut tumour. Acute appendicitis may present in sometimes with diarrhoea when the appendix is of preileal or pelvic position. There are some causes of intestinal obstruction which can present with diarrhoea such as intussusception, Richter's hernia and mesenteric ischaemia. While taking the history, it is important to note about the history of medical diseases liked diabetes and menstrual history in women as well.

Signs

The most important findings to look for in general examination are features of peritonitis such as very ill, toxic, anxious looking and dehydrated patient with high fever or subnormal temperature, low blood pressure and tachypnea, acidotic breathing,

oliguria or anuria. The conditions which can present abdominal pain with shock include haemoperitoneum caused by ruptured ectopic pregnancy, ruptured spleen or liver, and ruptured abdominal aortic aneurysm. It can also be caused by mesenteric thrombosis, massive peritoneal sepsis and haemorrhagic pancreatitis.

In abdominal examination, the sign of peritonitis are abdomen that does not move with respiration, guarding, rigidity, tenderness and rebound tenderness. During abdominal examination, any abdominal distension, visible peristalsis, any scar over abdomen and hernia orifices are important to find out on inspection. Any palpable mass including liver, gall bladder, spleen and kidney should also be searched for. Abnormal percussion note and free fluid can be detected on percussion. Bowel sound that can be either increased or reduced and any bruit should be found out in auscultation. Digital rectal examination should be done in patient with intestinal obstruction.

Investigations for acute abdomen

Base line investigations that are necessary in acute abdomen are full blood count (FBC), Urine RE, Urea and Electrolytes, random blood sugar and liver function test, etc). Special investigations are serum amylase and lipase in suspected acute pancreatitis, C reactive protein (CRP) to detect ongoing inflammatory process in response to infection and sepsis. Imaging are very useful modalities in acute abdomen that can detect certain emergencies -

- GUD X'ray to detect Pneumoperitoneum (Gas under diaphragm)
- Plain X ray (Abdomen) Erect and Supine - to detect any features of Intestinal obstruction
- Ultrasound (Abdomen and Pelvis) in acute abdomen with hepatobiliary causes and gynaecological causes
- CT (Abdomen) to detect exact nature of acute pancreatitis and its complications that can sometimes necessary to do emergency laparotomy, rupture abdominal aortic aneurysm

Each investigation requested should be justified, but not necessarily delay patient management.

Scoring in acute abdomen

There are several scoring systems in acute abdominal conditions that can be useful to suggest provisional diagnosis in certain diseases. For examples, Alvarado Score, if that is more than 7 out of 10, it is highly suggestive of acute appendicitis. Ranson's Score and Glasgow Score are very useful to find out the severity in acute pancreatitis.

Treatment

The acute abdomen is very important emergency condition in surgical practice. The patient needs to be admitted. Bowel rest and Ryle's tube suction are advised to relieve

some obstruction. Replacement of body fluid and electrolyte loss according to previous day output, daily requirement and ongoing loss should be given. Parenteral antibiotics should be given as necessary. The successful management of acute abdomen cannot be accomplished without the process of monitoring vital signs and frequent abdominal examination as some cases are in grey zone for urgent laparotomy and some cases treated by conservative management. Decision making for operation is particularly important, 'when to operate, how to operate and when not to operate' should be carefully decided and sometimes need opinion from senior surgeons.

Here are some examples of conditions presenting with acute abdomen and their management. Although there are some studies about conservative management with parenteral antibiotics in treatment of acute appendicitis, emergency appendectomy should be advisable in most cases of acute appendicitis. In case of appendicular abscess, extra or intra-abdominal drain must be done. In peptic ulcer perforation, laparotomy, peritoneal toilet, suturing and omentoplasty should be taken as soon as the patient revived from shock and being optimized. Cases of intestinal obstruction are treated according to etiology that can be either due to adhesion, obstructed hernia and malignancy. In case of adhesive intestinal obstruction, if it is no feature suggestive of peritonitis, conservative management should be taken first because of 'once there is an adhesion, always adhesion'. Acute pancreatitis is the sometimes fatal condition according to its severity and complications. Severe cases of acute pancreatitis should be kept and treated at ICU. Generally the most cases of acute pancreatitis are conservatively managed, surgery is only indicated in cases with doubtful intestinal perforation, necrotizing or abscess. Early cholecystectomy is indicated in acute biliary pancreatitis. Intestinal obstruction due to obstructed or strangulated hernia should undergo emergency surgery. In laparoscopic era, the gold standard management is laparoscopic cholecystectomy after successful conservative management.

Conclusion

Diagnosis of acute abdomen is the art of the surgery which reflects the experience of a particular surgeon and mental work of decision making process. Although investigations are essential to allow accurate and timely patient assessment and diagnosis, these should not take the place of good history-taking and proper clinical examination.

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**Abnormal Uterine Bleeding (AUB)****Myanmar Obstetrical and Gynaecological Society**

Abnormal uterine bleeding is a common and debilitating condition in gynaecology. It is defined as any variation from the normal menstrual cycle which includes changes in regularity and frequency of menses, duration of flow or amount of blood loss.

Acute AUB is defined as bleeding in a non-pregnant women of reproductive age of sufficient quantity which requires immediate intervention to prevent further loss.

Chronic AUB is defined as bleeding from the uterine corpus that is abnormal in volume, regularity and/or timing that has been present for the majority of the last 6 months.

Previous terminology such as menorrhagia, metrorrhagia, oligomenorrhoea, polymenorrhoea are excluded. AUB is the term which encompasses heavy menstrual bleeding (HMB), inter-menstrual bleeding (IMB) and post menopausal bleeding (PMB). In 2009, FIGO menstrual disorders group was formed. FIGO World Congress of Gynaecology and Obstetrics accepted the new terminology. In 2011, The PALM-COEIN classification system was created.

- P - Polyp
- A - Adenomyosis
- L - Leiomyoma
- M - Malignancy & Hyperplasia
- C - Coagulopathy
- O - Ovulatory dysfunction
- E - Endometrial
- I - Iatrogenic
- N - Not yet classified

Polyp (AUB-P)

Endometrial polyps are epithelial proliferation arising from the endometrial stroma and glands. The majority are asymptomatic. It can be diagnosed by transvaginal ultrasound, hysteroscopy and saline infusion of hysterosalpingography.

Adenomyosis (AUB-A)

It is defined as ectopic endometrial glands and stroma within the myometrium and hypertrophy and hyperplasia of surrounding myometrium. It is associated with increasing age and may co-exist with fibroids.

**Leiomyoma (AUB-L)**

It is smooth muscle tumours of the uterus. According to location, there is a classification type 0 to type 8.

Malignancy (AUB-M)

Endometrial cancer is the most common gynaecological malignancy and the common presentation is post-menopausal bleeding. Increasing obesity and rising prevalence of the metabolic syndrome markedly increased in frequency.

Coagulopathy (AUB-C)

It is reported to affect 13% of women presenting with heavy menstrual bleeding. The majority of these women suffer from Von-Willebrand disease. Anticoagulant and antiplatelet therapy has been considered as a part of AUB-C.

Ovulatory (AUB-O)

Anovulatory cycles may contribute to AUB by unopposed oestrogen effects on the endometrium causing marked proliferation and thickening resulting in heavy menstrual bleeding along with an altered frequency of menstruation. It is associated with others endocrine abnormalities such as polycystic ovarian syndrome (PCOS), hyperprolactinaemia, hypothyroidism, as well as factors such as obesity, anorexia, weight loss, mental stress and extreme exercise.

Endometrial (AUB-E)

AUB that occurs in a structurally normal uterus with regular menstrual cycle without evidence of coagulopathy is likely to have an underlying endometrial cause. Diagnosis depends on careful history taking and exclusion of other contribution.

Iatrogenic (AUB-I)

Breakthrough bleeding (BTB) using gonadal steroids is the major component of AUB-I such as oral contraceptives, intrauterine devices, or implants.

Not yet classified (AUB-N)

Disorders that would be identified or defined only by biochemical or molecular biology assays (eg. Arterio venous malformations, endometrial pseudo aneurysms, myometrial hypertrophy and chronic endometritis).

Diagnosis of AUB

Detailed menstrual history, sexual and reproductive history, associated symptoms such as pain, discharge and bowel and bladder symptoms should be taken.

Any weight changes, drug history (antiplatelets, anticoagulant, tamoxifen, HRT, dopamine agonists), social history (smoking, stress, occupation), endocrine history (thyroid, PCOS, liver, adrenal diseases) should be taken.



Examination should focus on signs of anaemia, body mass index, systemic disorders such as thyroid disease, Cushing syndrome, hyper androgenism, palpable mass in abdomen.

Laboratory testing for evaluating acute AUB such as complete blood picture, blood groups, coagulation-profile should be done. Thyroid function test, liver function test, chlamydia trachomatis swab test should be considered if needed.

Imaging study is indicated when there is a risk of malignancy, when conservative management has failed or examination suggests structural causes for bleeding.

If imaging is indicated, TVS should be the first line imaging modality to assess myometrium, cervix, tubes and ovaries, endometrial polyps, adenomyosis, leiomyoma, uterine abnormalities, endometrial thickening associated with hyperplasia and malignancy.

Saline infusion sonography (SIS) improves the differentiation of intrauterine pathology such as polyps and fibroids.

Hysteroscopy can visualize the uterine cavity. Endometrial sampling is indicated in women with abnormal uterine bleeding over 40 years, patients with risk factors for endometrial cancer (obesity, hypertension, diabetes, PCOS), women with failed medical treatment and significant intermenstrual bleeding.

Treatment

Medical treatment

Aim is to control bleeding, to prevent recurrence and to correct anaemia and improve quality of life.

Medical treatment includes non-steroidal anti-inflammatory drugs (NSAID) eg: mefenamic acid, ibuprofen and naproxen. It can reduce menstrual blood loss by 33 to 55%. It can be given at the first day of menses and continued for 5 days or until cessation of menstruation. If it does not improve symptoms within 3 menstrual cycles, stop treatment.

Antifibrinolytic agent (tranexamic acid) one gram orally every 6 hours for the first four days of the cycles and it can reduce the menstrual blood loss by up to 40%.

Antifibrinolytic medication and NSAID can be used together but should be stopped after 3 months if there is no symptomatic improvement. If they are beneficial, these may be continued indefinitely.

Combined oral contraceptive pill and progestin are also alternative treatment to control menstrual cycle regularly.

Oral progestin, long course 21 days per cycles can reduce menstrual blood loss 60%. Short course luteal phase progestin does not produce significant benefit. Injectable progestin (depo-provera) can be administered every 12 weeks. It induces amenorrhoea by inhibition of FSH thus inhibiting follicular development, reducing oestradiol synthesis and secretion resulting in a thin endometrium. In trials, over half of the women became amenorrhoeic after one year but many reported unscheduled bleeding in the first few months.



Intrauterine system (LNG-IUS) is the first line of treatment in AUB according to NICE guideline 2007. It should be advised to preserve for at least 6 cycles to see the benefits of the treatment.

GnRHa can be given monthly injection for 3-6 months. Side effects are menopausal symptoms such as hot flushes, increased sweating and vaginal dryness.

Surgical treatment

First generation technique

Endometrial ablative method. Trans cervical resection of the endometrium (TCRE) involves resection of the endometrium using a 3 mm electrosurgical loop with resectoscope. Roller ball endometrial ablation uses a roller ball electrode instead of a loop. It can destroy up to 5 mm depth. Endometrial laser ablation is rarely used because of its costs and prolonged operating time.

Second generation technique

Thermal balloon ablation using the combination of high temperature and high pressure causes endovascular coagulation in the endometrial lining and subsequent fibrosis. It is contraindicated in patients with caesarean section and history of myomectomy. Bipolar radio frequency endometrial ablation - Novasure delivers radio frequency energy to the endometrium until trace impedance reaches 50 ohms.

Hydrothermal ablation can be done under hysteroscopic vision and endometrial destruction is achieved by circulating heated saline at 90°C in the endometrial cavity.

Management of AUB-L depends on fertility desire, impact of pressure symptoms, co-morbidities and patient's age. Treatment should be individualized.

Myomectomy (hysteroscopic or laparoscopic) is the option for AUB with leiomyoma who are young age and who preserve uterus for fertility.

Hysterectomy (abdominal or laparoscopic) is the most common major surgical procedure performed in gynaecology.

Conclusion

AUB is a common and debilitating condition. A structured approach to establishing the cause using the FIGO-PALM-COEIN classification system will facilitate accurate diagnosis and treatment options. Treatment should be individualized and encompass the impact of pressure symptoms, desire for fertility and contraceptive needs as well as address the management of AUB in order to achieve improved quality of life.



Dengue Virus Infection

Myanmar Pediatric Society

DENGUE VIRUS INFECTION

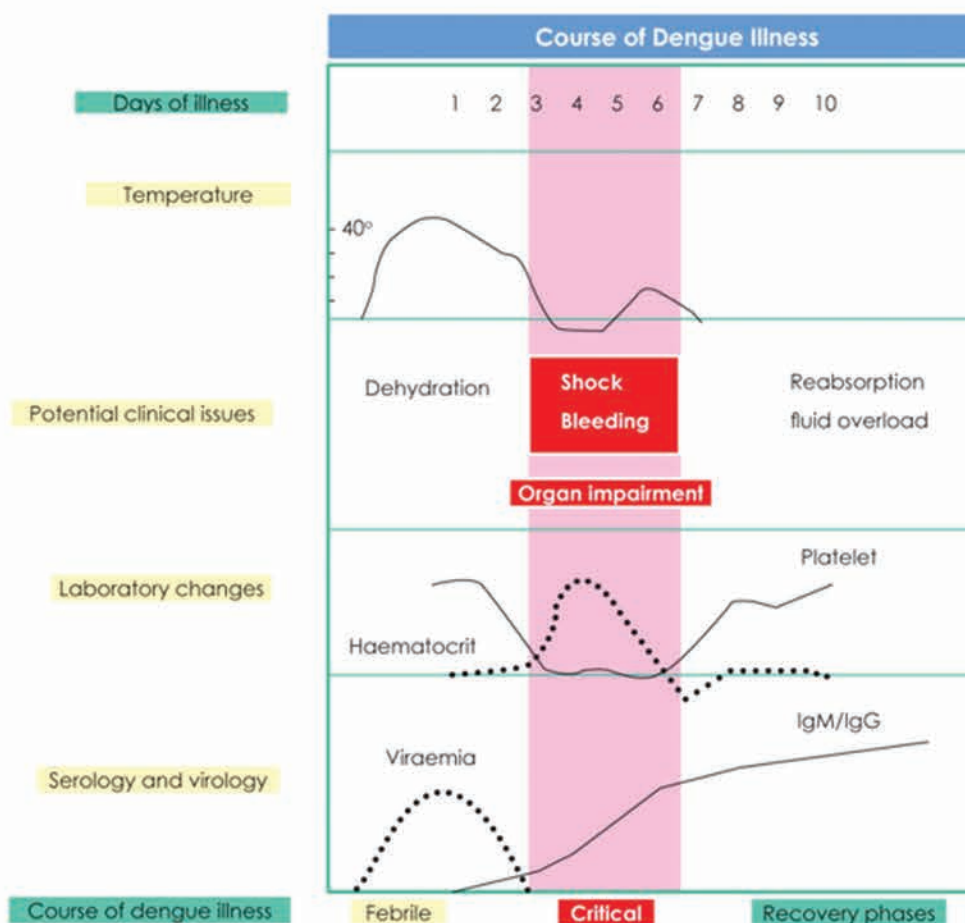
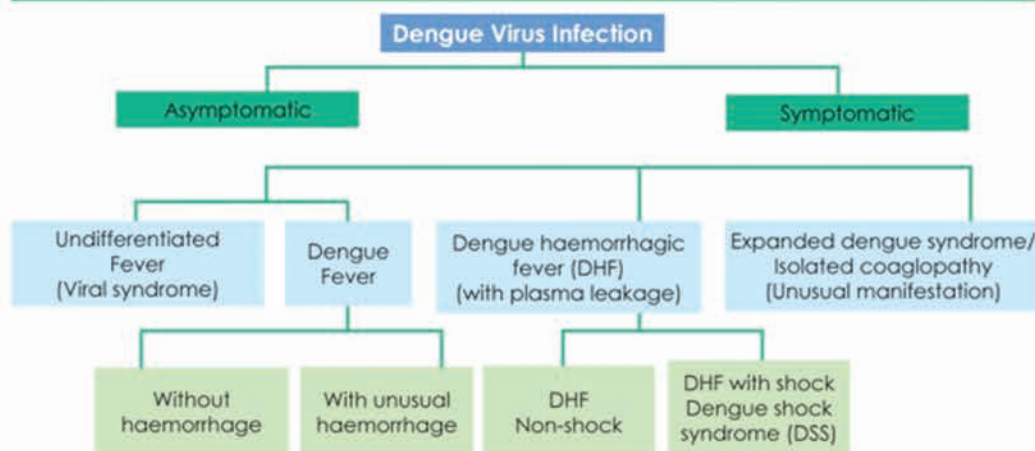


Table 1. WHO classification of dengue infection and grading of severity of DHF

DF/DHF	Grade	Signs and symptoms	Laboratory
DF		Fever with two of the following: <ul style="list-style-type: none"> Headache Retro-orbital pain Myalgia Arthralgia/bone pain Rash Haemorrhagic manifestations Hess test* + (>70%) No evidence of plasma leakage 	<ul style="list-style-type: none"> Leucopenia (WBC $\leq 5,000$ Cells/mm³) Thrombocytopenia (Platelet count $< 150,000$ cells/mm³) Rising haematocrit (5%-10%) from base line No evidence of plasma loss
DHF	I	Fever and haemorrhagic manifestation <ul style="list-style-type: none"> Hess test + (>90%) Evidence of plasma leakage 	<ul style="list-style-type: none"> Thrombocytopenia $< 100,000$ cells/mm³; HCT rise $\geq 20\%$ majority of cases $< 50,000$ cells/mm³ HCT rise $\geq 20\%$ from base line (due to plasma leakage)
DHF	II	As in Grade I plus spontaneous bleeding	<ul style="list-style-type: none"> Thrombocytopenia $< 100,000$ cells/mm³ HCT rise $\geq 20\%$
DSS (Compensated Shock)	III	As in Grade I or II plus circulatory failure (weak pulse, narrow pulse pressure (≤ 20 mmHg), hypotension, restlessness)	<ul style="list-style-type: none"> Thrombocytopenia $< 100,000$ cells/mm³ HCT rise $\geq 20\%$
DSS (Hypotensive Shock)	IV	As in Grade III plus profound shock with undetectable BP and pulse	<ul style="list-style-type: none"> Thrombocytopenia $< 100,000$ cells/mm³ HCT rise $\geq 20\%$
Expanded Dengue Syndrome#		<ul style="list-style-type: none"> Complications of severe profound shock or associated with underlying host conditions/ diseases or coinfections. Central nervous system (CNS) manifestations including convulsions, spasticity, changes in consciousness and transient paresis have been observed. 	

Source: <http://www.who.int/csr/resources/publications/dengue/Denguepublication/en/>



Stepwise approach to the management of dengue patients

Step I

Overall assessment

History

The history should include:

- Date of onset of fever or illness
- Quantity of oral intake
- Assessment for warning signs
- Gastrointestinal disorders (nausea, vomiting, diarrhea, gastritis)
- Change in mental state: restlessness, drowsiness, lethargy, lipothymia, dizziness, seizures, and vertigo
- Urine output (frequency in last 24 hours, volume, and time of last voiding)
- Relatives with dengue or within the neighborhood, or recent travel to dengue endemic areas (14 previous days) other patient characteristics: e.g. infant (29 days to 6 months), older adult >65 years of age, pregnant, obese, asthmatic, has diabetes or hypertension, others
- Travelling to malaria endemic area (consider malaria)

Physical examination

The physical examination should include

- Assessment of mental state
- Assessment of hydration status
- Assessment of haemodynamic status
- Checking for tachypnoea/acidotic breathing/pleural effusion
- Checking for abdominal tenderness/hepatomegaly/ascites
- Examination for rash and bleeding manifestations
- Tourniquet test (repeat if previously negative or if there is no bleeding manifestation)

Step II. Diagnosis, assessment of disease phase and severity

To determine the phase (febrile, critical or recovery), warning signs (WSs), hydration and haemodynamic status of the patient, and whether the patient requires admission

Febrile phase, usually 4 to day 7 of illness

- May have WSs
- Normal WBC
- Platelet count $\geq 100,000$ cells/mm³

Hess test positive (or petechiae) + WBC $\leq 5,000$ cells/mm³

WSs = Warning Signs



Clinical Warning Signs

Significant abdominal pain

- Severe enough to be patient's chief complaint
- Could be mistaken as surgical condition
- Is associated with increased vascular permeability and/or shock in the defervescence phase
- Tense abdomen due to ascites + liver congestion can cause abdominal pain
→ Consider fluid overload instead

Persistent vomiting

- Three or more times per day and patient is not able to tolerate oral fluid.
- Important sign of plasma leakage

Lethargy

- Patient is confined to bed for most of the day.
- Patient sleeps most of the time.
- Patient is uninterested in food or television.
- Patient is too weak to walk to toilet.

Restlessness

- Sign of severe shock + cerebral hypoperfusion

Mucosal bleeding

- warning of more severe manifestations

Fluid accumulation

- Volume of fluid accumulation = severity of vascular permeability + fluid therapy

Table 2. Laboratory warning signs

Leucopenia
<ul style="list-style-type: none"> • Occurs 24 hours before rapid decrease in platelet count • Not predictive of plasma leakage • Good indicator that patient could have dengue
Rapid decrease in platelet count + rising trend in haematocrit
<ul style="list-style-type: none"> • Occur shortly before or at defervescence • May precede changes in blood pressure and pulse pressure • Indicate an increase in vascular permeability
NOTE: Changes in haematocrit May be masked by IV fluid therapy

Rapid Diagnostic Test of Dengue Infections*: helps in differentiating dengue from other AFI but does not guide clinicians for IV fluid management. It cannot replace CBC.

