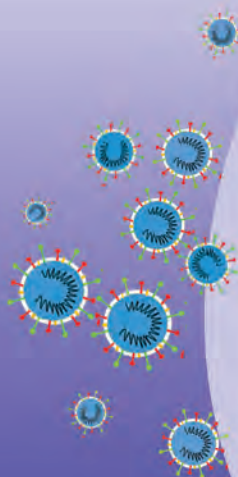




MYANMAR MEDICAL ASSOCIATION

# MMA CME Book 2021





# **MMA CME Book 2021**

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# Foreword

The 67<sup>th</sup> Myanmar Medical Conference is different from previous conferences because we are going 100% online. The Covid-19 pandemic is presenting us with many challenges and we are taking this as an opportunity to adapt to the new normal. This is the third CME book published to supplement the CME activities that we have been carrying out for our members including our yearly Myanmar Medical Conference. Mostly these activities will be in the form of conferences, lectures, seminars and panel discussions. Providing CME in the (digital) print form is aimed at those who wish to read some material later on and to be kept for reference. Topics are chosen and written in a way that will be easy to understand but also contain updated information.

MMA would like to thank all the speciality societies who provided the articles.

It is the humble wish of those who made this book possible that the information included in this book might help a patient suffer less, heal faster and even save a life.



Professor Htin Aung Saw  
President  
Myanmar Medical Association  
January 2021

## Editorial Board

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## Interpretation of Laboratory Results for COVID-19 Diagnosis

Microbiology Society

Etiological confirmation of COVID-19 virus (SARS-CoV-2) infection can only be made by laboratory tests. In general, the currently available assays for COVID-19 can be classified into two groups: The first group (virological tests) includes tests that can detect the presence of the components of the virus (genetic material or antigens). These tests can confirm the diagnosis of patients with symptoms compatible with COVID-19, detect infections in populations with high-risk of infection (such as health workers) or severity (hypertension, diabetes, obesity, cardiovascular history, chronic respiratory, immuno-suppression, cancer, etc.), and assess whether an individual recovered from COVID-19 may still be infectious. The second group of tests (serological) detects antibodies (IgM or IgG) generated as part of the individual's immune response against the SARS-CoV-2 virus, that is, they indicate previous or ongoing contact. The immunity (protection) conferred by the antibodies is still under investigation. Once sufficient evidence is available, serological tests would be, together with direct virus detection, an essential tool in the development of strategies that allow relaxation of current public health measures.

The appropriate interpretation of the results obtained in any type of assay must be carried out carefully and considering the dynamics of the infection (when is the sample collected and the quality of this sample) and the objective for which a sample is taken (diagnosis, seroprevalence, etc.).

### 1. Interpretation of results in COVID-19 symptomatic cases

#### Molecular detection:

The diagnostic confirmation of COVID-19 is based on the molecular detection of the viral genome (RNA detection by PCR) or of its proteins (antigens). Although the dynamics of the infection including viral secretion in different fluids is still under study, to date it has been possible to establish that the virus can be detected from at least 48 hours before the onset of symptoms (pre-symptomatic cases) and up to 12-14 days (at least 6-7 days) after, in samples from the upper respiratory tract (nasal / oropharyngeal swabs) and up to 20 days (or more) in samples from the lower respiratory tract including sputum, tracheal aspirate, bronchioalveolar lavage, etc. (Figure 1).

#### Serological detection:

Since antibodies (Ig M / Ig G) against the virus are detectable around day 7 from the onset of symptoms (in approximately 50% of cases), a negative serology result during the first 7 days of illness cannot be used as a rule out criterion. Although the sensitivity of antibody detection increases after day 7, a negative serology result after day 7 should be carefully interpreted before ruling out a case (Figure 2). On the other hand, a positive result



between days 7 to 14 indicates a previous contact and does not rule out the presence of the virus. For this reason, serology alone should not be used as a criterion to rule out a case or to consider the patient as non-infectious. Likewise, a patient who has had previous contact with the virus but who later becomes infected with another circulating pathogen that generates respiratory symptoms (influenza or another pathogen), may present to a clinical consult and a positive result for COVID-19 antibodies would lead to a wrong diagnosis; for this reason, the use of serology (by itself) to confirm a case must be carefully evaluated.