- **NS₁Ag**: The highest percentage of positive test is on the first 2 days of fever (Sensitivity ranges – 40-70%). On day 4 of fever the percentage of positive test may be reduced to 30-40%.
- **IgM/IgG** is recommended from day 5 onwards (Sensitivity – 60-80% on day of shock or defervescence and reached 100% one day after shock/defervescence)



- **Duo test ($NS_{1Ag} + IgM/IgG$)** is more expensive and is recommended between day 4 onwards, the overall sensitivity may increase to >90%
(*Those tests are not recommended as compulsory tests)

Critical Phase

• Severe dengue includes

- o Sudden drop of temperature, patient develops features of **shock**, leucopenia followed by thrombocytopenia and rise of Haematocrit $\geq 20\%$ above the base line
- o Major bleeding
- o Organ impairment

Table (3) Haemodynamic assessment: Continuum of haemodynamic changes

Parameters	Stable circulation	Compensated shock	Hypotensive shock
Conscious level	Clear and lucid	Clear and lucid (shock can be missed if you do not touch the patient)	Change of mental state (restless, combative)
Capillary refill time	Brisk (<1 Sec)	Prolong (>2 Sec)	Very prolong, mottled skin
Peripheral pulse volume	Good volume	Weak and thready	Feeble or absent
Heart rate	Normal for age	Tachycardia	Severe tachycardia with bradycardia in late shock
Blood pressure	Normal for age	Normal systolic pressure but rising diastolic pressure	Narrow pulse pressure (<20 mmHg)
	Normal pulse pressure for age	Narrowing pulse pressure Postural hypotension	Hypotension (See definition below) Unrecordable blood pressure
Respiratory rate	Normal for age	Tachypnoea	Metabolic acidosis hyperpnoea/ Kussmaul's breathing



Definition of Hypotension

- Systolic blood pressure of <90mmHg or mean arterial pressure < 70 mmHg in adults
- Systolic blood pressure decrease of >40 mmHg or < 2 SD below normal for age
- In children up to 10 years of age, the 5th centile for systolic blood pressure can be determined by the formula $70 + (\text{age in years} \times 2)$ mmHg

Narrow pulse pressure, 20 mmHg alone is seen in many normal children. Therefore other criterion + pulse pressure 20 mmHg must be fulfilled for diagnosis of compensated shock

Major bleeding occurs usually from the gastrointestinal tract. Internal bleeding may not become apparent for many hours until the first black stool is passed.

Patients at risk of major bleeding are those who

- Have prolonged/refractory shock
- Have hypotensive shock and renal or liver failure and/or severe and persistent metabolic acidosis
- Are given non-steroidal anti-inflammatory agents
- Have pre-existing peptic ulcer disease
- Are on anticoagulant therapy
- Have any form of trauma, including intramuscular injection

Step III. Management

- Disease notification
- Management decisions. Depending on the clinical manifestations and other circumstances, patients may:
 - **Group A:** Be sent home
 - **Group B:** Be referred for in-hospital management
 - **Group C:** Emergency treatment and urgent referral

**Group A—Patients who may be treated at home**

- Are able to tolerate adequate volumes of oral fluids
- Pass urine at least once every six hours
- Do not have any of the warning signs
- Do not have any of co-existing conditions

Those with stable haematocrit can be sent home after being advised **to return to the hospital immediately if they develop any of the warning signs** and to adhere to the following action plan

Fluids: Encourage oral intake of oral rehydration solution (ORS), fruit juice and other fluids containing electrolytes and sugar to replace losses from fever and vomiting

Antipyretics: paracetamol for high fever if the patient is uncomfortable. The interval of paracetamol dosing should not be less than six hours

Instruct the care-givers that the patient should be brought to hospital immediately if any of the following occur

- No clinical improvement
- Deterioration around the time of defervescence
- Severe abdominal pain
- Persistent vomiting
- Cold and clammy extremities
- Lethargy or irritability/restlessness
- Bleeding (e.g. black stools or coffee-ground vomiting)
- Not passing urine for more than 4-6 hours

Group B—Patients who require in-hospital management

- Patients with warning signs
- Those with co-existing conditions that may make dengue or its management more complicated (infancy, obesity, diabetes mellitus, renal failure, chronic haemolytic diseases)
- Those living far from a health facility without reliable means of transport

Group C— Patients who Require Emergency Treatment for Severe Dengue

- Fluid resuscitation will depend on whether the patient is having
 - o Compensated shock OR
 - o Hypotensive shock

**Special consideration**

For infant dengue—Use isotonic fluid during critical phase except in infants <6 months in whom ½ Strength Saline is to be used

Note for infant

- Basal Hct may be lower than the Hct of older children e.g. 30%
- Therefore, Hct level 36% may be 20% rise from basal level and consider as hemoconcentration
- Critical phase will last shorter than that of older children (may be 12 hours)
- More difficult to diagnose
- Investigate—FBC, Hct, NS1, Ig G& IgM + LFT, ABCS

For obese patient—Use ideal body weight



How to manage a patient with newly diagnosed type 2 diabetes mellitus

Myanmar Endocrinology & Metabolism Society

Diabetes mellitus is a complex chronic medical illness which require continuous medical care involving multi-factorial risk-reduction strategies beyond glycemic control. According to the National Survey of Diabetes conducted in 2014, Type 2 Diabetes is an ongoing trend in Myanmar with the prevalence of 10.5% in adult population. Based on the UKPDS study, achieving good glycemic control is an important factor for the prevention of long-term microvascular and macro vascular complications. In an attempt to achieve an optimal diabetes management, an organized and systematic approach is the main priority.

Majority of newly diagnosed type 2 diabetes mellitus are likely to be uncovered at the primary health care level and hence the primary care physicians are the frontier persons to encounter both newly diagnosed diabetes, both early and late.

The following steps are the initial approach of a case of hyperglycemia at the primary care level.

The **diagnosis** of diabetes mellitus should be confirmed by the following methods.

HbA1c \geq 6.5%

or

Fasting plasma glucose \geq 126 mg/dl (7.0 mmol/L);

fasting refers to no caloric intake for at least eight hours

or

2 hour plasma glucose \geq 200 mg /dl (11.1 mmol/L) during an OGTT;

test should be performed as described by the World Health Organization using a 75 g anhydrous glucose load dissolved in water

or

Random plasma glucose \geq 200 mg per dl with classic symptoms of hyperglycemia

(In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing)

Management

The diabetes care is best provided by a multidisciplinary team of health professionals with expertise in diabetes, working in collaboration with the patient and family. Management includes the following steps:

1. Appropriate goal setting for glycemic target, hypertension goal and lipid management
2. Lifestyle management
3. Medications
4. Appropriate self-monitoring of blood glucose (SMBG)
5. Regular monitoring for complications
6. Laboratory assessment



1. Target should be individualized (patient- centered approach)

For general,

Glycemic parameters	
Fasting plasma glucose	80-130 mg/dl
2-hr post-prandial glucose	< 180 mg/dl
HbA1c	< 7%

More stringent A1c goals (< 6.5%)

- without significant hypoglycemia or other adverse effects of treatment
- long life expectancy
- no significant cardiovascular disease

Less stringent A1c goals (< 8%)

- severe hypoglycemia and hypoglycemia unawareness e.g. autonomic neuropathy
- limited life expectancy
- advanced microvascular or macro vascular complications
- extensive co-morbid conditions

2. Lifestyle Management

- Diabetes Self-Management Education and Support
- Nutrition Therapy
- Physical Activity
- Smoking Cessation: Tobacco and e-Cigarettes
- Psychosocial Issues

3. Medications: Oral anti diabetic agents (OAD)

I. General guidelines for use of oral anti diabetic agents

- OAD can be used as mono therapy or in combination with other OAD(s), and/or injectable agents (e.g. insulin, GLP-1 receptor agonist (GLP-1RA)).
- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent. Other OAD agents are acceptable alternatives.
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, impact on weight, potential side effects, co-morbidity, cost and patient preferences.
- Compliance may be improved with once daily dosing OAD agents.
- OAD agents are usually not the first line therapy in stress hyperglycemia. Insulin therapy is recommended.
- When indicated, especially in patients with high risk for hypoglycemia, start with a minimal dose of OAD agent, while re-emphasizing diet and physical activity. The dose should be optimized gradually.
- If glycemic targets are not achieved (HbA1c or more than 75% of FBS and/or



2HPP in SMBG), intensification of treatment should be made every 3 months after assessing the drug and dietary compliance.

- If mono therapy at maximum tolerated dose does not achieve or maintain the A1c target after 3 months, combination of second agent is recommended. (Dual therapy)

Table. Initiation of OAD according to FBS, HbA1c or RBS

HbA1c if available	FBS (mg/dl)	plasma glucose (mg/dl)	Starting OAD
< 9%	< 150	< 250	Mono therapy
> 9%	150 - 200	250 - 350	Dural therapy
> 10%	> 200	> 350	Combination injectable therapy

II. Algorithm of management of type 2 diabetes mellitus

Treatment Algorithm

HbA1c < 9% - Consider Monotherapy Metformin

↓
Not well controlled (After 3 months)
Titration of the dose to be done within 3 months

Metformin + SU or

Metformin + TZD or

Metformin + DPP4 Inhibitor or

Metformin + SGLT2 Inhibitor

↓
Not well controlled (After 3 months)
Titration of the dose to be done within 3 months

Metformin + SU + TZD/ DPP4-I/ SGLT2-I

Metformin + TZD+ SU/ DPP4-I/SGLT2-I

Metformin + DPP4-I+ SU/ TZD/ SGLT2-I

Metformin+ SGLT2-I + SU/ TZD/ DPP4-I

↓
Titration of the dose to be done within 3 months

Not well controlled (After 3 months)

Oral triple therapy + Basal insulin

e.g. If patient is obese, drugs that cause weight loss (SGLT2 inhibitor, GLP1RA) or weight neutral (Metformin, DPP4-I) should be first choice. If patient has high risk of hypoglycemia, Sulphonylurea should be avoided or used with caution. Patient has atherosclerotic cardiovascular disease (ASCVD), SGLT2 inhibitor should be used. Metformin usage should be reevaluated at an **eGFR < 45 mL/min/1.73 m²** with a **reduction** in maximum dose to **1,000 mg/day** and **discontinued** when **eGFR is < 30 mL/min/1.73 m²**.



Table. Drug-specific and patient factors to consider when selecting OAD in adults with T2DM

	Efficacy	Hypo-glycaemia	Weight Change	CV Effects		Cost	Renal Effects		Additional Considerations
				ASCVD	CHF		Progression of DKD	Dosing / Use considerations	
Metformin	High	No	Neutral (Potential for modest Loss)	Potential Benefit	Neutral	Low	Neutral	Contraindicated with eGFR < 30	- Gastrointestinal side effects common (diarrhoea, nausea) - Potential for B ₁₂ deficiency
Sulphonylureas (2 nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Neutral	- Glyburide: not recommended - Glipizide & Glimepiride: initiate conservatively to avoid hypoglycaemia	- FDA Special Warning on increased risk of CV mortality based on studies of an older sulphonylurea (Tolbutamide)
Thiazolidinediones	High	No	Gain	Potential Benefit (Pioglitazone)	Increased risk	Low	Neutral	- No dose adjustment required - Generally not recommended in renal impairment due to potential for fluid retention	- FDA Black Box: CCF (Pioglitazone, rosiglitazone) - Fluid retention (Oedema; heart failure) - Benefit in NASH - Risk of bone fractures - Bladder cancer (pioglitazone) - ↑ LDL cholesterol (rosiglitazone)
DPP4 inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk (Saxagliptin, Alogliptin)	High	Neutral	Renal dose adjustment required; can be used in renal impairment	- Potential risk of acute pancreatitis - Joint pain



	Efficacy	Hypo-glycaemia	Weight Change	CV Effects		Cost	Renal Effects		Additional Considerations
				ASCVD	CHF		Progression of DKD	Dosing / Use considerations	
SGLT-2 inhibitors	Inter-mediate	No	Loss	Benefit: Canagliflozin Empagliflozin	Benefit: Canagliflozin Empagliflozin	High	Benefit: Canagliflozin Empagliflozin	Canagliflozin - Not recommended with eGFR < 45 Dapagliflozin - Not recommended with eGFR < 60. Contraindicated with eGFR < 30 Empagliflozin - Contraindicated with eGFR < 30	- FDA Black Box: Risk of amputation (Canagliflozin) - Risk of bone fractures (Canagliflozin) - DKA risk (all agents, rare in T2DM) - Genitourinary infections - Risk of volume depletion, hypotension - ↑ LDL cholesterol GI side effects
α-Glucosidase Inhibitors (AGIs)	Inter-mediate	No	Neutral	Neutral	Neutral	Variable	Neutral	No dose adjustment required	GI side effects
Meglitinides	High	Mild	Neutral	Neutral	Neutral	Inter-mediate	Neutral	CrCl 40-80 ml/min: No adjustments necessary, CrCl 20-40 ml/min: Titrate slowly, CrCl < 20 ml/min: No data	wait for longer intervals to make dosage adjustments in hepatic impairment
Quick-release dopamine receptor agonist bromocriptine mesylate	Slight	No	Neutral	Safe	Neutral	Inter-mediate	Neutral	No dose adjustment required	- Moderate GI side effects - should not be used in patients taking antipsychotic drugs

**How to monitor**

HbA1c

- **quarterly a year (3 monthly)** (in patients whose therapy has changed or who are not meeting glycemic goals)
- **at least two times a year (6 monthly)** (patients who are meeting treatment goals)
If HbA1c is not available, glycemic control can be monitored by SMBG.

Frequency of SMBG depends on glycemic status. If it is poor control, frequent monitoring is required.

(Notes: SMBG should be done at a specific time e.g., FBS rather than RBS.

To aware of the discrepancies between HbA1c and SMBG where HbA1c is taken as standard)

Co-morbidities or cardiovascular risk assessment

- Obesity (BMI must be calculated in all patients)
- Dyslipidemia (Fasting lipid profile)
- Hypertension (BP Target < 140/90 mmHg)
- Albuminuria (Urine micro albumin, Creatinine)
- Smoking and family history

Look for complications**Macro vascular complications****Cardiovascular disease**

- ECG at the time of diagnosis and yearly thereafter and necessary

Cerebrovascular disease

- Stroke, TIA by history and physical examination

Peripheral vascular disease

- Symptoms of intermittent claudication, pulse, ABI - Ankle Brachial Index

Micro vascular Complications

- Screening should be done at the time of diagnosis and yearly thereafter and as necessary

Renal

- Urinary micro albumin
- Creatinine (Cr Clearance)

Neuropathy / foot care

- Foot screening and risk assessment (ABI, Monofilament)

Retinopathy

- Dilated eye examination by fundoscope or retinal photography

When to refer to Physicians?

- Newly diagnosed Type 1 Diabetes
- Uncertain diagnosis or classification
e.g. MODY, LADA, Secondary diabetes



- Any Diabetic patient who is pregnant or considering pregnancy
- Complications
- Other Medical problems

In conclusion, as DM is life-long disease, it requires a continuous care. It is important to have a collaboration and multi-disciplinary approach between family physician (GP), endocrinologist, internist, surgeon, ortho-surgeon and other specialists to achieve the best outcomes.

References

1. Standards of medical care in diabetes, 2018
2. Report on national survey of diabetes mellitus and risk factors for non-communicable diseases in Myanmar, 2014



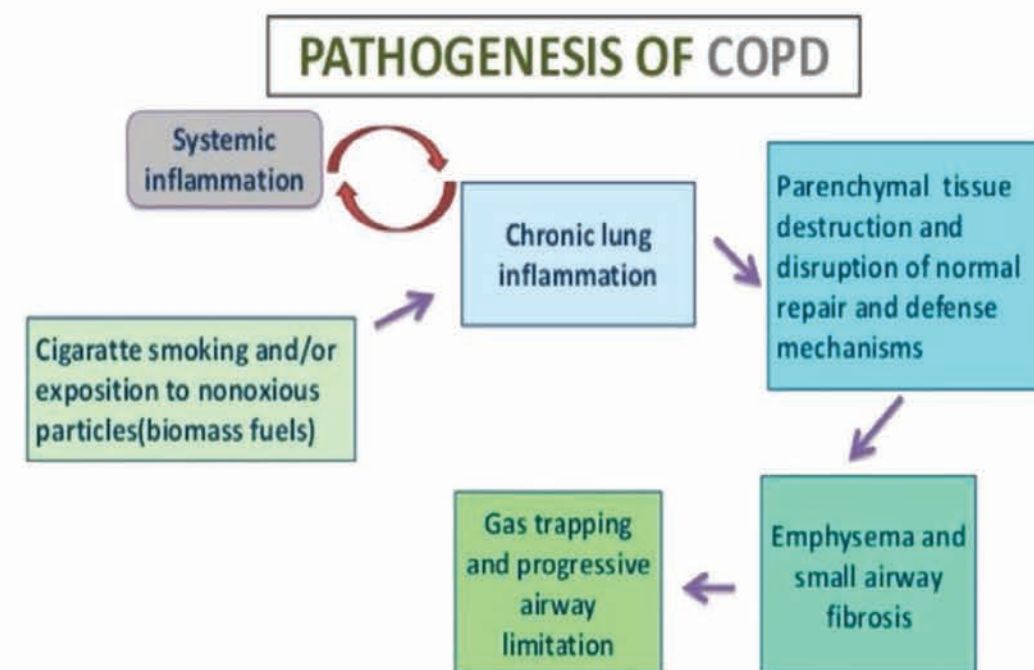
Chronic Obstructive Pulmonary Disease

Myanmar Thoracic Society

Chronic Obstructive Pulmonary Disease

Definition

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is 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.



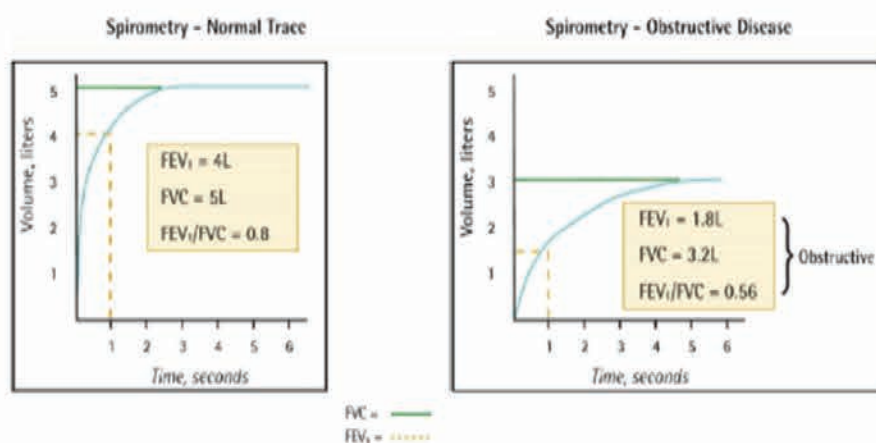


Diagnosis of COPD

Diagnosis of COPD is based on "GOLD Criteria"

- Symptoms : cough, sputum and shortness of breath
- Exposure to Risk Factors : like tobacco, occupation and indoor and outdoor pollution
- Spirometry : is required to establish the diagnosis

Spirometry



Classification of Severity of Airflow Limitation in COPD

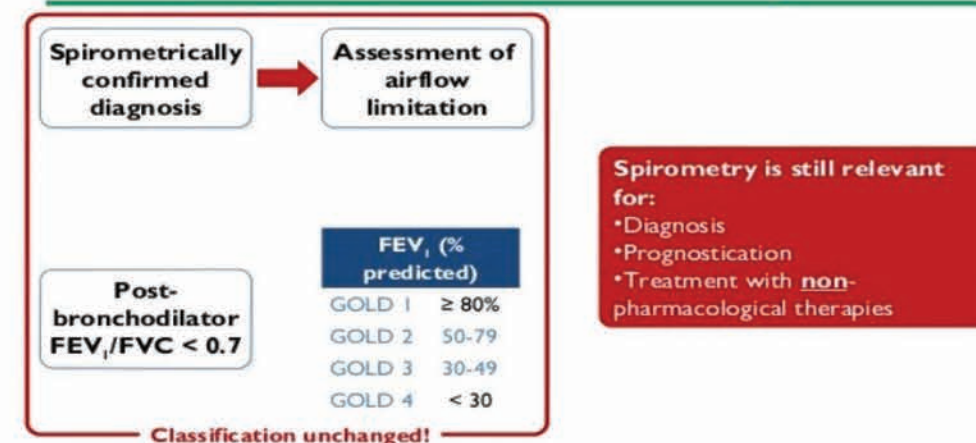
(Based on post-bronchodilator FEV₁)

In patients with post-bronchodilator FEV₁/FVC < 0.70

- GOLD 1 – mild: FEV₁ ≥ 80% predicted
- GOLD 2 – moderate: 50% ≤ FEV₁ < 80% predicted
- GOLD 3 – severe: 30% ≤ FEV₁ < 50% predicted
- GOLD 4 – very severe FEV₁ < 30% predicted



ABCD assessment 2017 has been refined: Spirometry



Modified Medical Research Council (MMRC) dyspnea scale

Grade	Description of breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

Adapted from: Fletcher CM, Elmes PC, Fairbairn MB, et al. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *British Medical Journal* 1959; 2:257.

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Adapted from: Fletcher CM, Elmes PC, Fairbairn MB, et al. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *British Medical Journal* 1959; 2:257.



Your name:

Today's date:

**How is your COPD? Take the COPD Assessment Test™ (CAT)**

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy (0) **X** (1) (2) (3) (4) (5) I am very sad

		SCORE
I never cough	(0) (1) (2) (3) (4) (5) I cough all the time	
I have no phlegm (mucus) in my chest at all	(0) (1) (2) (3) (4) (5) My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	(0) (1) (2) (3) (4) (5) My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	(0) (1) (2) (3) (4) (5) When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	(0) (1) (2) (3) (4) (5) I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	(0) (1) (2) (3) (4) (5) I am not at all confident leaving my home because of my lung condition	
I sleep soundly	(0) (1) (2) (3) (4) (5) I don't sleep soundly because of my lung condition	
I have lots of energy	(0) (1) (2) (3) (4) (5) I have no energy at all	
TOTAL SCORE		

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For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

		SCORE
Example: Cough	(3) (4) (5) I am very sad	
Sputum	(3) (4) (5) I cough all the time	
Chest	(3) (4) (5) My chest is completely full of phlegm (mucus)	
Tightness	(3) (4) (5) My chest feels very tight	
Waking Up	(3) (4) (5) When I walk up a hill or one flight of stairs I am very breathless	
Hill	(3) (4) (5) I am very limited doing activities at home	
ADLs	(3) (4) (5) I am not at all confident leaving my home because of my lung condition	
Leaving the House	(3) (4) (5) I don't sleep soundly because of my lung condition	
Sleep	(3) (4) (5) I have no energy at all	
Energy Levels	(3) (4) (5)	
TOTAL SCORE		

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Symptoms Assessment in GOLD A,B,C,D

SYMPTOMS	
Less symptoms mMRC=0-1 CAT<10	More symptoms mMRC≥2 CAT≥10
C	D
A	B

Risk Assessment in GOLD A,B,C,D

RISK	High risk GOLD 3-4 (i.e. FEV ₁ <50%) Exacerbations ≥2/year	C	D
	Low risk GOLD 1-2 (i.e. FEV ₁ ≥50%) Exacerbations ≤1/year	A	B

PATIENT GROUP		SYMPTOMS	
		Less symptoms mMRC=0-1 CAT<10	More symptoms mMRC≥2 CAT≥10
RISK	High risk GOLD 3-4 (i.e. FEV ₁ <50%) Exacerbations ≥2/year	C	D
	Low risk GOLD 1-2 (i.e. FEV ₁ ≥50%) Exacerbations ≤1/year	A	B

TREATMENT OF STABLE COPD IS BASED ON INDIVIDUALIZED ASSESSMENT OF SYMPTOMS AND FUTURE RISK OF EXACERBATIONS!

AIMS OF TREATMENT:

- 1) SUPPORT TO QUIT SMOKING
- 2) REDUCTION OF SYMPTOMS
- 3) REDUCTION OF FUTURE RISK OF EXACERBATIONS
- 4) ADD NON-PHARMACOLOGIC TREATMENT(S)

Manage Stable COPD:

Pharmacologic Therapy

Beta2-agonists	• Short-acting beta ₂ -agonists • Long-acting beta ₂ -agonists
Anticholinergics	• Short-acting anticholinergics • Long-acting anticholinergics
Corticosteroids	• Inhaled Corticosteroids
Inhaled Combination	• Short-acting beta ₂ -agonists + anticholinergics • Long-acting beta ₂ -agonists + anticholinergic • Long-acting beta ₂ -agonists + corticosteroids
Others	• Methylxanthines • Phosphodiesterase-4 inhibitors

Long-Acting Bronchodilators

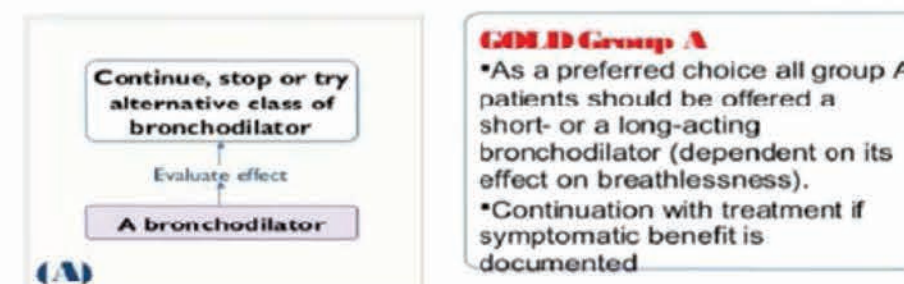
• LAMAs

- Block acetylcholine-mediated bronchoconstriction (via M₃ receptors)
 - Tiotropium
 - Aclidinium
 - Glycopyrronium (glycopyrrolate)
 - Umeclidinium

• LABAs

- Direct relaxant activity on airway smooth muscle (via β₂ adrenoceptors)
 - Formoterol
 - Salmeterol
 - Indacaterol
 - Olodaterol
 - Vilanterol

Pharmacological Treatment in detail: GOLD Group A patients



In patients with a major discrepancy between the perceived level of symptoms and severity of air-flow limitation, further evaluation is warranted.

Pharmacological Treatment in detail: GOLD Group B patients

- For Group B patients, therapy should begin with a long-acting bronchodilator **LABA** or **LAMA**, (no evidence to recommend one over another), and should be escalated to two bronchodilators if breathlessness continues with monotherapy.
- If breathlessness is severe, starting the patient on dual long-acting bronchodilators can be considered, however if the second therapy does not improve symptoms, the guidelines suggest stepping down to one bronchodilator.

Pharmacological Treatment in detail: GOLD Group C patients

- For Group C patients, it is recommended that treatment be started with a single long-acting bronchodilator, preferably a LAMA (LAMA was superior to the LABA regarding exacerbation prevention).
- A second long-acting bronchodilator or the combination of LABA/ICS may be used for persistent exacerbations.
- The guidelines recommend LABA/LAMA as the addition of ICS has been shown to increase pneumonia risk in some patients.

The use of ICS-containing Therapies in COPD

- Compared to non-ICS containing therapies in COPD, therapies containing ICS, eg, LABA/ICS FDC are associated with greater risk of:
 - Pneumonia
 - Bone density decline and fractures
 - Candidiasis and skin lesions
 - Cataracts
- Evidence linking ICS-containing therapies with increased risk of diabetes mellitus.

Patients at a higher risk of developing pneumonia

- Current Smokers
- ≥ 55 years of age
- History of prior exacerbations or pneumonia
- Body mass index (BMI) < 25 kg/m²
- Poor MRC dyspnea grade
- And/or severe airflow limitation

Pharmacological Treatment in detail: GOLD Group D patients

- For Group D patients, a LABA/LAMA combination is preferred as initial therapy over LABA/ICS as these patients may be at higher risk of developing pneumonia with ICS use.
- For patients with high blood eosinophil counts or those with asthma-COPD overlap, LABA/ICS could be considered first-line therapy.

The use of ICS-containing Therapies in COPD

- Bronchodilators are central to symptom management in COPD
 - GOLD 2017 guidelines recommend bronchodilators in all patients with COPD
- ICS-containing therapies currently over-used in management of COPD
 - More than 70% of patients with COPD are currently receiving an ICS-containing therapy but, based on GOLD guidelines, this should be less than 20%
 - ICS should be reserved for those patients in whom additional bronchodilation is failing to control their exacerbations
- ICS in combination with LABA have limited role in COPD

The significance of the assessment and evaluation of inhaler technique has been considerably enhanced

- Inhaler technique needs to be assessed regularly to improve therapeutic outcomes
- Importance of education and training cannot be over-emphasised
- Choice of inhaler device has to be individualised and will depend most importantly on patient's ability and preference
- Instructions and demonstration of a proper inhalation technique are essential also a re-check at each visit to ensure a correct use of the inhaler
- Inhaler technique (and adherence) should be evaluated before a treatment is assessed as insufficient

Therapeutic Options

Occupational Exposure

- Elimination or reduction of exposures in the work place.
- Surveillance and early detection

Indoor & Outdoor Air Pollution

- Reduce or avoid burning biomass for cooking and heating in poorly ventilated dwellings.
- Advice patient to monitor public announcements of air quality.

Physical Activity

- Remain active.
- All COPD patients benefit from regular physical activity.

Smoking Cessation

- | | | |
|--------------------------------|---|---|
| • Prevention | : | Programs with clear, consistent and repeated non-smoking message
Smoke-free schools |
| • Counseling | : | Even short counseling results quit rates of 5-10% |
| • Nicotine Replacement Therapy | : | Nicotine gum, inhaler or spray, transdermal patch, sublingual tablet etc.
Varenicline?
Bupropion?
Nortriptyline? |

Other Pharmacological Treatments

Vaccines

- Influenza vaccines can reduce serious illness (LRTI) requiring hospitalization up to death in COPD patients.
- Pneumococcal polysaccharide vaccine recommended for COPD patients ≥ 65 years, younger patients with significant comorbid condition.

α -1 Antitrypsin Augmentation

- Only young patients with severe hereditary α -1 antitrypsin deficiency and established emphysema may be candidates.
- Very expensive, is not available in most countries.

Other Treatments

Oxygen Therapy

- Increased survival in patients with severe resting hypoxaemia.
- Indicated for $\text{PaO}_2 \leq 8.0 \text{ kPa}$ / $\text{SaO}_2 \leq 88\%$, pulmonary hypertension, congested cardiac failure, polycythemia.

Ventilatory Support

- Non-invasive ventilation (NIV) is increasingly used in patients with stable very severe COPD.

Surgical Treatments

Lung Volume Reduction Surgery

- Part of the lungs are resected.
- Reduce hyperinflation making respiratory m/s more effective improving their mechanical efficiency thus improve expiratory flow rate & reduce exacerbation.
- More significant among patient with predominant upper lobe emphysema & low ex capacity prior to treatment.

Lung Transplantation

- Appropriately selected patients with very severe COPD improve quality of life & functional capacity.
- Post operative mortality, acute rejection, fungal or bacteria infection etc;
- Limited by shortage of donar organs & costs.



Antinuclear antibodies (ANA) for Systemic lupus erythematosus (SLE)

Myanmar Rheumatology Society

SLE is an autoimmune disease involving multiple organs, characterized by a vast array of autoantibodies, particularly antinuclear antibodies, in which injury is caused mainly by deposition of immune complexes and binding of antibodies to various cells and tissues. It has acute or insidious onset characterized by chronic, remitting and relapsing, often febrile illness characterized by injury to skin, joints, kidney and serosal membranes. Prevalence may be as high as 1 in 2500 in certain populations predominantly affecting women, with a frequency of 1 in 700 among women of childbearing age with female-to-male ratio of 9:1.

The fundamental defect in SLE is a failure of the mechanisms that maintain self-tolerance and the hallmark of the disease is the production of autoantibodies. Most of the visceral lesions are caused by immune complexes (Type III hypersensitivity) ie. DNA- anti-DNA complexes deposit in the glomeruli and small blood vessels giving rise to glomerulonephritis and vasculitis. Autoantibodies specific for red cells, white cells & platelets opsonize these cells and promote their phagocytosis & lysis (Type II hypersensitivity) causing anemia, leucopenia and thrombocytopenia.

Antinuclear antibodies (ANA) are a group of autoantibodies produced by a person's immune system when it fails to adequately distinguish between "self" and "nonself." The ANA test detects these autoantibodies in the blood. ANA react with components of the body's own healthy cells and cause signs and symptoms such as tissue and organ inflammation, joint and muscle pain, and fatigue. ANA specifically target substances found in the nucleus of a cell, hence the name "antinuclear." They probably do not damage living cells because they cannot access their nuclei. However, ANA can cause damage to tissue by reacting with nuclear substances when they are released from injured or dying cells.

The ANA test is one of the primary tests for helping to diagnose a suspected autoimmune disorder or rule out other conditions with similar signs and symptoms. The ANA test may be positive with several autoimmune disorders. Patients with the autoimmune disorder systemic lupus erythematosus (SLE) are almost always positive for ANA, but the percentage of patients with other autoimmune disorders who have positive ANA results varies. Also, a significant number of patients with a variety of other types of disorders (and even some healthy people) may be positive for ANA, especially at low levels.

Antinuclear antibodies (ANAs) is a good screening test for SLE, since high levels of ANAs can be found in more than 98% of patients with SLE. However, there are other conditions that can cause high levels of ANA, so this test cannot be used in isolation for the diagnosis of SLE. An ANA titer of 1:40 or higher is considered positive. An ANA titer of less than 1:40 is useful for ruling out SLE in children (sensitivity of 98%). A repeated negative



result makes a diagnosis of SLE unlikely but not impossible. ANAs are grouped into four categories: Ab to DNA, Ab to histones, Ab to nonhistone proteins bound to RNA and Ab to nucleolar antigens. There are several ANA subtypes that can be found in SLE patients. These are anti-double stranded DNA (anti-ds DNA), anti-Smith (Anti-Sm), anti-Ro (also called anti-SSA), anti-La (also called anti-SSB), and anti-histone antibodies.

Anti-ds DNA antibodies can be found in 70% of SLE patients and are characteristic of active disease. High levels often indicate kidney involvement. Anti-ds DNA levels tend to fluctuate over time in correlation with disease activity and are good for monitoring SLE patients for signs of disease exacerbation. Anti-Ro antibodies characterize several lupus subtypes, but they are not lupus-specific, as they are often found in patients with Sjogren's syndrome. They are also associated with neonatal lupus syndrome, in which maternal antibodies cross the placenta and cause photosensitive rashes and congenital heart block in affected babies. Therefore, all SLE female patients of child-bearing age should be screened for this antibody. Anti-histone antibodies are found in 60% of all patients with SLE and in 90% of patients with drug-induced lupus.

There are several methods used to test for ANAs which further complicates the interpretation and comparison of the values obtained. The most widely used method for detecting ANAs is indirect immunofluorescence, which can identify antibodies that bind to a variety of nuclear antigens, including DNA, RNA, and proteins (collectively called *generic ANAs*). This test involves viewing fluorescent-labeled antibodies on a glass slide under the microscope and determining the pattern and intensity of the fluorescence. FANA test results are reported in titers and the patterns that the autoantibodies make, e.g., homogeneous, speckled, centromere, etc. This titer reading is determined by dilution of serum in normal saline making 1:80, 1:160, 1:320 and 1:640 dilutions, respectively. Laboratories vary in their standards for "positive," e.g., some labs will report any titer above 1:160 as positive. The physician will interpret the ANA results based on the clinical history.

A positive ANA test result means that autoantibodies are present. Positive ANA test results may be reported in different ways, depending on the test method. In addition to a titer, positive results on IFA will include a description of the particular type of fluorescent pattern seen. Different patterns have been associated with different autoimmune disorders, although some overlap may occur. Some of the more common patterns include:

- Homogenous (diffuse) - associated with SLE, mixed connective tissue disease, and drug-induced lupus
- Speckled - associated with SLE, Sjögren syndrome, scleroderma, polymyositis, rheumatoid arthritis, and mixed connective tissue disease
- Nucleolar - associated with scleroderma and polymyositis
- Centromere pattern (peripheral) - associated with scleroderma and CREST (Calcinosis, Raynaud syndrome, Esophageal dysmotility, Sclerodactyly, Telangiectasia)

An example of a positive result using the IFA method would give the dilution titer and a description of the pattern, such as "Positive at 1:320 dilution with a homogeneous pattern."

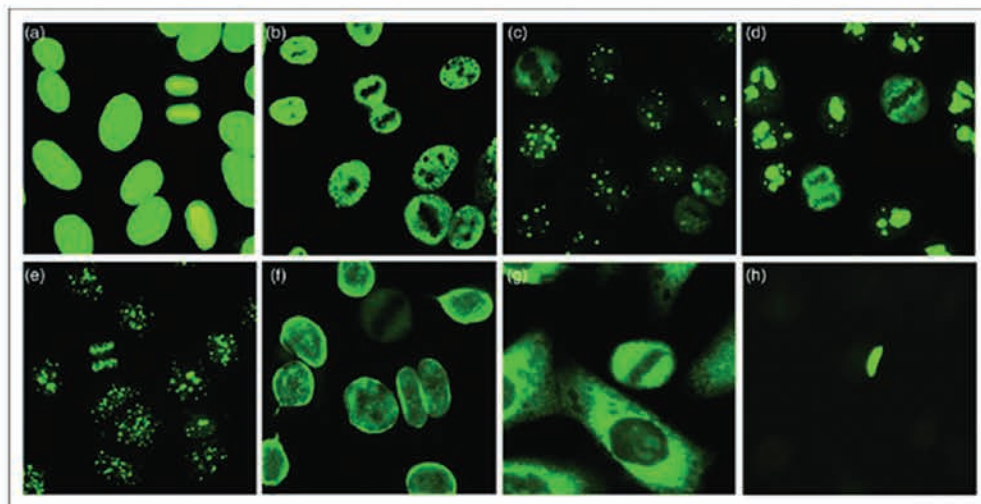


Fig 1: Indirect Immunofluorescence Patterns (a) homogeneous, (b) speckled, (c) nuclear dots, (d) nucleolar and (e) centromeres. Additionally, (f) nuclear membranes and (g) cytoplasmic. Negative and unspecific results (h)

A negative ANA result makes lupus or another autoimmune disease unlikely. It usually is not necessary to immediately repeat a negative ANA test; however, due to the episodic nature of autoimmune diseases, it may be worthwhile to repeat the ANA test at a future date if symptoms recur. A person previously diagnosed with an autoimmune disease may have a negative ANA test if the condition is in a period of remission. Apart from rare cases, further autoantibody (subset) testing is not necessary if a person has a negative ANA result. About 3 - 5% of healthy individuals may be positive for ANA, and it may reach as high as 10 - 37% in healthy individuals over the age of 65 because ANA frequency increases with age. These would be considered false-positive results because they are not associated with an autoimmune disease. Such instances are more common in women than men.

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Management Guideline of Acute Stroke

Neurology Society

Definition

Stroke is defined by the World Health Organization as "a clinical syndrome, of presumed vascular origin, typified by rapidly developing clinical signs of focal or global disturbance of cerebral functions lasting more than 24 hours or leading to death".

Types of stroke

(1) Ischemic stroke (85%)

Acute ischemic stroke is caused by thrombotic or embolic occlusion of a cerebral artery.

(2) Haemorrhagic stroke (10%)

This usually results from rupture of a blood vessel within the brain or ventricular system that is not caused by trauma.

(3) Subarachnoid haemorrhage (SAH) (5%)

It is a haemorrhage from a cerebral blood vessel, aneurysm or vascular malformation into the subarachnoid space.

(4) Cerebral venous thrombosis (< 1%)

It is due to occlusion of cerebral veins and venous sinuses.

(5) Transient ischemic attack (TIA)

It is defined as an acute loss of cerebral or ocular function with symptoms lasting less than 24 hours.

Risk factors of Ischemic stroke

Non-Modifiable

- Gender (male > female, except in the very young and very old)
- Race (Afro-Caribbean > Asian > European)
- Hereditary
- Previous vascular event, e.g. myocardial infarction, previous stroke or TIA, peripheral vascular disease, high fibrinogen

Modifiable

- Hypertension
- Heart disease (heart failure, atrial fibrillation, endocarditis)
- Diabetes
- Hyperlipidaemia
- Smoking
- Excess alcohol consumption
- Polycythemia
- Oral contraceptives, social deprivation

Differential Diagnosis of stroke (stroke mimics)

1. Structural intracranial lesion (tumour, hematoma, encephalitis, abscess)
2. Metabolic / toxic encephalopathy (hypoglycemia, non-ketotic hyperglycemia, hyponatraemia, hepatic encephalopathy, alcohol and drug intoxication)
3. Head injury, hypertensive encephalopathy
4. Epileptic seizure (todd's paralysis) NCSE
5. Hemiplegic migraine, multiple sclerosis
6. Functional / non-neurological (e.g. hysteria)

Management of Acute Stroke

(A) Acute stroke care

1. Emergency department evaluation and management
2. Immediate diagnostic tests
3. Neuroimaging
4. General supportive care
5. Specific management according to the type of stroke
6. Stroke rehabilitation

(B) Secondary Prevention

1. Life style modification
2. Hypertension
3. Dyslipidaemia
4. Blood glucose
5. Atrial fibrillation

(A) Acute stroke care

1. Emergency department evaluation and management

- Emergency evaluation
History and physical examination: such as assessment of neurological deficits, possible co-morbidities and exclusion of stroke mimics (eg, hypoglycemia, seizure)
- Stabilization of ABCs (airway, breathing and circulation)
Supplemental oxygen: only if oxygen saturation drops below 95%

2. Immediate diagnostic tests

For all patients

- Non contrast CT or MRI
- Blood glucose
- Serum electrolytes / renal function tests
- Full blood count including platelet count
- Coagulation screen (PT/INR, APTT)
- ECG (atrial fibrillation, left ventricular hypertrophy, myocardial infarction)

For selected patients

- Hepatic function tests
- Toxicology screen
- Blood alcohol level
- Pregnancy test
- Arterial blood gas tests (if hypoxia is suspected)
- Chest radiography (if lung disease is suspected)
- Thrombin time and / or clotting time if patient is taking new anticoagulants
- Lumbar puncture (if subarachnoid hemorrhage is suspected and CT scan is negative for blood)
- Electroencephalogram (if seizure are suspected)
- D-dimer (if cerebral venous thrombosis is suspected)

3. Neuroimaging

- Emergency imaging of brain is recommended within 30 minutes before initiating any specific therapy.
- **CT Head**
Non-enhanced CT (NECT) of the brain accurately identifies most cases of intracranial haemorrhage and helps discriminate nonvascular causes of neurological symptoms (eg, brain tumor).
- **MRI Brain**
Diffusion weighted imaging is highly specific and sensitive in detection ischemia within minutes of symptom onset.

4. General supportive care of acute stroke

4.1 Cardiac monitoring

- Patients should be monitored for at least first 24 hours to screen for atrial fibrillation and other potentially serious cardiac arrhythmias.

4.2 Fever

- Identify sources of hyperthermia (temperature > 38°C) and treat with antipyretic medications

4.3 Swallowing assessment

- Dysphagia screening before the patient begins eating, drinking, or receiving oral medications.

4.4 Nutrition and hydration

- For patients with dysphagia, use nasogastric feeding
- if there are signs of dehydration, give fluid parenterally
- Provide nutritional supplements
- Care of oral hygiene to reduce the risk of pneumonia

4.5 Bladder care

- Indwelling urinary catheterization under aseptic condition if necessary

4.6 Prevention of pressure sore

- Daily inspection of skin at pressure area
- Regular turning, good skin hygiene, and use of specialized mattresses, wheelchair cushions, and seating
- Maintain adequate nutrition and hydration to prevent skin breakdown

4.7 DVT prophylaxis

- Intermittent pneumatic compression (IPC) is recommended in immobilized patients to prevent DVT

4.8 Blood sugar control

- Persistent in-hospital hyperglycemia > 180 mg/dl
 - Treat accordingly (preferably with insulin)
 - Target 140 to 180 mg/dL
- Hypoglycemia (blood glucose < 60 mg/dL)
 - Correct with IV glucose

4.9 Blood pressure management

Hypotension and hypovolemia

- correct with normal saline to maintain systemic perfusion levels necessary to support organ function

Hypertension

▲ Patients eligible for thrombolytic therapy with rt-PA:

- Blood pressure can be lowered safely (to below 185/110 mmHg) with antihypertensive agents

▲ Patients not eligible for thrombolytic therapy with rt-PA:

- Target - lower blood pressure by 15% during the first 24 hours after onset of stroke
- Medications should be withheld unless blood pressure is > 220/120 mmHg

S.B.P < 220 mmHg or DBP < 120 mmHg

- Observe unless there is other end-organ involvement, eg. aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy
- Treat other symptoms of stroke such as headache, pain, agitation, nausea, and vomiting
- Treat other acute complications of stroke, including hypoxia, increased ICP, seizures, or hypoglycemia

S.B.P > 220 mmHg or DBP < 121 - 140 mmHg

- Labetalol 10 - 20 mg I.V over 1 - 2 min, may repeat or double every 10 min (maximum dose 150 mg) or
- Nicardipine infusion 5 mg/hr as initial dose, titrate to desired effect by increasing 2.5 mg/hr every 5 min to maximum of 15 mg/hr. (Aim for a 10% to 15% reduction of blood pressure)

Diastolic > 140 mmHg

- Nitroprusside 0.5 µg/kg per min I.V infusion as initial dose with titration to a maximum of 5 g/kg/min (aim for a 10% to 15% reduction of blood pressure)

For primary intracerebral haemorrhage

- For ICH patients presenting with SBP between 150 and 220 mmHg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mmHg is safe.

For acute subarachnoid haemorrhage

- Between the time of SAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding and maintenance of cerebral perfusion pressure.

4.10 Intracranial pressure monitoring and treatment

General care

1. Daily assessment and monitoring of signs and symptoms of increased ICP (headache, projectile vomiting, impaired vision)
2. Head elevation up 30 degrees
3. Position, airway and ventilation control
4. Sedation and analgesia if patient is severe headache and restless

Medical treatment

Hyper osmolar therapy

- Intravenous mannitol can be given (0.25 - 0.5 g/kg for every 6 hours). The usual maximum dose is 2 g/kg.
- Corticosteroids (in conventional or large doses) are not recommended.

Surgical treatment

- Ventriculostomy
 - In obstructive hydrocephalus after cerebellar infarct.
- Decompressive sub occipital craniectomy with dural expansion
 - Cerebellar infarct with neurological deterioration from brainstem compression despite maximal medical therapy.
- Decompressive craniectomy with dural expansion
 - In patients ≤ 60 years of age with unilateral MCA infarctions who deteriorate neurologically within 48 hours despite medical therapy.

4.11 Seizure treatment

1. Use anti epileptic drugs in recurrent seizure depend on seizure type and patient's characteristic. (e.g. focal seizure-carbamazepine/levetiracetam, generalized seizure-sodium valproate)
2. Prophylactic use of anti-seizure drugs is not recommended.

5. Specific management according to type of stroke

Management of acute ischaemic stroke (AIS)

(a) Thrombolysis therapy

- Intravenous r-tPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within to **3 - 4.5 hours** of onset of ischemic stroke.
- In patients eligible for intravenous r-tPA, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. The door-to-needle time (time of bolus administration) should be within 60 minutes from hospital arrival.
- Endovascular therapy - in selective patients

(b) Antiplatelet agent

For patient who are not eligible for intravenous r-tPA.

- Oral administration of **aspirin (initial dose is 325 mg)** within 24 to 48 hours after stroke onset is recommended for treatment of most patients

(c) Anticoagulation treatment

- Anticoagulation treatment should not be used routinely for the treatment of acute stroke.

Management of Transient ischemic attack (TIA)

i. Assessing the risk of stroke

Timely assessment and interventions is crucial to reduce risk of stroke

ABCD 2 scores: should be used to assess the risk of stroke for prompt or emergency referral

1. Age (> 60 years, 1 point)
2. Blood pressure (> 140/90 mmHg, 1 point)
3. Clinical features (unilateral weakness, 2 points or speech disturbance without weakness, 1 point)
4. Duration of symptoms (> 60 minutes, 2 points or 10 - 59 minutes, 1 point)
5. Diabetes (1 point)

High risk of subsequent stroke

- High risk patients include:
- ABCD 2 score 4 or more
 - Crescendo TIAs or > 1 TIA in 1 week
 - TIA that occurred in last 24 hours

These patients should be assessed urgently within 24 hours by a physician or Neurologist.

Lower risk of subsequent stroke

- Low risk patients include:
- ABCD 2 score of 3 or below
 - one TIA that occurred more than a week previously

These patients should be assessed as soon as possible within 7 days.

ii. Investigations

- ECG
In transient ischemic attack of undetermined source, prolong ECG monitoring to detect AF
- Brain imaging study: CT or MRI within 24 hours of onset of symptoms in high risk patients and within 1 week of onset of symptoms in low risk patients
- Electrocardiography: Recommended within 48 hours if possible
- Vascular imaging is recommended within 1 week of onset of symptom to identify significant symptomatic extracranial carotid artery.
Carotid ultrasound (for extracranial vascular imaging) and MR angiography are acceptable alternatives to CT angiography.

iii. Medical management

- Patients with suspected TIA should be given aspirin 300 mg immediately followed by aspirin 75 mg or clopidogrel 75 mg daily
- In patients with high-risk TIA (ABCD 2 score ≥ 4), dual antiplatelet therapy (aspirin 75 - 300 mg + clopidogrel 300 mg) should be given within 24 hours after onset followed by aspirin 75 mg + clopidogrel 75 mg for 21 days followed by clopidogrel 75 mg alone for 90 days.

5.3 Management of acute intracerebral hemorrhage (ICH)

ALL cases of spontaneous ICH should be discussed with neurosurgical team on call or general surgeon with expertise in neurosurgery.

5.4 Management of subarachnoid hemorrhage (SAH)

Patients with spontaneous subarachnoid haemorrhage should receive:

- nimodipine 60 mg 4 hourly unless contraindicated
- frequent neurological observation for signs of deterioration
- Bed rest, analgesia, and sedation
- Triple H therapy (hypertension, hypervolemia, and hemodilution)
- Should be referred to neurosurgical unit
- Specific treatment of aneurysm (endo vascular embolization or surgical clipping if available) should be undertaken within 48 hours

5.5 Management of cerebral venous thrombosis (CVST)

- Patients with suspected cerebral venous thrombosis should be referred to specialist center.
- Early diagnosis is important since the condition is potentially fatal but appropriate treatment aids full recovery in the majority of patients.

Stroke rehabilitation

- All patients with stroke must have access to a Stroke Rehabilitation Program as an inpatient and outpatient after discharge from hospital.
- It should begin in the acute-care hospital after overall condition has been stabilized (within 24 to 48 hours), depends on type of disabilities (paralysis or problems controlling movement; sensory disturbances including pain; language problems; problems with thinking and memory; emotional disturbances).
- All appropriate patients receive a minimum of 45 minutes of physiotherapy (occupational and speech therapy if available)

(B) Secondary prevention

1. Life style modification

Healthy diet, regular exercise, limiting alcohol intake, stops smoking

2. Antithrombotic therapy

For patients being investigated for an acute embolic ischemic stroke or TIA of undetermined source, ECG monitoring at least 24 hours is recommended as part of the initial stroke work-up to detect paroxysmal atrial fibrillation in patients who would be potential candidates for anticoagulant therapy.

Non-cardioembolic AIS or TIA

Antiplatelet agents

Aspirin 80 mg to 325 mg per day (or)

Combination of aspirin and extended-release dipyridamole 25/200 mg twice per day (or)

Clopidogrel 75 mg per day

Cardioembolic AIS or TIA

AF with valvular heart disease

For patients with ischemic stroke or TIA who have rheumatic valve disease and AF, long-term VKA therapy with INR target 2.0 to 3.0 is recommended.

AF without valvular heart disease

Vitamin-K antagonist therapy or new oral anticoagulant (apixaban, dabigatran, rivaroxaban) are indicated for the prevention of recurrent stroke in patients with non-valvular AF.

Optimal timing to start anticoagulant therapy after stroke

- should be based on individual benefit / risk assessment taking into account the clinical circumstances, infarct size, imaging appearances, age, co-morbidities, and estimated stroke recurrence risk.
- For most patients, it is reasonable to initiate oral anticoagulation **within 4 to 14 days** after the onset of neurological symptoms.
- In the presence of **high risk for hemorrhagic conversion** (ie. large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation **beyond 14 days**.
- For patients with ischemic stroke or TIA and atrial fibrillation who are unable to take oral anticoagulant therapy (DOAC or warfarin), aspirin alone is recommended [AHA, Evidence Level A]. (New for 2017)
- In patients with ischemic stroke or TIA in sinus rhythm who have **left atrial or left ventricle thrombus** demonstrated by echo cardiography or another imaging modality, anticoagulant therapy is recommended for greater than 3 months [AHA, Evidence Level C].
- In patients with ischemic stroke or transient ischemic attack in sinus rhythm with **severe left ventricular dysfunction** (ejection fraction $\leq 35\%$) without evidence of left atrial or left ventricular thrombus, the net benefit of anticoagulant therapy compared with antiplatelet therapy is uncertain, and the choice of management strategies should be individualized [AHA, Evidence Level B].

3. Hypertension

- Goals for target BP level: $< 140/90$ mmHg ($< 130/80$ in DM)
- The choice of specific drugs and targets should be individualized on the basis of pharmacological properties, mechanism of action, and consideration of specific patient characteristics

4. Blood Glucose

- After stroke or TIA, all patients should be screened for DM with testing of fasting plasma glucose, HbA1c, or an oral glucose tolerance test.
- Glycemic target - to achieve a glycated hemoglobin (A1c) level $\leq 7.0\%$, fasting plasma glucose or pre-prandial plasma glucose target of 4.0 to 7.0 mmol/l or two-hour postprandial plasma glucose target is 5.0 to 10.0 mmol/l.

5. Dyslipidemia

- Statin therapy is recommended to achieve an LDL cholesterol of less than 2.0 mmol/l, or a 50% reduction in LDL cholesterol from baseline.

6. Carotid Revascularization

- Carotid endarterectomy (CE) is recommended in patients with 70 - 99% Internal Carotid Artery angiographic stenosis.
- For patients with severe stenosis and a recent TIA or non-disabling stroke, CE should be performed without delay, preferably within two weeks of the patient's last symptomatic event (Level C).

(C) Discharge planning, Follow-up appointments and Referral

Discharge planning

Discharge planning begins early during rehabilitation. It involves the patient, family, and rehabilitation staff. It includes instruction for medication and life style, rehabilitation program, career education and living environment. Patients are usually discharged from rehabilitation soon after their goals have been reached.

Follow-up appointments

After a stroke survivor returns to the community, regular follow-up appointments (after two weeks, one month and three months initially) are usually scheduled with doctor and sometimes with rehabilitation professionals.

Referral

Indications for referral to specialist center where neurology expertise is available

1. Patients with significant intracranial and extracranial artery stenosis
2. Patients with special conditions (eg., hypercoagulation, homocysteinemia, valvular heart disease, prosthetic heart valve, cardiomyopathy, patent foramen ovale, antiphospholipid syndrome, sickle cell disease, pregnancy)
3. Patients who require resumption or initiation of anticoagulation after acute ICH, SAH or subdural haematoma
4. Patients with AF who had previous history of ICH for decision of anticoagulation therapy to prevent recurrent stroke

Acute intracranial haemorrhage and Subarachnoid haemorrhage

1. Patients who needs decompressive hemicraniectomy
2. Patients with aneurysmal haemorrhage who needs surgical clipping
3. Patients who needs surgical interventions for carotid artery stenosis

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Starting ART in a person living with HIV

Myanmar Society of HIV Medicine

Currently, every HIV Clinical Management Guideline states that ART (Antiretroviral Therapy) can be started regardless of CD4 or WHO stage (treat all) in all persons with HIV. But some factors need to be considered before starting straightaway.

Diagnosis

First and foremost is the certainty of HIV diagnosis. Once the patient is already on ART, it will be impractical to test again. WHO recommends 3 positive rapid tests as a confirmation of HIV diagnosis. Previously, this was enough to start ART but since 2016 WHO introduced the policy of “retesting before ART”, called verification, which again needs 3 tests to be positive. The most commonly used 3 rapid tests (in Myanmar) are: Determine (test 1), Unigold (test 2) and Stat Pak (test 3); the first being 99.9% sensitive and the last 2 being 100% specific. The interval between “confirmation” and “verification” can be as close as a few days, in a patient starting ART rapidly. In a patient who chooses to defer ART when being diagnosed at high CD4, despite the physician’s advice to start ART, the interval between the confirmation and verification might be longer. It is helpful to ask questions about the time HIV diagnosis was made. Sometimes, the patients might, for various reasons, avoid disclosing a previous history of HIV diagnosis or ART exposure. Some example questions are: Have you ever been tested for HIV before? Have you ever received TB treatment? If so, did they test for HIV at that time? Where did you deliver your child(ren)? During AN care, did they test for HIV? Did you take any medications to prevent your baby from being infected? etc.

Clinical Staging

Second is to determine how well is the patient. In other words, determining the WHO clinical stage or to look for major opportunistic infections, the most important being TB. In a patient who has fever, significant weight loss, abdominal pain, dyspnea or headache, It is not prudent to start ART, before optimizing the patient’s clinical condition. On the other hand, time should not be wasted with repeated investigations and counseling sessions in an apparently well patient. Recently WHO classifies patients as those with **advanced disease** (WHO stage 3 or 4 disease and/or CD4 < 200 cells/ml) and those who are **clinically well**; such individuals may be ART naïve or have interrupted treatment. In 2017, WHO recommended rapid (ie within one week from diagnosis) initiation of ART in clinically well patients.

Some helpful questions to assess the likelihood of OIs (Opportunistic Infections) are: have you ever had a zoster eruption? Do you have itchy lesions on your legs? Do you have sore tongue? Show me your tongue, please. Do you have swellings on the neck? The standard four screening questions for TB are: fever more than 2 weeks, cough, loss

of weight and night sweats. If any one of them is positive, the clinician should run some investigations to look for active TB such as CXR (PA), sputum AFB and gene Xpert. Test for Urinary LAM antigen if available (especially for patients with TB S/S & CD4 < 100) can also assist in the diagnosis of TB, although it is not very specific. USG (Abdomen) is a good tool to diagnose intra-abdominal lymph nodes, micro abscesses of spleen and liver, and long segment bowel wall thickening, which are used as surrogate markers of TB abdomen in a resource poor country. When CD4 count is available and if less than 100, serum Cryptococcal antigen test should also be offered.

Initial Clinical Management

In practice, while the HIV diagnostic tests, baseline investigations and co-infection diagnosis and OI screening investigations are in process, the patient is offered CPT (co-trimoxazole prophylaxis therapy) which is 2 tablets of single strength (480 mg) or one tablet of double strength (960 mg) septrin, daily. In a busy, overcrowded public hospital or clinic, where most patients’ health literacy is poor - asking for septrin hypersensitivity, can be very challenging. Fortunately it is not very common. WHO recommends IPT (Isoniazid Preventive Therapy), which actually is a treatment for latent TB infection for all people with HIV, if there is no active TB. In high TB burden countries, like Myanmar - all PLHIV are assumed to have one form of TB: either latent or active. All people with HIV who are considered as not having active TB, after screening with the four questions, are considered as having latent TB and prescribed IPT. Myanmar currently adopts a 6-month isoniazid 300 mg OD IPT regimen. Theoretically in a well patient, IPT, CPT and ART can be started on the same day.

Baseline Investigations

Investigations done before starting ART are: CD4, STS, HBsAg, HCV antibody, CBC, Serum creatinine, none of which is compulsory. Counseling sessions comprise of pretest, post-test, follow-up adherence counseling and ART counseling, which can be spread over two or three visits. In a clinically well patient, ART can be started on 3rd visit. In the first visit, confirmation of HIV, baseline investigations and pretest counseling are done. In the second visit, post-test counseling, starting CPT and IPT and ordering of HIV verification test are done. In the 3rd visit, verification result is available. Follow up adherence and ART adherence counseling are done and ART is initiated.

Antiretroviral Therapy

Usually an ART regimen is to be chosen from two first line ART regimens. TDF (Tenofovir) and 3TC (Lamivudine) should be included, especially in the case of HBV coinfection. If there is a contraindication to TDF ie - GFR < 50 ml/min, AZT (Zidovudine) + 3TC should be considered. AZT should not be used if Hb is < 8 g/dl. For patients with advanced infection who cannot be prescribed either TDF, because of increased creatinine and AZT, due to anemia, ABC (Abacavir) + 3TC is an alternative. These 2 NRTI must be



combined with either EFV (NNRTI) or DTG (Dolutegravir, an integrase inhibitor). In clinically well males, postmenopausal females with little risk of TB IRIS, DTG is the drug of choice. Women of childbearing age should be on consistent contraception to be able to take DTG, as its safety in the first trimester is still unknown. After 8 weeks of pregnancy, and especially in pregnant women who present in the third trimester, DTG is the drug of choice because it rapidly suppresses viral load compared to other regimens. If TB IRIS (Immune Reconstitution Inflammatory Syndrome), develops while taking DTG, the regimen should not be changed to EFV. Instead, the dose is increased from 50 mg once to twice daily, and reduced backed to once daily after completion of anti TB. For those already on anti TB drugs, EFV containing regimen is the preferred one.

ART regimens for Adults

First line ART	Second Line ART	Thrid Line ART
Tenofovir + Lamivudine + Efavirenz	Zidovudine + Lamivudine + Dolutegravir	Boosted Darunavir + INSTI + NRTI
Tenofovir + Lamivudine + Dolutegravir	Zidovudine + Lamivudine + Efavirenz	Boosted Darunavir + INSTI + NRTI

HBV coinfectd patients should always receive TDF regimen.

Patients with significant anamia should avoid Zidovudine.

The usual dose of EFV is 600 mg once daily. This dose of daily EFV 600 mg is associated with higher drug levels in Asians - so EFV 400 mg daily has been recently introduced, in the Myanmar National Guidelines. But 400 mg daily dose is not recommended to be used together with rifampicin and during pregnancy - in which case the usual 600 mg dose should be used. The possible side effects of EFV include CNS side effects like dizziness, insomnia (which are seen in the first few weeks), depression and frank psychosis with self-harm (which are very rare), severe hepatitis (also very rare) and maculopapular rash (which is seldom severe). When switching ART regimens was limited in the past, patients were encouraged to continue the regimen by adding sedatives, anti psychotics and antihistamines, but in case of severe symptoms, the drug is stopped and changed to a PI/r (ritonavir boosted Protease Inhibitor) regimen. Now since DTG is available, it is a suitable substitute to change if patients experience EFV side effects. EFV 400 is hoped to reduce these symptoms, but EFV 400 mg is for new initiation, but rather, it is intended to replace EFV 600 mg being taken by many patients. DTG plasma level is reduced when taken together with polyvalent Cat ions (Mg, AL, Ca, Zn, Fe). So DTG should be taken 2 hours before or 6 hours after vitamins with minerals and cation containing antacids, laxatives and buffered medications.

The general recommendation is to first treat the opportunistic infection(s) eg. TB, PCP, cerebral toxoplasmosis or penicilliosis - and start ART, 2 weeks later. There are two other specific recommendations regarding the timing of ART initiation: the first is in patients with CD4 < 50 cells/mm³ and active TB. ART should be started within 2 weeks of



TB treatment initiation. Another is in patients with Cryptococcal meningitis, it is better to start ART 4 - 6 weeks after the initiation of amphotericin infusion.

The first few weeks and months after ART initiation usually requires more frequent follow-up visits. Drug hypersensitivity reactions (usually associated with EFV, Cotrim, Anti TB, if present are more commonly seen in the first few weeks) and unmasking or paradoxical IRIS (seen in the first three months) are complications - if immediate attention is given, more serious consequences can be prevented.

Monitoring

The expected CD4 improvement is approximately - a rise of 100 - 150 cells/mm³/year. If a person is started on ART with a very low CD4 count, i.e 100 cells/mm³ or less-immune reconstitution, in terms of rise in CD4 will take longer. In those whose baseline CD4 is higher, the response is more robust. Time to achieve an undetectable HIV viral load can take up to 24 weeks after starting ART. Regular viral load monitoring is more preferable than CD4 for assessing ART treatment response.

The best monitoring tool for treatment success is viral load which is done at 6 and 12 months after ART and then annually. Viral load is not required when a patient is not taking ART ie after defaulting and reentering into care. CD4 is monitored every 6 months, but in those with suppressed viral load (< 1000 copies/ul) for one year it might not be necessary. Side effect monitoring is regimen-based: in a person taking TDF regular monitoring of serum creatinine, plasma potassium and urine RE is necessary. For a person receiving Zidovudine containing ART, CBC needs to be checked regularly.

Success vs Failure of Treatment

The goal of ART is to achieve and maintain an undetectable HIV viral load. On the other hand if the viral load is more than 1000 copies/ul in a person who has been on ART for more than 6 months, and if this result is confirmed on a repeat test 2 - 3 months later, and non-adherence of ART can be ruled out, first line ART treatment failure can be defined. Switching of ART to second line needs to be considered.

The long-term success of treatment depends much on treatment adherence and regular follow up. As there is still no cure yet for HIV, life long ART is the only option. People on ART might have pill fatigue, emotional exhaustion in the need to visit regularly their health care provider and social economic factors that might have a negative effect on their treatment adherence. Health care workers need to be aware of the challenges they face - and be prepared to address them accordingly.

In Myanmar there are more than 100 ART treatment centers in the public sector providing comprehensive care. HIV Counselling, expert medial consultation, necessary diagnostic investigations and treatment support including ART can be assessed in these places for all who are in need. Proper timely referral of those already diagnosed and those who need HIV testing is a duty of all health care providers.



When Should We Consider Transfusion?

Myanmar Society of Haematology

- ❖ Blood Transfusion, although lifesaving, is not without serious risk. Even with advanced technology for pre-transfusion testing and improved transfusion practice, blood transfusion is still associated with **following complications**:⁽¹⁾
- ❖ **Infectious complications** including bacteria contamination and transfusion transmitted infections like syphilis, HBV, HCV, HIV, human T-cell lymphotropic virus, CMV, West Nile virus and nowadays, Zika virus.
- ❖ **Non-Infectious complications:**
 - **Transfusion-associated circulatory overload**
 - **Transfusion-related acute lung injury** which is a non cardiogenic pulmonary edema occurring within 6 hours after transfusion characterized by hypoxemia and bilateral pulmonary infiltrates on chest films and the diagnosed by exclusion in the absence of other risk factors for the acute respiratory distress syndrome
 - **Acute hemolytic transfusion reactions** mainly due to administration of ABO-incompatible red cells as a result of human error in blood sampling or patient identification
 - **Delayed hemolytic transfusion reactions** mediated by non-ABO antibody when the patient is transfused with red cells expressing the cognate antigen followed by an anamnestic response with rise in the antibody titer 3 to 21 days after transfusion resulting in extravascular destruction of the transfused red cells
 - **Transfusion-associated graft-versus-host disease**, a rare but almost always fatal complication (refractory to treatment with mortality > 90%), due to engraftment of viable donor T cells from the blood component in a susceptible recipient where T cells mediate a graft-versus-host reaction leading to rash, diarrhea, mucositis, jaundice and pancytopenia which can only be prevented by irradiation of blood components to inactivate T cells
 - **Complications of massive transfusion**, including hypothermia, hyperkalemia, dilutional coagulopathy, and citrate toxicity
 - **Iron overload**
 - **Anaphylaxis and immunomodulation**
- ❖ Therefore, blood transfusion is considered only when benefits outweigh the risks.
- ❖ This article reviewed the most recent guidelines and literatures (between 2012 to 2018) to help your transfusion practice.



Red cell transfusion

- ❖ **Red Cell Transfusion** is indicated in bleeding (acute blood loss) and to treat anaemia.
- ❖ **Red cell transfusion for anaemia**
 - Anemia is associated with adverse clinical outcomes. red cell transfusion increases oxygen-carrying capacity by increasing the hemoglobin (Hb) concentration and circulating red cells mass. In adults, one unit of RC increases haemoglobin (Hb) by 1 g/dl or haematocrit (Hct) by 3% in an average sized (70 kg) adult. In children, 8-10 ml/kg of whole blood/packed red cell increases Hb by 1 g/dl (Hct by 3%) and 2 g/dl (Hct by 6%) respectively.
 - **Before consider transfusion in anaemia, ideally, the cause of anaemia should be established first** if possible. If there is effective alternatives, (eg. treatment of iron deficiency or autoimmune hemolytic anaemia), red cell transfusions should not be given unless anaemia is life threatening.
 - **Decision to transfuse red cell for anaemia** should be based not only on **Hb concentration**, but also on other factors like **symptoms, the patient's clinical condition or vital signs and ability to compensate, underlying disease and co-morbidities, severity and chronicity of the anaemia, other factors including availability of alternative therapies and patient preferences, etc.**⁽²⁻⁴⁾
 - **Clinical judgement plays a vital role in the decision to transfuse or not.**
- ❖ **Using Restrictive rather than Liberal transfusion**
 - **Restrictive transfusion** strategy targets lower hemoglobin level where transfusion is **not advised until it falls to the level of 7 to 8 g/dL** while **liberal transfusion** strategy transfuse at a higher level, ie transfusion is **indicated under the threshold of 9 to 10 g/dL**.
 - Based on evidence from a 2018 systematic review and meta-analysis of 37 randomized clinical trials comparing higher versus lower transfusion thresholds in over 19,000 medical and surgical patients (adults and children), compared with higher hemoglobin thresholds, **a hemoglobin threshold of 7 or 8 g/dL is associated with fewer red blood cell units transfused without adverse associations with mortality, cardiac morbidity, functional recovery, or length of hospital stay.**⁽⁴⁻¹⁰⁾
- ❖ **Recommendations from recent transfusion guidelines**
 - **Based on recent evidences and randomized trials, in general, for most hemodynamically stable medical and surgical patients including those in intensive care unit or with septic shock, except those with acute coronary syndrome, restrictive transfusion threshold of 7 to 8 g/dL has been recommended in the most reputable guidelines.**^(2, 3, 14)
 - However, the evidence is **not strong enough to make any recommendation for patients with:**



- Symptomatic patients
- Acute coronary syndrome
- Patients requiring massive transfusion
- Severe thrombocytopenia and
- Chronic transfusion-dependent anaemia
- **Transfusion of one unit of red blood cells (RBCs) at a time** is reasonable for hemodynamically stable patients, with assessment of symptoms immediately after transfusion and post-transfusion hemoglobin levels, which can be done as early as 15 minutes and as late as 24 hours after transfusion.
- ❖ Examples of recent international guidelines: New evidence based clinical practice guidelines from the American Association of Blood Banks (AABB) updated in 2016 include the following recommendations for **hemodynamically stable patients without active bleeding**.⁽²⁾
 - **Hemoglobin < 6 g/dL** - Transfusion recommended except in exceptional circumstances.
 - **Hemoglobin 6 to 7 g/dL** - Transfusion generally likely to be indicated
 - **Hemoglobin 7 to 8 g/dL** - Transfusion may be appropriate in patients undergoing orthopedic surgery or cardiac surgery, and in those with stable cardiovascular disease, after evaluating the patient's clinical status.
 - **Hemoglobin 8 to 10 g/dL** - Transfusion generally not indicated, but should be considered for some populations (eg, those with symptomatic anemia, ongoing bleeding, acute coronary syndrome with ischemia, and hematology/oncology patients with severe thrombocytopenia who are at risk of bleeding).
 - **Hemoglobin > 10 g/dL** - Transfusion generally not indicated except in exceptional circumstances.

Evidence and Recommendations for Transfusion in Specific Conditions

Clinical Condition	Hb level at which RC transfusion is indicated
Symptomatic anaemia	Transfuse regardless of the Hb level (no strong recommendation)
Asymptomatic hospitalized patient	Hb 7 - 8 g/dL, for most hemodynamically stable medical and surgical patients
Asymptomatic patients with stable coronary artery disease	Hb 8 g/dL is safe as supported by subgroup analysis of two randomized trials. ^(16, 17)
Symptomatic patients with coronary artery disease & Acute Coronary Syndrome	Transfusion is guided by the symptoms and clinical judgment, and no strong evidence for the optimal threshold



Cardiac Surgery with cardio-pulmonary bypass

Transfusion when Hb < 7.5 g/dL versus a higher level had similar outcome and that older cardiac surgery patients appeared to benefit even more from restrictive transfusion in recent large trial of Transfusion Requirements in Cardiac Surgery III.⁽⁵⁾ To maintain Hb > 7.5 - 8 g/dL or hematocrit > 21 - 24% appears to be reasonable based on meta-analysis of recent trials.^(5, 10, 17, 18, 19)

Critical Care (ICU) including septic shock with the possible exception of patients with ischemic heart disease/acute coronary syndrome

Studies demonstrated that a restrictive strategy of RBC transfusion is at least as effective as a liberal transfusion strategy in critically ill patients in the ICU. **Hb < 7 g/dL** is at least as effective and possibly superior to transfusion at Hb < 10 g/dL in hemodynamically stable patients in the ICU according to Transfusion Requirements in Critical Care (TRICC) trial.⁽¹¹⁾ The use of a threshold of 7 g/dL was also shown to be safe in patients with septic shock. The Transfusion Requirements in Septic Shock (TRISS) trial^(12, 13) **Stable Critically ill Children - transfusion at Hb < 7 g/dL** decreases transfusion requirements without increasing adverse events.⁽¹⁴⁾

Acute bleeding/ Trauma/ massive transfusion who are haemodynamically unstable

Transfusion should be guided by **hemodynamic parameters (eg. pulse, BP), amount and rate of bleeding, presence of coagulopathies, the risk of further bleeding, other risk factors, the ability to stop the bleeding, etc.**

Acute upper GI bleeding, hemodynamically stable Chronic Anaemia

Hb < 7 g/dL, restrictive transfusion is safe when there is access to rapid endoscopic treatment according to two randomized trials.^(15, 20, 21)

The cause of anaemia should be established and treated first for anaemia treatable by specific therapy, (eg. iron deficiency or AIHA). **Red cell transfusion is not usually required even if Hb is < 7 g/dL unless the anaemia is life threatening.**

Symptomatic: Transfuse to maintain haemoglobin just above the lowest level that is not associated with symptoms.

Haemoglobinopathy

Haemoglobinopathy patients frequently require individualised Hb thresholds for transfusion depending on their age and the precise indication; discussion with a haematologist is advised.

Transfusion Dependent Thalassaemia (Thalassaemia Major) (TIF Guidelines)

Hb < 7 g/dl on 2 occasions, > 2 weeks apart (excluding all other contributory causes such as infections) **OR**
Hb > 7 g/dl with facial changes or poor growth or fractures or clinically significant extramedullary haematopoiesis.

Platelet transfusion

Platelets are used in 3 distinct situations -

1. Prophylactic (WHO bleeding grade 0 or 1) to prevent bleeding/to reduce the risk for spontaneous bleeding
2. Pre-procedure to prevent bleeding expected to occur during surgery/invasive procedure
3. Therapeutic (WHO bleeding grade > 2) to treat active bleeding

Dose

A platelet unit refers to 1 apheresis platelet unit or a pool of 4 to 6 whole blood-derived platelet concentrates, typically containing 3 to 4 × 10¹¹ platelets.

Possible alternatives to platelet transfusion

- Apply surface pressure after superficial procedures and correct surgical causes for bleeding
- Surgical patients expected to have at least a 500 ml blood loss, use tranexamic acid (TXA) unless contraindicated Trauma patients who are bleeding / at risk of bleeding, early use of TXA
- Severe bleeding replace fibrinogen if plasma concentration less than 1.5 g/L
- Anti-platelet agents - discontinue or if urgent procedure / bleeding use TXA if risk/benefit would support
- Uraemia with bleeding or pre procedure - dialyse, correct anaemia, consider desmopressin
- Inherited platelet function disorders - specialist haematology advice required. Consider desmopressin
- Chronic BMF with bleeding - consider TXA

Indications for use of platelet transfusion

Based on a systematic review of randomized, clinical trials and observational studies (1900 to September 2014) developed recommendations for platelet transfusions which are summarized in the following table.^(23, 24, 25)

Indication	Platelet Count at which Transfusion is indicated (threshold)/not indicated
Prophylactic use (No bleeding or WHO grade 1) Dose: One adult dose up to a single apheresis unit or equivalent required (strong recommendation; moderate-quality evidence, ABB)	≤ 10 × 10 ⁹ /L - <i>standard practice</i>
-Thrombocytopenia due to reversible bone marrow failure (BMF) due to disease like acute leukemia / hematologic malignancies and Therapy induced Hypoproliferative thrombocytopenia due to chemotherapy or irradiation - Reversible BMF in adult patients undergoing hematopoietic cell transplantation (HCT)	≤ 10 × 10 ⁹ /L standard practice ≤ 20 × 10 ⁹ /L - for greater risk of bleeding ≤ 10 × 10 ⁹ /L (can safely delay platelet transfusion until the first sign of bleeding - guidelines from the American Society of Clinical Oncology (ASCO, 2018) ⁽²⁴⁾
- Critical illness	≤ 10 × 10 ⁹ /L
- Chronic BMF receiving intensive therapy including chemotherapy-induced thrombocytopenia in patients with solid tumors	≤ 10 × 10 ⁹ /L (ASCO 2018)
- Chronic BMF to prevent persistent bleeding of grade > 2	- Count variable
- Chronic stable BMF: eg. aplastic anaemia or myelodysplasia :	- Not indicated (best managed on an individual risk of bleeding)
- Abnormal platelet function	- Not indicated
- Platelet consumption / destruction (e.g. DIC, TTP)	- Not indicated
- Immune thrombocytopenia (ITP, HIT, PTP)	- Not indicated

Prophylactic use in the presence of risk factors for bleeding in patients with reversible/chronic bone marrow failure/critical care (e.g. sepsis/fever ($T \geq 38^\circ\text{C}$), antibiotic treatment, has coagulopathy, recent hemorrhage, on heparin, hyper leucocytosis, serious mucositis or cystitis, liver dysfunction, lesion that is likely to bleed or rapid decline in count or for outpatient)

≤ 10 to $20 \times 10^9/\text{L}$
(clinical judgment based on risk of bleeding)

Platelet transfusion pre-procedure

- Central venous catheter (CVC) excluding PICC line	$\leq 20 \times 10^9/\text{L}$ (weak recommendation; very-low-quality evidence, AABB)
- Lumbar puncture	$\leq 40 \times 10^9/\text{L}$
- Percutaneous liver biopsy	$\leq 50 \times 10^9/\text{L}$
- Major surgery (major elective non-neuraxial surgery)	$\leq 50 \times 10^9/\text{L}$ (weak recommendation; very-low-quality evidence, AABB)
- Epidural anaesthesia, insertion & removal	$\leq 80 \times 10^9/\text{L}$
- Neurosurgery	$\leq 100 \times 10^9/\text{L}$
- Ophthalmic surgery involving the posterior segment of the eye	$\leq 100 \times 10^9/\text{L}$
- Bone marrow aspirate or trephine biopsies	- Not indicated
- PICC line insertion	- Not indicated
- Traction removal of central venous catheters (CVCs)	- Not indicated
- Cataract surgery	- Not indicated

Therapeutic use (Bleeding WHO grade 2 or above)

- Severe bleeding	$\leq 50 \times 10^9/\text{L}$
- Multiple trauma, brain or eye injury, spontaneous intracerebral haemorrhage	$\leq 100 \times 10^9/\text{L}$
- Bleeding (WHO grade > 2) but not severe	$\leq 30 \times 10^9/\text{L}$

Bleeding in specific clinical conditions

Platelet function defect	- Count variable
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Congenital Platelet function defect - Pre-procedure or therapeutic use when alternative therapy contraindicated or ineffective.

- Directed by specialist in haemostasis

- **Acquired Platelet function defect (anti-platelet agents, uraemia)** for patients receiving antiplatelet therapy who have intracranial hemorrhage (traumatic or spontaneous)

- only indicated for severe bleeding
(cannot recommend for or against platelet transfusion. (uncertain recommendation; AABB)

Disseminated intravascular bleeding (Pre-procedure or therapeutic use) There is no evidence to support the administration of platelets if they are not bleeding. However, platelet transfusion is justified in patients who have serious bleeding, are at high risk for bleeding, or require invasive procedures.

Consider threshold counts above but may not be achievable and individual case review required.
 $\leq 10-20 \times 10^9/\text{L}$ in non-bleeding patients who develop DIC after chemotherapy.
 $\leq 20 \times 10^9/\text{L}$ or higher with a high risk of bleeding

Immune thrombocytopenia (ITP, HIT, PTP) Pre-procedure when other therapy ineffective/procedure urgent or to treat severe bleeding.

Individual case review required

Contraindications to Platelet Transfusion

Thrombotic thrombocytopenic purpura: Platelet transfusion contraindicated unless life-threatening bleeding

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Approach to Diagnosis of Anemia

Myanmar Society of Haematology

Introduction

According to World Health Organization (WHO), anaemia is defined as haemoglobin less than 13 g/dL in men (15 years of age and above), less than 12 g/dL in non-pregnant women (15 years of age and above), and less than 11 g/dL in and pregnant women.¹ Anaemia is a common clinical presentation in day-to-day clinical practice for every clinician. It is so common and frequent finding that clinicians sometimes fail to notice mild anaemia and sometimes fail to think it as a serious condition.

Diagnosis Approach

Anaemia is sometimes asymptomatic especially when it is mild or moderate. When anaemia is moderate to severe, it can present with symptoms like fatigue, dizziness, faints, pallor of lips and palms, weakness, shortness of breath, palpitation, chest pain, loss of appetite, and sometimes ankle swelling. Seeing the anaemia should not prompt a clinician to prescribing iron tablets or blood transfusion without searching for the underlying cause. Actual cause of anemia should be found out first before starting any treatment. Diagnosis of anemia can be done through history taking, physical examination, investigations and monitoring for treatment response.

Basic Mechanisms of Anemia

Mechanisms of anaemia should be kept in mind while trying to diagnose the cause of anemia. Three basic mechanisms that can lead to anaemia are -

- (1) Blood Loss
- (2) Decrease Production of red cells
 - a. Deficiency anaemia
 - b. Bone Marrow failures
- (3) Increase Destruction of red cells
 - a. Haemolytic anaemia

Anaemia due to blood loss can further be classified into acute blood loss and chronic blood loss. Acute blood loss has usually more symptoms than chronic one. Blood loss can be from gastrointestinal tract, respiratory tract, and genitourinary tract, etc.

Deficiency anaemia includes anaemia due to deficiency of iron, folate, vitamin B₁₂, protein, erythropoietin, thyroid hormone and androgenic hormones.

Bone marrow failures causing anaemia are aplastic anaemia, myelodysplastic syndrome, leukemias and bone marrow infiltrations.

Haemolytic anaemia can be due to -

(a) Congenital

- Membrane defect e.g. South East Asian Ovalocytosis, Hereditary Spherocytosis
- Haemoglobin defect e.g. Beta and alpha thalassaemia, Hb E, Hb S, etc.
- Enzyme defect e.g. Glucose 6 phosphate dehydrogenase (G6PD) deficiency, Pyruvate kinase deficiency

(b) Acquired

- Immune mediated e.g. Autoimmune, Alloimmune, Drug-induced
- Non-immune mediated e.g. Paroxysmal nocturnal haemoglobinuria, infections, microangiopathic haemolytic anaemia

History Taking in Diagnosis of Anaemia

While history taking to find out the cause of anaemia, above mechanisms of anaemia should be kept in mind.

Blood loss from gastrointestinal tract is a frequent cause of anaemia. So, asking about history of peptic ulcer, use of non-steroidal anti-inflammatory drugs (NSAIDs), habit of alcohol drinking, dyspepsia, loss of appetite, loss of weight, history of piles, bleeding from piles, passing melaena stool, passing of worms, etc. are important in finding the cause of anaemia. Although patients say that they have piles which have no active bleeding, there can be unrecognized daily loss leading to significant anaemia.

Bleedings from genitourinary tract are also a common cause of anaemia. So, thorough history taking about menstruation (duration of menstruation per cycle, interval between each cycle, unusual large amount of menstrual bleeding, passage of blood clots and dysmenorrhea, etc.) may sometimes give a clue to underlying cause of anaemia. Haematuria history is also important in anaemia diagnosis.

Bleeding from respiratory tract like chronic haemoptysis, chronic epistaxis, etc. can also lead to significant anaemia. Bleeding from skin telangiectasia may also associate with bleeding from mucosal telangiectasia and can lead to anaemia.

Reduced intake of iron-rich foods (liver, redmeats, etc.), folate, vitamin B₁₂ and protein can also lead to anaemia. So dietary history must be involved about intake of these haematinic foods.

Chronic diarrhoeas, gastrectomy, gastroenterostomy can lead to malabsorption which in turn can lead to deficiency anaemia. Omeprazole and metformin can impair vitamin B₁₂ absorption. Phenytoin and oral contraceptive pills can impair to late absorption. Chronic administration of above drugs can cause deficiency anaemia. Repeated pregnancy and prolonged lactation can increase the daily requirement of mother and if it is not fulfilled by increased dietary intake, deficiency anaemia can occur.



Presence of chronic kidney disease, rheumatoid arthritis, tuberculosis, human immunodeficiency viral infection, thyroid disease, cancer, etc. can also be associated with anaemia of chronic disorder.

Involvement of other cell lines like white cell and platelet in addition of red cells as evident by repeated infections, mucocutaneous bleedings, lymph node enlargement, abdominal masses, bone and joint pain etc. gives a clue that bone marrow may have involved.

Jaundice with high-colored urine and stool associated with pallor can be seen in patient with haemolytic anaemia.

Apart from that, brittle hair and nail, dysphagia and ice pica (pagophagia) can be seen in iron deficiency anaemia. Sore tongue with intolerance to hot spicy food due to glossitis can be seen in iron deficiency as well as in vitamin B₁₂ or folate deficiency.

Sudden onset of anemia progressively worsening with blood transfusion can be seen in patients with autoimmune haemolytic anaemia. Delayed haemolytic transfusion reaction occurring in repeatedly transfused patients can present with shortened transfusion interval and fall in post-transfusion haemoglobin compared to pre-transfusion haemoglobin.

Previous history of gastric surgery is associated with deficiency anaemia. Previous history of worm infestations can be seen in patient with iron deficiency anaemia. Piles and peptic ulcer diseases are also common causes of iron deficiency anaemia. Whether these are actively bleeding or not, iron deficiency anaemia can occur due to undiagnosed occult bleeding. Asking recent **drug intake** is every important in diagnosing drug-induced haemolytic anaemia (e.g. primaquine in G6PD deficiency) and drug-induced bone marrow failure (e.g. Chloramphenicol, zidovudine or azathioprine in aplastic anaemia). Taking beans and dyed foods can also be seen in haemolysis due to G6PD deficiency.

Family history of members with anaemia can be seen in hereditary diseases like thalassaemias, hereditary spherocytosis, Southeast Asian ovalocytosis, etc. **Menstrual history** is also very important in diagnosis of anaemia. Heavy menses associated with uterine myoma in patient's history can lead to diagnosis of iron deficiency anaemia. Repeated pregnancies and breast feeding can also cause iron deficiency anaemia in women by depleting iron store.

Personal history like alcohol drinking is very helpful in diagnosing macrocytic anaemia. Food faddists like daily taking of tea leave (Let-phet) and drinking too much plain tea every day are rare cause of iron-deficiency anaemia. **Occupational exposure** to lead is associated with hypochromic microcytic anaemia and exposure to insecticides and chemicals is associated with bone marrow failure. **Travelling** to endemic area may help in diagnosis of malaria and leishmania as underlying cause of anaemia.



Physical Examination

Sometimes, patients with anaemia having pale skin and pale conjunctivae may also have other physical signs exposing the underlying cause of anaemia.

Fanconi's anaemia is a congenital bone marrow failure associated with abnormal thumbs, absent radii, short stature, skin hyperpigmentation, café au lait spot, triangular face, microcephaly, kidney problems, etc. Growth retardation can also be seen in congenital anaemia like thalassaemia. Frontal bossing, parietal bossing and malar prominence can be seen in patient with thalassaemia. Butterfly rash, sparse hair and oral ulcers can be seen in patient with systemic lupus erythematosus. Patient with hypothyroidism can have pallor, jaundice, puffy face and coarse facial appearance.

Angular stomatitis and glossitis can be seen in patient with iron, vitamin B₁₂ and folate deficiency. Perioral pigmentation in Peutz-Jegher syndrome, and telangiectasia in hereditary haemorrhagic telangiectasia (Osler-Rendu-Weber Syndrome) can be associated with gastrointestinal bleeding. Anaemia with gum hypertrophy can be seen in acute myeloid leukemia, folate deficiency due to phenytoin and pregnancy. Associated mucocutaneous bleedings may give a clue that vascular, platelet or coagulation defect may also be present e.g. hereditary haemorrhagic telangiectasia (Osler-Rendu-Weber Syndrome), aplastic anaemia, immune thrombocytopenia, leukemia, von Willebrand disease, haemophilias, etc. Bleeding from venipuncture site can be seen in patient with disseminated intravascular coagulation (D.I.C).

Orthopnoea, raised jugular venous pulse (JVP), enlarged tender liver and ankle swelling can be seen in severe anaemia with heart failure.

Koilonychia is a tell-tale sign of iron deficiency anaemia but brittle nail with longitudinal ridging can also be seen in the same condition. Anaemia in a patient with rheumatoid hands can be due to anaemia of chronic disorder, folate deficiency anaemia due to associated pernicious anaemia or long-term methotrexate, iron deficiency anaemia due to long-term pain killers and steroids, and bone marrow failure due to drugs like leflunamide and salphasalazine. Sometimes combination of causes may be seen in such patients. Similarly, anaemia in a patient with sclerodactyly and scleroderma may be due to anaemia of chronic disorder or malabsorption or chronic kidney disease. Anaemia with hepatosplenomegaly can be seen in malaria, thalassaemia, myeloproliferative disorders, lymphoproliferative disorders, malignancy, multiple metastases, miliary tuberculosis, visceral leishmaniasis, etc.

Investigations for Anaemia

Investigations for anaemia should be started with complete blood count which can give a lot of information such as type of anaemia, severity of anaemia, cause of anaemia etc.



According to World Health Organization (WHO), anaemia is defined as haemoglobin less than 13 g/dL in men (15 years of age and above), less than 12 g/dL in non-pregnant women (15 years of age and above), and less than 11 g/dL in and pregnant women. Haemoglobin level less than 11 g/dl in children 6 to 59 months of age, less than 11.5 g/dl in children 5 to 11 years of age, and less than 12 g/dl in children 12 to 14 years of age can be defined as anaemia.¹

Mean Corpuscular Volume (MCV) is a very useful parameter in anemia work-up. Low MCV (< 80 fL) can be due to iron deficiency, thalassaemia, anaemia of chronic disorder, sideroblastic anaemia, lead poisoning and aluminum toxicity. **Mentzer Index** can be helpful in differentiating iron deficiency from beta thalassaemia. The index is calculated by dividing MCV (in fL) by red blood cell count in (millions per μ L). If the index is less than 13, thalassaemia is more likely, and if the index is more than 13, iron deficiency anaemia is more likely. The principle is red cell production is reduced in iron deficiency anaemia (thus index will be more than 13) but not in thalassaemia (thus index will be less than 13).

Anaemia with normal MCV (80 - 100 fL) can be seen in early iron deficiency, anaemia of chronic disorder, renal failure, multiple myeloma, etc. Anaemia with high MCV(> 100 fL) can be seen in megaloblastic anaemia, haemolytic anaemia, myelodysplastic syndrome, aplastic anaemia, drugs (hydroxyurea, methotrexate), hypothyroidism, alcoholism and liver disease.

High MCHC (Mean corpuscular haemoglobin concentration) can be seen in patients with hereditary spherocytosis.

Red cell distribution width (RDW) is an index of red cell size variation and it can be used to quantitate anisocytosis. RDW of 1.5 - 14.5% is regarded as normal. RDW is useful in differentiating iron deficiency (increased RDW) from thalassaemia trait (normal RDW), and also in differentiating macrocytosis (normal RDW) from red cell agglutination (increased RDW).

Reticulocyte production index (RPI) (also known as corrected retic count) is calculated as follow.

$$\text{RPI} = \text{Retic count} \times \frac{\text{Observed Hb}}{\text{Normal Hb}} \times 0.5$$

RPI of < 2 is associated with hypo-proliferative anaemia and RPI > 2 is associated with hyper-proliferative index.

Measured retic count is sometimes misleading. It can be seen in following example. If a patient comes in with Hb 7.5 g/dl with retic count 7%, attending clinician may think that bone marrow is working alot and it is haemolytic anaemia with compensatory erythroid hyperplasia and reticulocytosis.

$$\text{RPI in this patient is } 7\% \times (7.5/15) \times 0.5 = 1.75$$



So, this patient actually is not producing enough reticulocytes and red cells to catch up with his low haemoglobin. This means that this patient has hypoproliferative anaemia.

RPI or corrected retic count can be used in conjunction with MCV and RDW in detecting the cause of anaemia as shown in Table (1).

Table (1) Corrected retic count and MCV/RDW for detection of cause of anaemia

	Corrected Retic < 2%	Corrected Retic > 2%
Low MCV, Normal RDW	Anaemia of Ch. Disease	
Low MCV, High RDW	Iron Deficiency Anaemia	Thalassaemia
Normal MCV, Normal RDW	Anaemia of Ch. Disease	
Normal MCV, High RDW	Early Fe, B12, folate ↓ Myelodysplastic \$	Sickle cell disease
High MCV, Normal RDW	Chemo/ Alcohol/ Antiviral Aplastic anaemia	Ch. Liver Disease
High MCV, High RDW	Folate or B12 ↓ Myelodysplastic \$	Immune H'lytic Anaemia Ch. Liver Disease

Associated leucopenia can be seen in malignancy, chemotherapy, hypersplenism, drugs, megaloblastic anemia, aplastic anemia, myelodysplastic syndrome, bone marrow infiltration, etc.

Associated thrombocytopenia can be seen in malignancy, chemotherapy, hypersplenism, drugs, megaloblastic anemia, aplastic anemia, myelodysplastic syndrome, bone marrow infiltration, thrombotic thrombocytopenic purpura (TTP), haemolytic uraemia syndrome (HUS), disseminated intravascular coagulation (D.I.C), etc.

Peripheral blood film examinations can also give much information about cause of anaemia. Spherocytes can be seen in hereditary spherocytosis and autoimmune hemolytic anaemia. Coomb's test is very helpful in differentiating these 2 conditions. Positive Coomb's test is seen in AIHA but hereditary spherocytosis has negative Coomb's test.

Schistocytes (fragmented red cells) can be seen in *big vessel diseases* like prosthetic valve haemolysis, intracardiac myxomas and Bongo drumming, as well as in *small vessel diseases* like thrombotic thrombocytopenia purpura (TTP), haemolytic uraemic syndrome (HUS), disseminated intravascular coagulation (DIC), malignant hypertension and pre-eclampsia.

Specific morphology of red cell can give a clue to the cause of anaemia. For example:

- Ovalocytes in Southeast Asian ovalocytosis
- Ring cells, pessary cell and pencil shaped cell in iron-deficiency anaemia
- Burr cell in uremia

- Target cells in thalassaemia
- Basophilic stippling in lead poisoning
- Bite cells, blister cells and Heinz's bodies in G6PD deficiency
- Sick cells in sickle cell disease
- Tear-drop cells in myelofibrosis

Morphology of white blood cell can also give a clue to the cause of anaemia. For example:

- Hypersegmented neutrophils in megaloblastic anaemia
- Hypogranular or agranular neutrophils in myelodysplastic anaemia
- Myeloblasts and lymphoblasts in leukemia

For deficiency anaemia, following investigations can be proceeded.

- Serum iron, TIBC, serum Ferritin for iron deficiency anaemia
- Serum folate, Red cell folate for folate deficiency
- Serum B₁₂, Methyl malonic acid, pernicious anaemia Ab for vitamin B₁₂ deficiency
- Total and differential protein - in malnutrition
- Urea, Creatinine - for chronic kidney diseases (erythropoietin deficiency)
- Thyroid function tests for hypothyroidism

Interpretation of plasma iron studies is shown in Table (2)². Transferrin saturation (i.e. serum iron/total iron binding capacity x 100) less than 16% can lead to a conclusion that the patient has iron deficiency anaemia, but serum ferritin measurement is more specific for estimation of iron store in the body.

Table (2) interpreting plasma iron studies
(Oxford Handbook of Clinical Medicine 10th edition, Page 327)

	Iron	TIBC	Ferritin
Iron deficiency	↓	↑	↓
Anaemia of chronic disease	↓	↓	↑
Chronic haemolysis	↑	↓	↑
Haemochromatosis	↑	↓ (or ↔)	↑
Pregnancy	↑	↑	↔
Sideroblastic anaemia	↑	↔	↑

Even after iron deficiency anaemia is diagnosed, it is still needed to do further investigations for underlying cause of iron deficiency. Stool examination should be done for hookworm eggs and ova. Urine parasite like Schistosoma haematobium can be diagnosed by examination of urine specimens for eggs. Upper and lower gut endoscopies must be done in patients with positive fecal occult blood test. Pelvis ultrasound is helpful for women with menorrhagia. Coeliac serology like anti-tissue transglutaminase, anti-gliadin antibody and anti-endomysial antibody can be done if coeliac disease is suspected. Fecal elastase can be done if malabsorption is suspected.

Haemolytic anaemia has following abnormalities.

- Retic count - increased
- Unconjugated bilirubin - increased
- Haptoglobin - decreased
- Urine haemosiderin - positive (intravascular haemolysis)
- LDH - increased

To identify the exact cause of haemolytic anaemia, following investigations can be done.

- Osmotic fragility test for Hereditary spherocytosis
- G6PD assay or activity for G6PD deficiency
- Haemoglobin electrophoresis (cellulose acetate, isoelectric focusing IEF, high performance liquid chromatography HPLC, capillary electrophoresis CE) for haemoglobinopathies
- Coomb's test - direct and indirect for immune haemolytic anaemia
- PNH screening tests, Ham's test, Flow cytometry or FLAER for CD 55, CD 59 for PNH
- Blood for MP, ICT-MP, Blood Cultures for infections

Thalassaemia is a common cause of anaemia in Myanmar. Some examples of haemoglobin electrophoresis results are shown in Figures (1), (2), (3), (4), (5) and (6). Assessment of iron status by doing iron studies in thalassaemis patients is an important next step. Not all the thalassaemia patients need blood transfusion. Referral to haematologists is needed to get the proper management of this common condition. Generally, regular blood transfusion is needed only in (1) those symptomatic before age 2 years, (2) those with haemoglobin persistently less than 7 g/dl, (3) those with anaemia limiting daily activities, (4) those with significant hepatosplenomegaly (more than 6 cm), (5) those with height and weight retardation and (6) those with frequent infections.

Figure (1) Normal haemoglobin electrophoresis **Figure (2) Haemoglobin electrophoresis of a Beta⁺ thalassaemia patient**

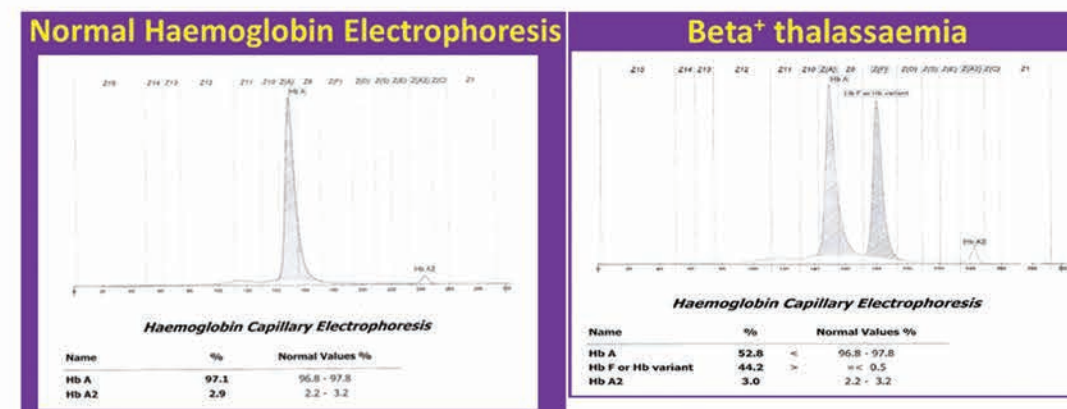


Figure (3) Haemoglobin electrophoresis of a Hb E Beta⁰ thalassaemia patient

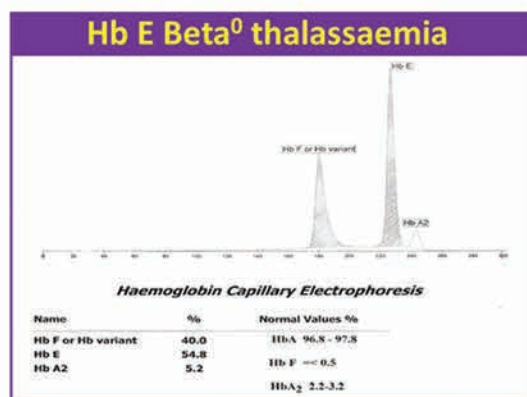
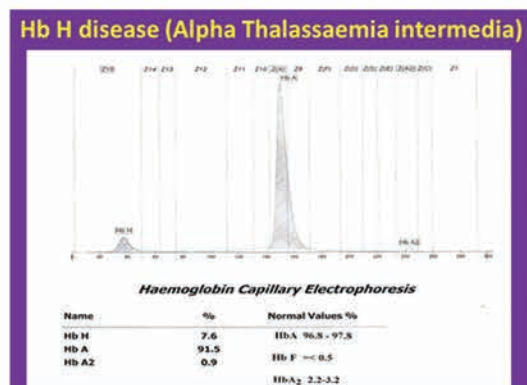


Figure (5) Haemoglobin electrophoresis of a Hb H disease (Alpha thalassaemia intermedia) patient



Bone marrow examination is sometimes needed to find out the cause of anaemia e.g pure red cell aplasia, myelodysplastic syndrome, aplastic anaemia, etc. Bone marrow infiltrations by military tuberculosis or histoplasmosis are sometimes diagnosed in immunocompromised patients.

Conclusion and Key Message

Anaemia does not necessarily mean that the patient requires blood transfusion. Anaemia does not necessarily mean that the patient requires oral iron supplement. Proper history taking and thorough physical examination, together with mindful investigations can lead to correct diagnosis and appropriate management of anaemia.

References:

- Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity: WHO/NMH/NHD/MNM/11.1.
- Oxford Handbook of Clinical Medicine (10th edition).

Current MDR-TB Situation in Myanmar

Tuberculosis Society

TB and MDR / XDR-TB burden

Myanmar is one the countries with the highest burden of tuberculosis, not only the most common drug-susceptible form but also its more severe forms, drug-resistant tuberculosis (TB) and TB associated with HIV infection. It is one of the 30 high MDR-TB burden countries; (6th position in global, 2nd position after India in SEARO). According to WHO estimation there were approximately 14,000 (8,000 - 21,000) MDR/RR-TB among notified pulmonary TB cases in the country in 2017. Three national Drug Resistant TB surveys (DRS) showed increasing prevalence of MDR/RR-TB among notified pulmonary TB cases. Five percent among new and 27.1% among retreatment cases were MDR-TB according to third DRS in 2011 - 2012.

Cases of extensively drug resistant TB (XDR-TB) have been identified in Myanmar. The NTP estimated that 1% of drug resistant-TB cases are XDR-TB. Case finding of XDR-TB was targeted to those with follow up culture positive at 3rd month among patients enrolled in PMDT. However, recently, more cases were diagnosed through Shorter Treatment Regimen (STR) screening. In brief, country has notified 127 pre-XDR TB cases and 66 XDR-TB cases in last three years (2015 - 2017).

Scaling up of case detection and treatment for MDR-TB

National TB Program has started treatment for MDR-TB since 2009 as pilot project; 359 patients received treatment during 2009 - 2011. After that the number patients enrolled in Programmatic Management of Drug Resistant TB (PMDT) has significantly increased [442, 667, 1537, 2207, 2539 and 2,666 in 2012, 2013, 2014, 2015, 2016 and 2017 respectively]. The Treatment Success Rate was 79%, 83%, 81% and 80% for 2012, 2013, 2014 and 2015 cohort, respectively. Gene Xpert was introduced in 2011; has scaled up to 73 machines across 17 States and Regions in 2017.

There were 10 selected townships for pilot MDR-TB project in 2009 - 2011 and later it was gradually expanded up to 108 townships by the end of third quarter 2015 and PMDT became borderless approach in 2016. The fact that 50% of MDR-TB case load is from Yangon Region, all township health departments in Yangon Region have been trained to manage MDR-TB cases.

International NGO like The Union and local NGOs such as Myanmar Medical Association, Myanmar Health Assistant Association and Pyi Gyi Khin have been engaged in community based TB/MDR-TB care providing evening DOT, patients' education and infection control at community level through trained project staff and community health workers. Funding for social support (transportation) towards patients and basic health staff taking care of MDR-TB patients were secured for (2018 - 2020) by GF.

Yangon MDR-TB Crisis

The third Drug Resistant TB Survey and routine M&E system highlighted special MDR-TB situation in Yangon Region. Therefore series of discussion and group work were conducted; a short term plan has been developed and implemented to curtail the MDR-TB crisis in Yangon.

Challenges of PMDT

Although the gap (proportion of patients on treatment among diagnosed RR/MDR-TB) between case detection and number of patients on treatment reduced from 61%, 57% in 2013 and 2014, 21% in 2015 and 2016 and 17% in 2017, there are challenges to achieve set targets for case detection and patients started on treatment.

Expansion of MDR-TB treatment centers (District level) has been ongoing. Due to limitation in human resources, professional stigma and complexity of (local) health system in some areas, NTP encounters many challenges to implement PMDT.

There was a human resource crisis in National TB Reference Laboratory in 2016-2017 which affected timely issuing culture results for treatment monitoring and decision. Quality of care would also be a challenge due to limited resources and weak in regular and systematic monitoring for clinical activities.

NTP needs to revise the NSP targets and prepare budget and human resource in order to provide timely treatment using new and repurposed drugs for all diagnosed XDR-TB and pre XDR-TB patients. The new agenda is relevant not only for NTP but also for the whole health system as a DSM (active anti-TB drug safety, monitoring and management) has to be in place in general hospitals.

New drugs, new diagnostic tools and new regimen

The National TB Program, in collaboration with MSF (H), has launched "Expansion of new drugs (End TB) Program in March 2016. The program plans to include 10 patients from public sector (NTP) and 10 patients from MSF (private sector) per year for four years. The patients enrolled in the End-TB program had to be admitted at least 2 - 3 months in Aung San TB hospital in Yangon. Patients had to be followed up in out patients' department of Aung San TB hospital for patients from public sector and in project clinics of MSF [Yangon Region, Shan State (North) and Kachin State] for patients from private sector. The enrolment criterion includes pre-XDR and XDR-TB cases and MDR-TB cases who cannot tolerate the drugs used in conventional MDR-TB treatment.

After a year, according to needs and demands, NTP has started using new drug (Bedaquiline) and repurposed drug (Linezolid) for patients with indication since mid-2017. By the end of September 2018, a total of 151 DR-TB patients including those enrolled in End TB program have initiated with new drugs.

National TB Reference Laboratory and reference laboratory in Mandalay have started using genotypic drug susceptibility test for second line anti-TB drugs in the last quarter 2017 to screen for Shorter Treatment Regimen (STR) enrolment. The pilot project (STR) has been launched since November 2017 after providing trainings towards concerned staff. The target for pilot project is 200 and NTP will evaluate the results as interim outcomes and final outcomes.

Case Findings of MDR / RR-TB

National TB Program targets following groups to perform Xpert testing. It is a must to proceed to MDR-TB treatment with one "RR" result for those with risk factor such as (previous TB history, HIV positive, contact of MDR-TB, TBDM, and non-converter). If patient has no risk factor(s), s/he needs to submit second specimen for second time Xpert testing and with second "RR" result, MDR-TB treatment will be introduced.

- Retreatment TB cases
- Close contacts of MDR-TB patients who develop active TB
- All TB patients and presumptive TB cases living with HIV/AIDS
- Sputum smear positive at the end of intensive phase (non-converter and positive converter)
- TB patients residing in area with high MDR-TB Prevalence (MDR-TB among new TB patients is > 10%): Yangon Region.
- TB patients with diabetes mellitus
- All smear positive new TB cases
- Other cases to be considered individually by MDR-TB committee
- All PTB cases

It is essential to fill in TB 05 (the requisition form) completely and accurately by referring clinicians so that "RR" results will reach back to patient without delay and treatment will be initiated by concerned MDR-TB center.

Treatment of MDR / RR-TB and model of care

TB centers at region/ state/ district level provide treatment initiation, follow up consultations and treatment monitoring (clinical signs and symptoms, drug side effect monitoring, body weight, CXR, sputum smear microscopy and cultures) of MDR-TB patients. The township health department takes care of daily injection in intensive phase, DOT and management of minor side effects during the whole course of treatment. There are also social support for MDR-TB patients to improve treatment adherence and treatment success.

When a patient is diagnosed as MDR / RR-TB wherever the diagnostic center (either in Myanmar or abroad / either in private sector or public sector), s/he can receive MDR / RR-TB treatment under a township health department in connection with a nearest MDR-TB center at district level.

NTP ensures quality of drugs by procuring through GDF and keeping systematic supply chain management. All MDR-TB drugs and majority of ancillary drugs to treat side effects of MDR-TB drugs as well as all essential baseline and follow up investigations are free of charge.

Counseling and support to MDR-TB patients

MDR-TB patients are extremely vulnerable to stigma and financial hardship. Provision of counseling and financial support may not only reduce their vulnerability, but also increase cure rates. The role of counselors is crucial in ensuring patients remain motivated to complete the arduous treatment regimen. Counseling focuses on treatment adherence, as well as psychosocial care, advice to families and caregivers and nutritional support. National Tuberculosis Programme provides social support and counseling service to MDR-TB patients.

Role of health programs other than NTP in MDR-TB prevention and care

Among the vertical programs, National AIDS Program (NAP) and Maternal and Child Health Program (MCH) are relevant to significantly contribute to MDR-TB prevention and care. The clinics taking care of HIV positive patients can refer every presumptive TB/MDR-TB patients who are HIV positive or send specimens (sputum, CSF, lymph node aspirate and gastric aspirate) to TB/MDR-TB diagnostic centers (Xpert sites) for early case detection and timely appropriate treatment. The basic health staff in the field and under 5 clinics has an opportunity to notify and refer presumptive paediatric TB / MDR-TB cases by close follow up for the babies and young children who have exposed to MDR-TB patients.

Role of Laboratory in MDR-TB diagnosis and treatment

TB laboratories in Region/ State/ District provide diagnostic services for MDR/RR-TB with Gene Xpert. Two BSL-3 laboratories in Yangon and Mandalay perform anti-TB drug Resistance testing other than Gene Xpert such as Line Probe Assay for first line and second line anti-TB drugs (genotypic tests) and Liquid and Solid cultures (phenotypic tests). To date, a total of three culture Laboratories each in Yangon, Mandalay and Taunggyi are performing follow up cultures for the monitoring of MDR-TB treatment. If culture is positive, they proceed to drug susceptibility testing for the second line drugs. The fact that TB laboratory activities are vital for MDR-TB care and surveillance, they should receive full support for financial assistance, technical assistance and adequate human resources for expanding activities.

Role of hospitals in MDR-TB prevention and care

There are two TB specialty hospitals in Myanmar: Aung San TB Hospital in Insein in Yangon and Patheingyi TB Hospital in Mandalay. They take care of MDR-TB patients with co-infections and co-morbidities, MDR-TB patients with additional resistance either to Fluoroquinolones or second line injectable and XDR-TB patients.

The general hospitals, district and township hospitals play a key role in MDR-TB infection prevention and control by adopting good infection control practices. It is extremely important to follow the national guidelines so as to minimize hospital acquired TB and MDR-TB. The administrative controls in each and every hospital need to be strengthened; separation of OPD area for presumptive TB cases from neonatal clinic or diabetic clinic would be one of the examples.

Furthermore, all required patients' information must be completely and correctly noted down in the requisition form (TB 05) if in-patients are tested for Xpert. Only then, the results would be given timely to appropriate person. Careful and active participation from hospital staff would contribute drastically to cut the transmission chain specifically to fellow health care workers and other in-patients.

Role of General Practitioners in MDR-TB prevention and care

General practitioners both PPM and non-PPM would be major contributors for early case detection when all presumptive MDR-TB patients come to their clinics and meet the NTP's criteria for Xpert testing are referred to the nearest diagnostic center.

Role of Medical Universities in MDR-TB prevention and care

In recent years, new diagnostic tools and new drugs have been developed; WHO recommendations for the treatment of DR-TB have been updated 2 yearly; many drugs are on the pipelines pinpointing unprecedented evolution in medical science about DR-TB. This is high time to update the current training curriculum and their contents for medical students in order to equip them with latest knowledge and to serve people of Myanmar with good clinical practices.

Role of community and civil society organization in MDR-TB prevention and care

People and family affected by MDR-TB suffer financial hardship due to long duration of illness and treatment period. Patients are asked to avoid crowded places or enclosed workplace; to use surgical mask for infection control and as consequences, they may need to stop working and family income is affected. Any assistance either financial support or advocacy for social protection like securing the job with continuum of salary till patients get well and come back to work would be contributed by community and civil society organizations, for instance.

Mandatory TB Case Notification

As per End TB strategy, mandatory TB case notification is one of the important policies to enhance TB case finding and to reduce the burden of TB / MDR-TB. In Myanmar, TB cases detected in the health facilities both public and private sectors generally get notified through routine reporting system. On the other hand, some TB cases that are



treated in private hospitals and Non-PPM clinics were not included in national figures. Therefore, implementation of Mandatory TB Case Notification was started in 2018 and actual TB burden will be known. Apart from that those patients treating at private sector can also access to test with Gene Xpert.

Summary

The burden of TB / MDR-TB in Myanmar is too heavy that many sectors need to share the responsibility with NTP to curtail it. TB / MDR-TB is a social disease; several factors outside health sector such as literacy, housing, transportation system, individual income determine the current situation and therefore development in those areas will definitely influence to reverse the situation. For the time being, it is noteworthy that engagement with different actors is as important as implementing routine TB / MDR-TB control activities and every citizen have opportunity to take part in the TB / MDR-TB control activities.

Below is the link to resources / documents regarding DR-TB management.

<https://www.dropbox.com/sh/a00zqa77swcgm2d/AAAd78qvj0bLNkvXnoiArTVVa?dl=0>



Syphilis

National AIDS/STD Programme

Epidemiology and Burden of Disease

Syphilis is a sexually transmitted bacterial infection (STI) caused by *Treponema pallidum* resulting in substantial morbidity and mortality. According to WHO estimation, in 2012, there were 5.6 million new cases of syphilis among adolescents and adults of age between 15 - 40 years worldwide. The estimates also stated global incidence rate of 1.5 cases per 1000 females and 1.5 per 1000 males. The 18 million cases in 2012 can be translated to a global prevalence of 0.5% among females and 0.5% among males aged 15 - 49 years while Africa region holding the highest prevalence.⁽¹⁾ The WHO Report on global sexually transmitted infection surveillance in 2015 stated that syphilis in pregnancy is the second leading cause of still birth globally and also results in, prematurity, low birth weight, neonatal death, and infections in newborns.⁽²⁾

Congenital syphilis (Mother to Child Transmission of Syphilis)

Untreated primary and secondary syphilis infections as well as latent syphilis in pregnancy results in serious adverse pregnancy outcomes. In 2012, an estimated 350,000 adverse pregnancy outcomes worldwide were attributed to syphilis, including 143,000 early fetal deaths or stillbirths, 62,000 neonatal deaths, 44,000 preterm/low-birth-weight babies and 102,000 infected infants.⁽²⁾ If the mother with syphilis had a chance to receive adequate treatment during pregnancy-ideally before second trimester, the transmission can be prevented and as a result, the fetus adverse outcomes will be minimal.

Elimination of Mother-To-Child Transmission of Syphilis (EMTCT)

As Congenital syphilis is a preventable disease, by adopting early screening and effective treatment strategies, elimination of mother-to-child transmission of syphilis can easily be achieved. Cuba became the first country to be validated for EMTCT of HIV and syphilis from public health problems in 1991. There are also some countries that have been validated for; Belarus, Moldova and Thailand in 2016, Anguilla, Antigua & Barbuda, Bermuda, Cayman Islands, Montserrat, St. Christopher & Nevis in 2017 and Malaysia in 2018, respectively.

In public health, elimination is generally defined as reduction to zero of the incidence of a disease or infection in a defined geographical area. PMTCT measures are highly effective but without 100% certainty, and it is the reason why it is not feasible in most settings to reduce MTCT of both HIV and Syphilis infection to zero. Therefore, the goal for EMTCT initiatives is to reduce and ensure services to maintain MTCT of syphilis at a very low level, such that it is no longer a public health problem. To get this achievement, strong political and public health commitment are required to maintain surveillance, prevention, and treatment program so that performance of the required indicators is preserved.

EMTCT of HIV and syphilis process indicators (must be achieved for 2 years)⁽³⁾

1. ANC coverage (at least one visit) (ANC - 1) of $\geq 95\%$
2. Coverage of HIV and/or syphilis testing of pregnant women of $\geq 95\%$
3. ART coverage of HIV-positive pregnant women of $\geq 95\%$
4. Adequate treatment (see Box 5) of syphilis-seropositive pregnant women of $\geq 95\%$

IMPACT INDICATOR FOR VALIDATION OF EMTCT OF SYPHILIS

Countries should have achieved and maintained for at least 1 year the following impact target for validating EMTCT of syphilis:

a case rate of congenital syphilis of ≤ 50 per 100,000 live births

EMTCT targets use a surveillance case definition for congenital syphilis rather than a clinical case definition. A surveillance case definition provides a uniform set of criteria to define a condition for public health surveillance purposes.

The global surveillance case definition for congenital syphilis is given below

[1] a live birth or fetal death at > 20 weeks of gestation or > 500 g (including stillbirth) born to a woman with positive syphilis serology and without adequate syphilis treatment

(Adequate maternal treatment is defined as at least one injection of 2.4 million units of intramuscular benzathine benzylpenicillin at least 30 days prior to delivery.)

OR

[2] a live birth, stillbirth or child aged < 2 years born to a woman with positive syphilis serology or with unknown sero-status, and with laboratory and/or radiographic and/or clinical evidence of syphilis infection (regardless of the timing or adequacy of maternal treatment).

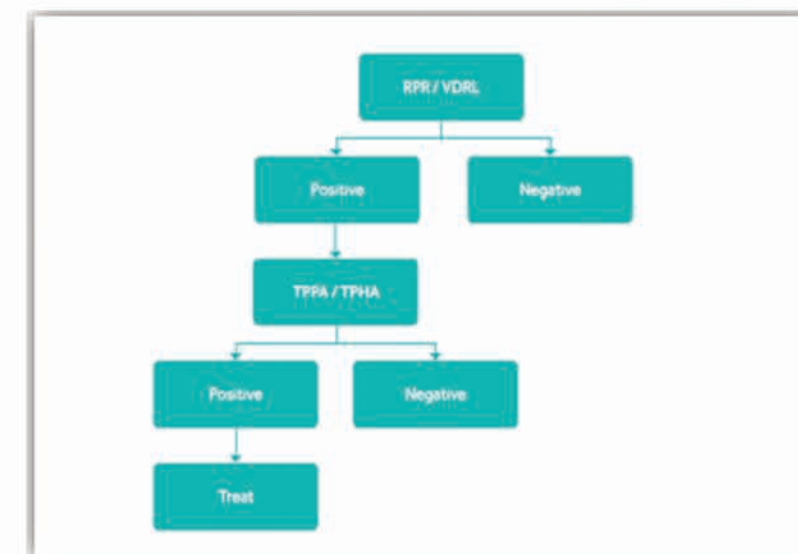
(Laboratory and radiographic evidence consistent with a diagnosis of congenital syphilis for more information at Global guidance on criteria and process for validation - Elimination of mother to child transmission of HIV and Syphilis second edition 2017)

Underreporting of congenital syphilis

Congenital syphilis is underreported for many reasons:

- (1) Access to laboratory and radiographic testing may not be available in clinical settings.
- (2) Congenital infections that result in spontaneous abortion or stillbirth may not be recognized. Stillbirths are often not delivered in health facilities, and providers may not realize that stillbirths are the most common adverse pregnancy outcome caused by maternal syphilis.
- (3) Health-care providers must rely on a combination of suggestive history, maternal and infant tests, and clinical findings; however, these findings may be non-specific, subtle or entirely overlooked.

Syphilis diagnosis testing to pregnant women



(2016 WHO guideline on syphilis screening and Treatment for pregnant women)

Treatment (Myanmar Sexually Transmitted Infections Guideline 2017)

1. For Pregnant Women with Early Syphilis

Preferred first choice

Benzathine penicillin G 2.4 million units (ATD) once IM

Second choice

Procaine penicillin G 1.2 million units IM (ATD) once daily for 10 days

When Benzathine or Procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock-outs) use with caution.

- Ceftriaxone 1 g IM once daily x 10 - 14 days OR
- Erythromycin 500 mg orally 4 times daily x 14 days

Although erythromycin treats the pregnant women, it does not cross the placental barrier completely and as a result the fetus is not treated. It is therefore necessary to treat the newborn infant soon after delivery (see in congenital syphilis). Doxycycline should not be used in pregnant women. Because syphilis during pregnancy can lead to severe adverse complications to the fetus or newborn, stock-outs of Benzathine penicillin G for use in antenatal care should be avoided.

2. Pregnant women with late syphilis or unknown stage of syphilis:

Preferred first choice

Benzathine penicillin G 2.4 million units (ATD) weekly for three consecutive weeks

Second choice

Procaine penicillin G 1.2 million units intramuscularly (ATD) once daily for 20 days

When Benzathine or Procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock-outs) use with caution.

- Erythromycin 500 mg orally four times daily for 30 days.

These women should be advised to seek medical attention following treatment if they experience any change in fetal movements or if they start to have contractions which may be due to Jarisch-Herxheimer reaction causing premature labor or fetal distress or both. Since treatment is to be given to prevent further fetal damage, this should not be a delay for therapy.

Follow-Up

Monthly serological check-up should be done until adequacy of treatment has been established by the appropriate antibody response for the stage of disease.

Alternative Regimen

There are no proven alternatives to penicillin. Desensitization, if possible, should be done before treating with penicillin. Tetracycline and doxycycline are contraindicated during pregnancy, and erythromycin may be used but infant treatment is needed.

Congenital Syphilis

Infants should be evaluated for congenital syphilis if the mother has the following criteria:

- The mother is sero-reactive (non-treponemal test confirmed by treponemal test, if possible)
- Had untreated syphilis at delivery (a woman who had been treated with a regimen other than those recommended in these guidelines for treatment of syphilis should be considered untreated)
- Serological relapse or re-infection suspected after treatment (antibody titre increases by at least two dilutions VDRL)
- Mother was treated with erythromycin or other non-penicillin regimen for syphilis during pregnancy
- Was treated for syphilis < 1 month before delivery
- No definite history of taking adequate treatment for syphilis
- Gave history of taking appropriate penicillin regimen for early syphilis during pregnancy but VDRL did not reveal any decrease in antibody titer by at least two dilutions
- Gave history of taking appropriate treatment before pregnancy but had insufficient serologic follow-up to assure that they had responded favorably to treatment and are not currently infected (i.e. at least a two-dilution decrease in VDRL test and a stable or declining antibody titres of < 1:4 for other patients)

Clinical features of congenital syphilis

Clinical features of Congenital syphilis (common during early 2 years of life)	Clinical stigmata of congenital syphilis (after 2 years of life)
<ol style="list-style-type: none"> 1. Maculopapular rash 2. Condylomata lata 3. Mucous Patches 4. Fissure around mouth, nose and anus 5. Rhinitis with nasal discharges (snuffles) 6. Hepatosplenomegaly 7. Osteochondritis/Periostitis 8. Generalised Lymphadenopathy 9. Choroiditis 10. Meningitis/Pneumonia 11. Anaemia 12. Failure to thrive, fever and Irritability in newborn babies 	<ol style="list-style-type: none"> 1. Hutchinson's teeth 2. Interstitial keratitis 3. Deafness 4. Frontal bossing 5. Saddle Nose 6. Hard palate defect 7. Swollen knees (Clutton's joints, Painless effusion into knee joints) 8. Saber shins 9. Short maxillae 10. Protruding Mandible

Recommended Regimens to exposed infants

- Aqueous benzyl penicillin G 50,000 unit/kg/dose intravenously every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days (OR)
- Procaine penicillin G 50,000 Unit/kg single daily dose intramuscularly for 10 days
- If the treatment is missed for more than 1 day, entire course should be restarted. (more info at [Myanmar Sexually Transmitted Infections Guideline 2017](#))

Follow-up to exposed infants

Treated infants also should be followed every 2 - 3 months to assure VDRL antibody titres decline and these infants should have become non-reactive by the age of 6 months, but the response may be slower for infants treated after the neonatal period.

References

- (1) WHO syphilis treatment guideline 2016
- (2) WHO Report on global sexually transmitted infection surveillance 2015
- (3) Global guidance on criteria and process for validation - Elimination of mother to child transmission of HIV and Syphilis second edition 2017
- (4) 2016 WHO guideline on syphilis screening and Treatment for pregnant women

Clinical approach to low back pain

Myanmar Orthopaedic Society

Introduction

Low back pain (LBP) is a very common symptom which can affect about 80% of the population at least once in lifetime. Each year, 15 - 20% of the population will have back pain. It is the second most common symptom seen in general practitioners' clinic; first being common cold.

It is usually a self-limiting condition but can go into chronicity in about 10% of the individuals. It is the most common cause of disability for people less than 45 years of age. Low backache which is acute and has red flag signs should be evaluated urgently to look for emergency and catastrophic causes which present with neurodeficits, absent pulses and dropping blood pressure.

Basics of low back pain

While evaluating of back pain - age of the patient, the duration of backache, character, aggravating and relieving factors, occupation of the patient, risk factors and presence of "red flags" are important.

Age of the patient is helpful in diagnosing low backache. Inflammatory LBP being common in 18 - 40 years. Degenerative conditions, malignancy and osteoporosis are common causes above 40 years. Infective causes can occur in all age groups.

History of trauma can help in diagnosis of prolapsed intervertebral disk (PID), spondylolisthesis and fractures. History of taking glucocorticoids can clinch the diagnosis of osteoporosis and osteoporotic fractures.

"red flags" should be asked like history of trauma, fever, urinary incontinence, weight loss, cancer, long-term steroid use, worsening night pains or rest pains and presence of neurodeficit that lead to prompt and urgent investigations and treatment.

Common etiological causes of LBP

Degenerative joint disease 15%	Lumbar spondylosis 10%
	Spinal canal stenosis 3%
Post-traumatic 10%	Disk prolapse 4%
	Spondylolisthesis 2%
	Trauma to ligaments < 1%
	Muscle sprain 70%
	Vertebral fractures 1%
Acquired causes 2%	Inflammatory arthritis (spondyloarthropathy) 0.3%
	Infections: Bacterial, mycobacterial, fungal, human immunodeficiency virus (HIV) (abscess, diskitis) 0.01%
	Hemoglobinopathies (sickle cell disease) 0.01%

Malignancy 1%	Primary: For example, multiple myeloma, leukemia Metastasis: For example, Ca prostate, Ca breast, Ca ovaries
Mechanical 50%	Poor posture Pregnancy Occupational Overuse of back
Psychogenic causes 15%	Anxiety Depression Fibromyalgia Adjustment disorders at workplace or in house
Referred pain < 1%	Kidneys, Pancreas, Pelvic inflammatory diseases
Others 5%	Osteoporosis and osteoporotic fractures 4% Aortic aneurysm / dissection < 1%
Congenital < 1%	Vertebral fusion, Spina bifida

Low back pain can arise from nerve roots, facet joints, disks, vertebral bodies, ligaments or soft tissues. Hence, it can present as radiculopathy (root pains), sciatica, shooting or stabbing pains, muscle weakness (myelopathy), fasciculation, numbness, urinary and fecal incontinence or urinary retention and constipation.

Catastrophic vascular causes like ruptured aortic aneurysm can have poor peripheral pulses in lower limb, sudden drop in blood pressure, change in color and temperature of the lower limbs.

Morning stiffness for more than 30 minutes with difficulty in turning in bed and pain radiating to hips / gluteal region in seronegative spondyloarthropathy is seen.

Multiple vertebral body pain and tenderness on pressure may be seen in osteoporosis, osteomalacia, metastatic tumors to the vertebrae, multiple myeloma.

Low-grade fever with evening rises in spinal tuberculosis, psoas abscess and malignancy.

Continuous pain worsening with activity may be seen in mechanical backache.

Abdominal pain (epigastric and lumbar) radiating to the back is seen in pancreatitis, renal stones / abscess indicates referred pain. During pregnancy, there is a risk of LBP. As high as 72% of pregnant females can complain of LBP during the course of pregnancy.

Chronic backache may be seen in patients who are depressed, who have chronic medical disorders, adjustment problems at workplace or at home and inability to cope up with stress can present as LBP.

Clinical examination should always consist of straight leg raising test, ankle reflexes, dorsiflexion of the ankle and great toe, muscle power testing of the quadriceps, gluteal muscles and calf muscles. Sensations over the medial and lateral aspect of the foot should be tested.

Investigations

Each case of backache will have to be evaluated on case to case basis after a good history and a thorough clinical examination.

Blood investigations like hemoglobin (Hb), complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein and human leukocyte antigen B27 (HLA-B27) should be done in the evaluation of inflammatory LBP.

Calcium, phosphorus, alkaline phosphatase and vitamin D3 levels are estimated in the evaluation of metabolic bone disease.

Serum protein electrophoresis and urinary Bence Jones proteins should be done in the workup of multiple myeloma.

X-rays of Lumbar spine in lumbar spondylosis, vertebral fractures; X-ray pelvis with both hip joints, in ankylosing spondylitis, pelvic fractures and osteomalacia.

Computed tomography scan / magnetic resonance imaging (CT/MRI) are mandatory in LBP with neurodeficit.

As high as 30% patients show MRI abnormalities even though they may be clinically asymptomatic.

Bone scan may be warranted in the diagnosis of vertebral metastasis.

Dual-energy X-ray absorptiometry (DEXA) scan is necessary to diagnose and stage osteoporosis. Rarely a bone biopsy may be required for diagnosis of infections or malignancy.

Treatment

Most of the backaches may be self-limiting hence require good counseling and reassurance. Patient education is the most important aspect in treating backache.

When the cause is not very serious and when the pain starts resolving with analgesics or non-steroidal anti-inflammatory drugs (NSAIDs), unnecessary battery of investigations can be avoided by gaining the confidence of the patient. The algorithm for evaluation of LBP is given below.

Paracetamol or tramadol can be used as the preferred analgesics. NSAIDs can be used for a short duration of 4 - 6 weeks. Muscle relaxants like thiocolchicoside, tizanidine, chlorzoxazone can be helpful in relieving muscle spasms.

Inflammatory backache requires disease-modifying antirheumatic drug (DMARD) like salazopyrine, methotrexate and biologics like infliximab, etanercept or adalimumab, in addition to NSAIDs.

Calcium supplements and vitamin D3 work excellently in rachitic and osteomalacic patients. Bisphosphonates (oral alendronate, risedronate, ibandronate or intravenous zoledronate), nasal calcitonin and teriparatide are used to treat osteoporosis.

Antibiotics and antitubercular drugs are used for the treatment of bacterial and mycobacterial infection respectively.

Malignancy should be treated according to the oncologist's opinion. Certain metastasis may require radiotherapy or chemotherapy.

Surgical decompression may be required in certain cases of vertebral metastasis causing weakness or urinary and fecal incontinence / retention.

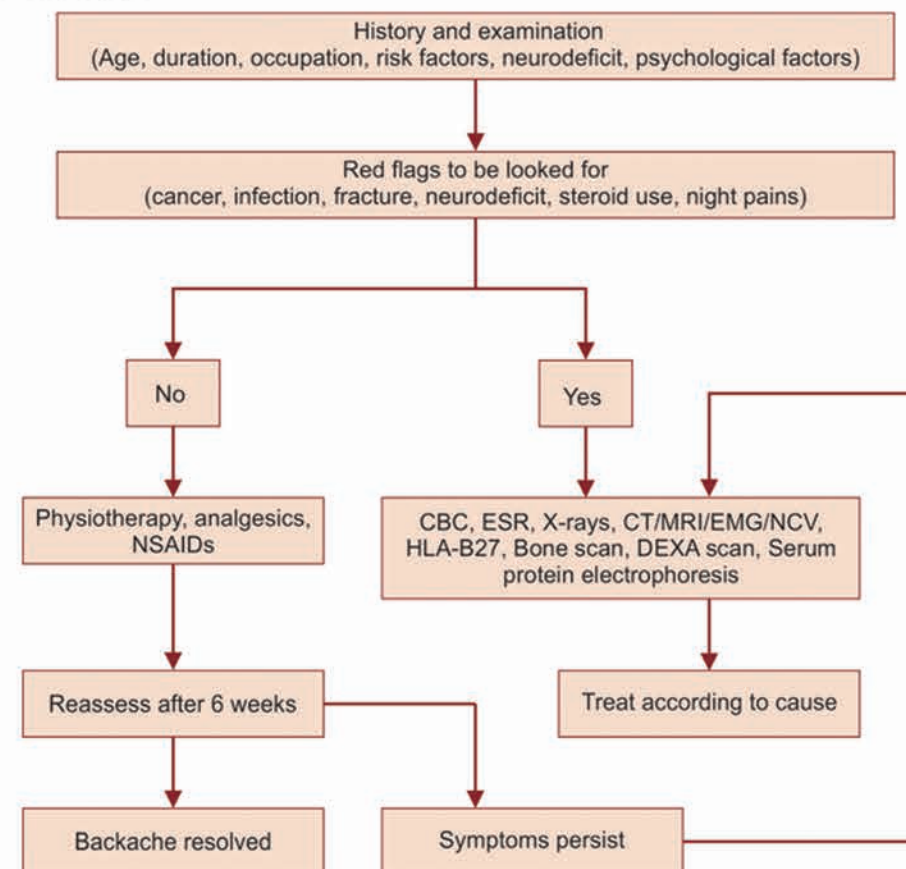
Patients of chronic LBP should be evaluated for underlying depression and treated with tricyclic antidepressants. Patients having stress and anxiety should be treated with anxiolytic agents, and stress management.

Physiotherapy should be initiated once the acute pain has settled. Supervised exercises under the guidance of trained personnel are recommended.

Facet block and epidural steroid injections are helpful in certain cases.

Surgical intervention consists of laminectomy, discectomy, vertebroplasty, spinal fusion depending on the primary condition in those who fail to show any benefit by conservative methods.

Surgery is indicated in caudaequina syndrome, malignancies, infections and certain fractures.

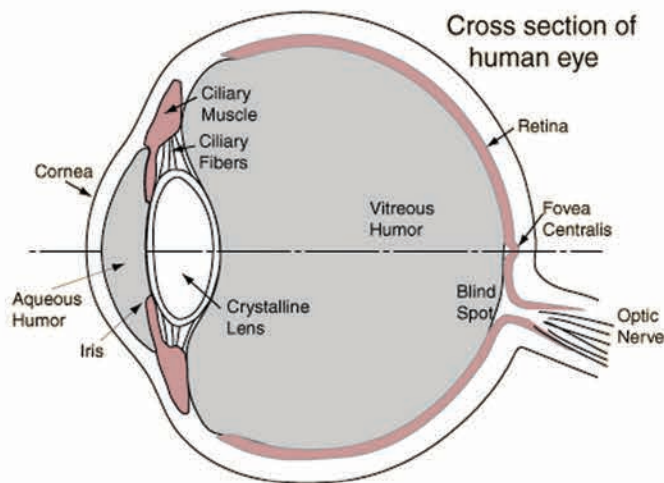


Overview

A cataract is a clouding of the lens in the eye which leads to decrease in vision. Cataracts often develop slowly and can affect one or both eyes. Cataracts cause half of all cases of 33% of visual impairment in worldwide.

Epidemiologic data from many Asian regions, including the Union of Myanmar remain scarce. The limited cataract survey data suggested that the prevalence of blindness in the adult population in rural regions of Myanmar may reach 90 per 1,000 persons. Among the 55 million population of Myanmar, 450,000 - 600,000 are estimated to have cataract-related blindness.

The burden of disability in terms of blind years represents a major social, emotional, and economic burden for the patients, the families, the communities, and the nation. Cataracts are a natural part of aging. Most people who develop them are old adults. Almost everyone who reaching their mid sixties has some form of a cataract. Untreated cataract can lead to blindness. Cataract is the preventable cause of blindness. All we need is timely referral and treatment.



Picture showing anatomy of crystalline len

Symptoms of cataract

Include faded colors, blurry vision, halos around light, trouble with bright lights, and trouble seeing at night. This may result in trouble driving, reading, or recognizing faces. Poor vision caused by cataracts may also result in an increased risk of falling and depression.

Sometimes intumescent cataract can present with lens induce glaucoma in which there is marked pain, sometimes associated with nausea and vomiting and reduced vision.

There will be cornea oedema, shallow anterior chamber, mature cataract, high intra ocular pressure. Which need urgent medical attention and removal of cataract is the definitive treatment.

Cataract maturity

- Immature cataract is one in which the lens is partially opaque.
- Mature cataract is one in which the lens is completely opaque
- Hyperature cataract has a shrunken and wrinkled anterior capsule (due to leakage of water out of the lens).
- Morgagnian cataract is a hyperature cataract in which liquefaction of the cortex has allowed the nucleus to sink inferiorly.

Ophthalmic preoperative assessment

- Visual acuity - is usually tested using a Snellen chart.
- Pupillary response - because cataract never produce and afferent pupillary defect, its presence implies substantial additional pathology.
- Ocular adnexa - should be examined to detect any infection in the adnexa to prevent enophthalmitis.
- Anterior segment - to examine any associated anomalies .
- Fundus pathology - pathology such as age related macular degeneration may affect the visual outcome.

Indications for surgery

- Visual improvement is by far the most common indication for cataract surgery. Operation is indicated when the opacity develops to a degree sufficient to cause difficulty in performing essential daily activities. Clear lens exchange (replacement of the healthy lens with an artificial implant) is an option for the management of refractive error.
- Medical indications are those in which a cataract is adversely affecting the health of the eye, for example phacolytic or phacomorphic glaucoma; clear lens exchange usually definitively addresses primary angle closure, but less invasive options are generally preferred. Cataract surgery to improve the clarity of the ocular media may also be required in the context of monitoring or treatment of fundus pathology.

How to treat cataract

Cataracts are removed by mean of

- Extracapsular Cataract extraction with IOL (intra ocular len) implantation.
- Phacoemulsification with IOL implantation in which ultrasonic power is used to emulsify cataract.
- Or Intracapsular technique for subluxated or dislocated lens with iris or scleral fixated IOL.

When posterior chamber IOLs began to be widely used in the 1980s most surgeons adopted extracapsular cataract extraction (ECCE), abandoning the older intracapsular technique (ICCE). In ICCE, a cryoprobe is used to remove the lens complete with its capsule.

Many types of IOL are also available nowadays like rigid PMMA lens or foldable acrylic or silicone. If both eyes have cataract, the eye surgeon will treat one eye first, and then the second eye.

Result of cataract surgeries are good with most patients attain visual acuity 6/12 or more within 3 months follow up.

Take home message are

- Cataract is one of the major causes of blindness in Myanmar.
- It is a treatable and preventable cause of blindness.
- Surgery is simple and cost effective.
- Many centers are available for rural and urban areas.
- Results of surgeries are great.
- All we need is timely referral and treatment.

Glaucoma

Myanmar Ophthalmic Society

Glaucoma is a worldwide leading cause of irreversible vision loss. It may be asymptomatic until a relatively late stage, diagnosis is frequently delayed. A general understanding of the disease pathophysiology, diagnosis, and treatment may assist primary care physicians in referring high-risk patients.

What is Glaucoma?

Glaucoma is a group of progressive optic neuropathies characterized by degeneration of retinal ganglion cells and resulting changes in the optic nerve head that is associated with visual field loss and in which IOP is a key modifiable factor.

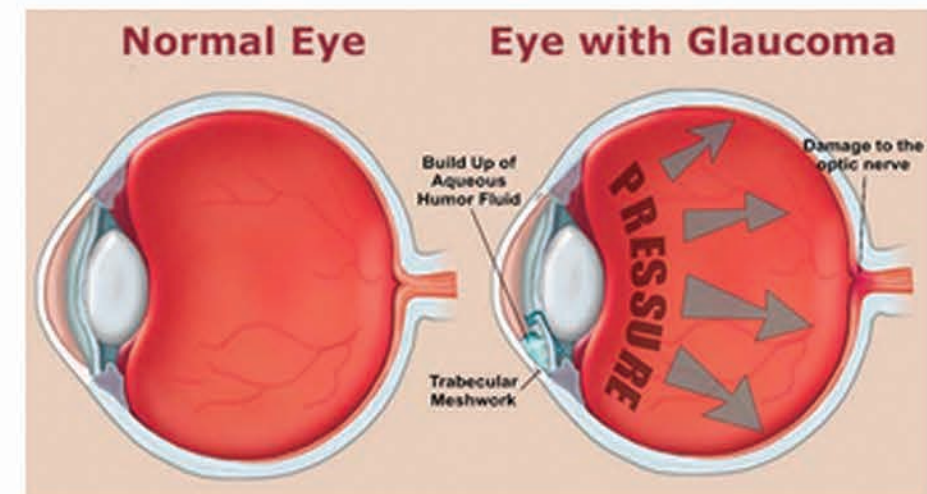


Figure. 1 shows normal eye and increase pressure inside the eye compressing the optic nerve head and damage nerve fiber layer

What causes Glaucoma?

The exact cause is unknown although the most important risk factor is an increase intraocular pressure. Direct mechanical theory and ischemic theory play an important role in the development of glaucoma.

It is important to remember that while it is more common as we age, glaucoma may occur at any age. People who are at high risk with

- | | |
|--------------------------------|------------------------------------|
| • High eye pressure | • Short sightedness |
| • A family history of glaucoma | • A previous history of eye injury |
| • Age over 50 | • Prolonged use of corticosteroid |
| • African or Asian ethnicity | • Thinner cornea |
| • Diabetes | • Migraine |

Types of Glaucoma

1. Open angle Glaucoma (Primary and Secondary)
2. Angle closure Glaucoma (Primary and Secondary)

(1) Primary Open Angle Glaucoma is a common bilateral disease of adult onset.

It is characterized by

- IOP > 21 mmHg at some stage
- Glaucomatous optic nerve damage
- An open anterior chamber angle
- Characteristic visual field loss
- Absent of signs of secondary glaucoma or non-glaucomatous cause of optic neuropathy

Pathophysiology is increased resistance to aqueous outflow through the trabecular meshwork and uveoscleral outflow pathway. The average IOP in general population is a range of 11 - 21 mmHg.

(2) Low-Tension or Normal Tension Glaucoma - A variant of POAG in which optic nerve damage can occur even though have normal or low eye pressure.

(3) Ocular Hypertension occur in 4 - 10% of the population over 40 years have IOP > 21 mmHg without detectable glaucomatous damage or causes of secondary glaucoma.

(4) Primary Angle Closure Glaucoma is also a common form of glaucoma particularly in Chinese and South-East Asians. Angle closure is primary when it occurs in an anatomically predisposed eye (hypermetrope) or secondary to another ocular or systemic factor. The mechanisms can be categorized into pupil block and non-pupil block (plateau iris).

(5) Acute Angle Closure is an ophthalmic emergency when the IOP rapidly increase due to iris blocking. An attack of acute angle closure is often severe and present to the general practitioners or physicians with chief complaint of severe headache, nausea and vomiting. If treatment is in time, the vision can be saved.

Typical signs of acute angle closure are 6/60 or hand movement in vision. The IOP is usually very high about 50 - 100 mmHg. Conjunctiva hyperemia with circumcorneal injection, cornea epithelium edema, shallow anterior chamber and flare are usually present. An unreactive mid-dilated vertically oval pupil is classic sign.

(6) Congenital Glaucoma is a rare form of glaucoma caused by an abnormal drainage system. It can be divided into three categories - true congenital glaucoma, infantile glaucoma, juvenile glaucoma. Presentation usually occurs when an abnormality such as cornea hazy, large eye (bupthalmos) or asymmetrical eyes, watering, photophobia or blepharospasm is noticed by parents or a health care professional.

(7) Secondary Glaucoma can develop as a result of other disorders of the eyes such as injuries, previous eye operation and inflammation, the prolong use of corticosteroid.

How is Glaucoma detected?

Comprehensive eye examination is the best way to detect glaucoma.

- Checking the optic nerve with an ophthalmoscope (increase cup disc ratio)
- Eye pressure check by tonometer (Goldman applanation tonometer is gold standard)
- Visual field assessment includes the sensitivity of the peripheral visual field, where glaucoma strike first
- Imaging analysis (ganglion cell and nerve fiber layer analysis by OCT)

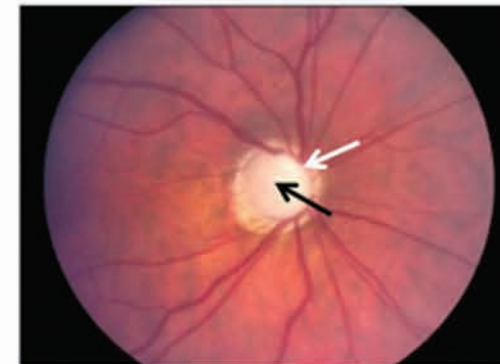


Figure. 2 shows enlarge optic disc cupping and notching

Can Glaucoma be treated?

Although there is no cure for glaucoma, it can usually be controlled and further loss of vision either prevented or slowed. Lowering the eye pressure to a level that is likely to cause no further optic nerve damage. This level is referred to as the target pressure and is likely a range rather than a single number.

Medications

This is the most common form of treatment and usually first line treatment. Most glaucoma medications are topically but significant systemic absorption can still occur.

- **Prostaglandin derivatives** - Their IOP lowering is typically greater than other alternatives and now typically prefer to a beta-blocker for first line treatment of glaucoma due to the latter's potential for systemic side effect. (Latanoprost, travoprost, bimatoprost and tafluprost)
- **Beta-blockers** - Timolol, Betaxolol, Levobunolol, Carteolol and Metipronolol reduce IOP by decreasing aqueous production. Their IOP lowering effect is 30% although side effects include heart block, bradycardia, worsening of heart failure and hypotension.
- **Alpha-2 agonist**, topical and systemic carbonic anhydrase inhibitor and miotics can also be used as second line.

Laser treatment

Therapeutic or prophylactic laser peripheral iridectomy is indicated in acute angle closure attack, primary angle closure and pupil block glaucoma. Laser beam creates a small hole in the iris to allow fluid to flow more freely into the anterior chamber of the eye.

Conventional surgery

If eye drops and laser surgery aren't controlling eye pressure, you may need a trabeculectomy. This filtering surgery creates a drainage flap. Fluid can then percolate into the flap and later drain into the vascular system.

Drainage implants

Drainage valve implant surgery may be an option for adults with uncontrolled glaucoma or secondary glaucoma or for children with glaucoma. A small silicone tube is inserted in the eye to help drain fluid.

Conclusion

Primary care physicians can play an important role in the diagnosis of glaucoma by referring patients with positive family history or with suspicious optic nerve head findings for complete ophthalmologic examination.

In Conclusion, although there is no cure for glaucoma, patients with glaucoma need to continue treatment for the rest of their lives. The disease can progress or change without warning, compliance with eye medications and undergoing eye examinations are essential. Early detection, prompt treatment and regular monitoring can help to control glaucoma and reduce the chances for visual morbidity.

Depressive Disorder

Mental Health Society

Depression is a common mental disorder. Globally, an estimated 350 million people of all ages suffer from depression. Depression is the leading cause of disability worldwide, and is a major contributor to the overall global burden of disease. More women are affected by depression than men. At its worst, depression can lead to suicide. There are effective treatments for depression.

Major Depressive Disorder → One or more period of depression (that meet the DSM 5 criteria of Depressive episode) without a history of either manic or hypomanic episodes.

Epidemiology

Annual Incidence	-	Male	0.8 - 2/1000
		Female	2.5 - 4.8/1000
Point Prevalence	-	Male	18 - 32/1000
		Female	20-93/1000
Life Time Expectancy	-		60 / 1000
Sex		Female: Male	2: 1
Age Group		(1) Any age group.	
		(2) Commonest age group is 40 +	

Clinical Features

Core Symptoms

- 1. Depressed mood:** Present most of the day, nearly every day, with little variation, and often lack of responsiveness to changes in circumstances. There may be diurnal variation in mood with mood being worse in the morning and improving as the day goes on.
- 2. Anhedonia / Lack of interest / Lack of pleasure:** Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
- 3. Weight change:** Loss of weight when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), associated with decreased or increased appetite.
- 4. Disturbed sleep:** insomnia (with early morning waking 2 - 3 hr sooner than usual) or hypersomnia. Psychomotor agitation or retardation: observable by others, not just subjective feelings of restlessness or being slowed down.
- 5. Fatigue or loss of energy**
- 6. Reduced libido**
- 7. Feelings** of worthlessness or excessive or inappropriate guilt (which may be delusional): not just self-reproach or guilt about being ill.

8. Diminished ability to think or concentrate or indecisiveness.

9. Recurrent thoughts of death or suicide (not 'fear of dying'), which may or may not have been acted upon.

Exclusion of substance induced depressive symptoms and depressive disorder due to direct effect of a general medicine condition.

Somatic symptoms

Also called biological or melancholic or vital symptoms. They are:

- Loss of emotional reactivity
- Diurnal mood variation
- Anhedonia
- Early morning waking
- Psychomotor agitation or retardation
- Loss of appetite and weight
- Loss of libido

Anxiety Symptoms

Anxiety symptoms are commonly seen in Major depressive disorder patients. Sometime doctor are difficult to decide that the patient is suffering from depressive disorder or anxiety disorder. Anxiety symptoms are

- Worry, fear and nervous tension
- Palpitation, breathlessness
- Headaches and other tension Pains
- Restlessness / agitation
- Panic attacks
- Obsession and hypochondriasis

Cognitive Symptoms

In patient with major depressive disorder, most of patients thinking are negative thinking and called depressive thinking or depressive cognition. They are

- Lack of concentration
- Lack of interest and initiation
- Lack of confidence
- Low self-esteem
- Pessimism for past, present and future
- Hopelessness and helplessness
- Idea of guilt and deserve punishment
- Thoughts of death
- Given-up concept
- Suicida ideas

Psychotic symptoms / features

Psychotic symptoms are not seen in all major Depressive disorders patients. It can be seen in some of severe major depressive disorder patients and some of untreated patients. They are

- *Delusions related to thinking about* poverty, personal inadequacy, guilt over presumed misdeeds, responsibility for world events - accidents, natural disasters, war, deserving of punishment and other nihilistic delusions.
- *Hallucinations seen in Major depressive disorder with psychotic patients are auditory* - defamatory or accusatory voices, cries for help or screaming or *olfactory* - bad smells, such as rotting food, faeces, decomposing flesh or *visual* - tormentors, demons, the Devil, dead bodies, scenes of death or torture.

Diagnosis of Major depressive disorder

Major depressive disorder can be diagnosed clinically according to following chart or according to DSM 5 criteria.

Major Depressive Disorder - Diagnostic Criteria (DSM 5)

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.



- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Differential Diagnosis

- (1) **Physical disorder which can cause depressive symptoms** (if organic cause is suspected by history, examination and investigations)

1. Pharmacological causes

Corticosteroids, Contraceptives, Reserpine, Methyldopa, Anti choline esterase, Insecticides, Amphetamine withdrawal, Cimetidine, indomethacin, Phenothiazines, Thallium, Mercury, Cycloserine, Vincristine, Vinblastine

2. Infections

General Paresis (Tertiarysyphilis), Influenza, AIDS, Viral pneumonia, Infectious mononucleosis, Tuberculosis.

3. Endocrine

Hypo and hyperthyroidism, Hyperparathyroidism, Menstrual cycle related, Post-partum, Cushing's disease, (Hyper adrenalism), Addison's disease (Adrenal insufficiency)

4. Collagen

SLE, Rheumatoid arthritis.

5. Neurologic

Multiple sclerosis, Parkinson's disease, Head trauma, Complex partial seizures (Temporal lobe epilepsy), Cerebral tumor, Strokes, dementing diseases in their early stages.

6. Nutritional deficiencies

Vitamin deficiencies (B_{12} , B_6 , Borate, Niacine, Thamine)

7. Neoplastic

Cancer of the head of the pancreas, disseminated carcinomatosis, Bronchogenic carcinoma etc.

- (2) **Dementia.** If cognitive function is impaired, especially in the elderly.

- (3) **Schizophrenia.** If a schizophrenic patient with negative symptoms or if a schizophrenic patient presents with prominent behavioural symptoms like stupor, retardation and agitation.

- (4) **Bereavement.** If symptoms follow the loss of a loved one.

- (5) **Bipolar disorder.** If history of manic episode is present.

- (6) **Neurotic disorder.** If neurotic symptoms are prominent.

- (7) **Alcohol and drug use.** If history of use is present.



Diagnosis of Depression (Flow chart Assessment Guide)

Common symptoms

low mood, sad, blue, loss of interest, guilt or low self worth, disturb sleep, disturb appetite, Agitation or retardation, fatigue, pain, helpless and hopeless



Medical condition

(organic illness, neoplasm, arthritis, endocrine disorder, chronic infectious disease, chronic medical condition e.g., heart problem, diabetes)



Use of medication (beta blocker, antihypertensive, contraceptives, corticosteroid)



Tense /worry/ anxious



Anxiety disorder



Alcohol use disorder



Alcohol use disorder



Life event / loss



Adjustment disorder



If still depressed, treat with antidepressant (adequate dose and period)

Complications

1. **Suicide** may be the first and the last presentation of depressive disorder.
2. **Extended Suicide** in which the patient killed the person / person whom he loved and then kills himself / herself.
3. Substance use disorder.
4. Impaired occupational and social functioning during the episodes of the illness.
5. Increase mortality from physical disease especially carcinoma.

**Management**

The aetiology of Major Depressive Disorder is related biological, psychological and social factors. That's why bio-psycho-social approach in treatment is important.

(1) Educate the Patient and Family

1. Depression is a very common condition that can happen to anybody.
2. 80% of cases can have complete remission.
3. The occurrence of depression does not mean that the person is weak or lazy.
4. Adequate maintenance treatment is necessary to prevent relapse.
5. The use of alcohol and drug is not the solution for depression.
6. Negative attitudes of others (e.g. "You should be stronger", "Pull yourself together") may be because depression is not a visible condition, unlike a fracture or a wound. There is also the misconception that people with depression can easily control their symptoms by sheer will power.
7. People with depression tend to have unrealistically negative opinions about themselves, their life and their future. Their current situation may be very difficult, but depression can cause unjustified thoughts of hopelessness and worthlessness. These views are likely to improve once the depression improves.
8. Thoughts of self-harm or suicide are common. If they notice these thoughts, they should not act on them, but should tell a trusted person and come back for help immediately.

(2) Reduce stress and strengthen social support

1. Assess for and try to reduce stressors.
2. Reactivate the person's previous social network. Identify prior social activities that, if started again, may potentially provide direct or indirect psychosocial support, e.g. family gatherings, visiting neighbours, and community activities.

(3) Counselling

1. Ask about "risk of suicide".
If present, close supervision is necessary by family and friends.
2. Plan short-term activities which give enjoyment or build confidence.
3. Resist pessimisms and self criticism. Do not act on pessimistic ideas. (ending marriage, leaving job). Do not concentrate on negative or guilty thought.
4. Discuss the link between physical symptoms and depression if physical symptoms are present.
5. After improvement, discuss signs of relapse, and plan with patient, for actions to be taken if signs of relapse occur.

(4) Promote functioning in daily activities and community life

Even if it is difficult, encourage the person to try to do as many of the following as possible:

- Try to start again (or continue) activities that were previously pleasurable.
 - Try to maintain regular sleeping and waking times.
 - Try to be as physically active as possible.
 - Try to eat regularly despite changes in appetite.
 - Try to spend time with trusted friends and family.
 - Try to participate in community and other social activities as much as possible.
- Explain to the person and carer that these activities can all help improve mood.

(5) Medication**Antidepressant Medication**

1. Consider antidepressants drugs in Moderate to severe Depression.

2. Choice of Antidepressant

All antidepressants are not different in antidepressants properties, but different in their side effects. Choice of antidepressants is depend on their **side effects, age of patients, comorbidity of physical diseases, cost of the drugs and availability.**

Usually first line antidepressant is SSRI.

Can give SSRI - Escitalopram 10 mg, Sertraline 50 mg, Fluoxetine 20 mg

Alternative Antidepressant is Tricyclic Antidepressant (TCA). Can Start with low dose (Amitriptyline 25 - 50 mg hs) and gradual increasing (Amitriptyline 100 - 150 mg hs) within 10 days. Lower does if physically ill.

Durations of antidepressant treatment

- first episode -- at least 6 to 9 months
- further episode -- depend on individual case

3. Explanation of drug administration

- a. Medication must be taken every day.
- b. For elderly patient, divided dose is suitable. Otherwise one single night dose is Preferable
- c. improvement will occur over 2 - 3 weeks.
- d. patient need to tolerate mild side effects, which usually fade in 7-20 days.
- e. Antidepressants are not addictive.

Antipsychotic Medication

Considered: -

- a. If Patient is severely agitated.
- b. If Patient is psychotic (having delusions and hallucinations.)

After improvement

- a. Maintain the same dosage of antidepressant for 4 to 6 weeks. (TCA)
- b. Then reduce to half of the previous dosage (maintenance dose) for another 6 to 9 months.

(TCA)

or

The same dose of SSRI for 9 to 12 months





(6) Regular Checkup

- a. Cases should be seen on every 3rd day in the 1st two weeks.
(Period of gradual increasing dosage.)
- b. Seen weekly in the next one month.
- c. Seen fortnightly in the next one month.
- d. Seen monthly for two months.

(7) Referral for Special is Consultation

- a. If suicide risk is severe.
- b. If significant depression persists with above treatment measures.

(8) Course and Prognosis

15% of depressive patients eventually commit suicide.

Untreated episodes last about 10 months. (average)

At least 75% of patients have 2nd episode of depression within 9 years.

(9) Prognosis

Generally good.

20% Chronic Course (un-recovered)

50% completely recovered.

30% partially recovered.

It depends on giving effective treatment.

Depression with psychotic features

Combined treatment with an antidepressant and antipsychotic is often the recommended first line.

1. **TCA**s are probably the drugs of first choice in psychotic depression.
2. **SSRIs/SNRIs** are a second-line alternative when TCAs are poorly tolerated.
3. Augmentation of an antidepressant with **olanzapine** or **quetiapine** is recommended.
4. The optimum dose and duration of antipsychotic augmentation are unknown. If one treatment is to be stopped during the maintenance phase, this should usually be the antipsychotic.

Depressive Episode of Bipolar Disorder

1. The combination of **olanzapine + fluoxetine** (Olan/Fluo - 5 mg/20 mg and 10 mg/40 mg) is probably the most effective treatment available for bipolar depression.
2. **Other SSRIs** may be effective but should be avoided unless clear individual benefit is obvious.
3. Other first-line choices are **quetiapine, olanzapine and valproate**. These drugs differ substantially in adverse effect profile, tolerability and cost, each of which needs to be considered when prescribing for an individual.
4. **Lamotrigine** is also effective.