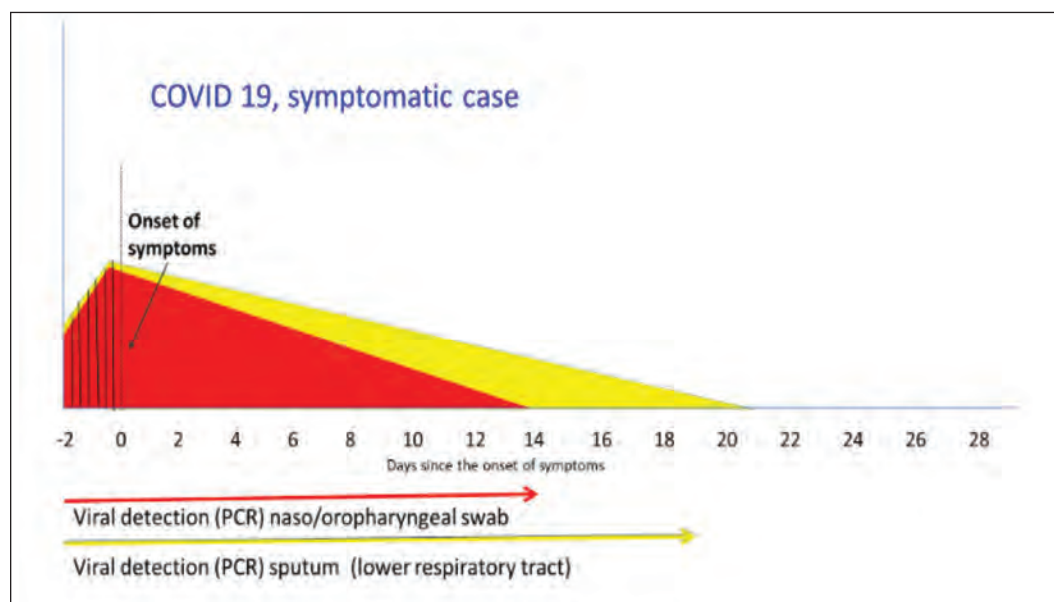


Figure. 1

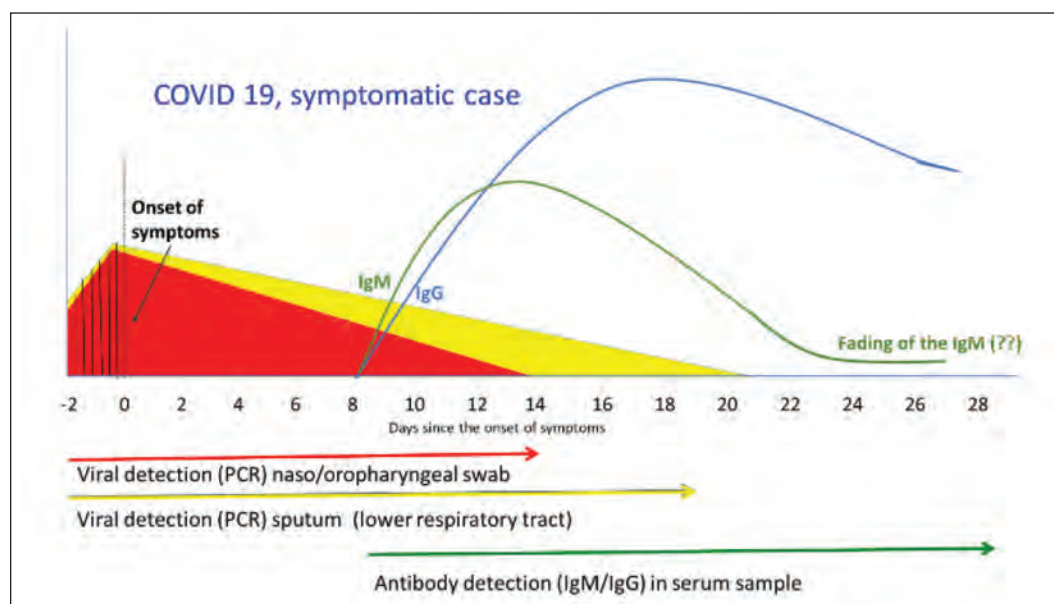


Figure. 2



## 2. Interpretation of results in contacts of COVID-19 symptomatic cases

In an individual identified as a contact of a confirmed case, the added value of conducting laboratory testing should be evaluated, keeping in mind that regardless of the result, the recommendation for the contact is at least 14 days of quarantine (from the day of last contact with the case). If a molecular assay (PCR) is performed, a negative result does not rule out previous contact, nor the possibility that the contact is in the incubation period. Regardless of the test result, the contact would have to be quarantined. Likewise, if a positive result is obtained by molecular diagnosis (PCR), the case is an asymptomatic or pre-symptomatic case, and must be isolated regardless. On the other hand, a positive antibody result only indicates previous contact with the virus but does not rule out nor it confirms an active infection; that is, it does not allow to rule out or confirm the presence of the virus (Figure 3).

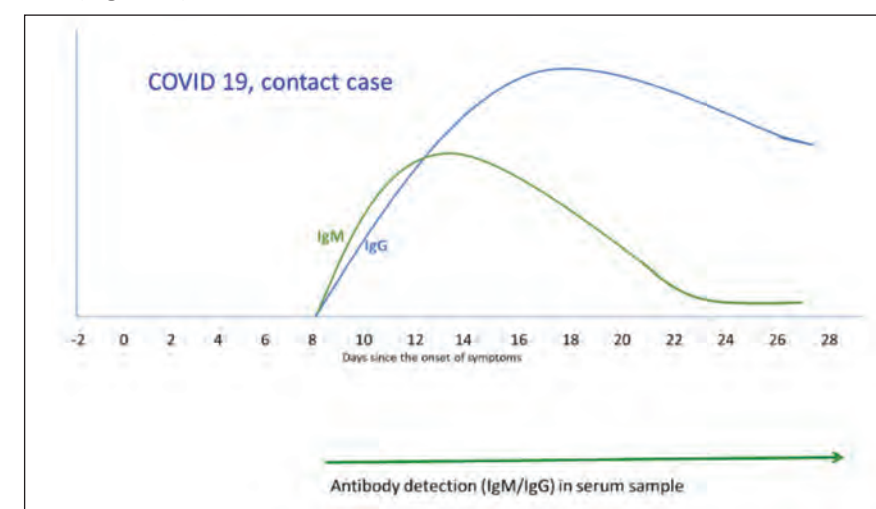


Figure. 3

## 3. Interpretation of results in asymptomatic individuals

In an asymptomatic individual, since there is no date that can be used as a reference, a negative molecular assay (PCR) result can occur because the amount of virus is not sufficient to be detected, because the individual is in the post-infection period, or simply because the individual has never been infected. Thus, a negative result does not rule out a possible infection (Figure 4). If as part of an active surveillance (health workers, caregivers in nursing homes, etc.) a positive result is obtained by molecular detection, the result constitutes an asymptomatic case and the individual should be isolated.

An asymptomatic individual may have a small amount of virus and antibodies will most likely be generated from contact with the virus. For this reason, although a positive serological test in healthy individuals indicates previous contact, it does not allow inferring the moment of contact. Some individuals develop Ig M antibodies very late after contact



and it is not yet clear for how long these antibodies can be detected. Likewise, Ig G levels may increase at the same time as Ig M levels, so detection of both antibodies at the same time or detection of only one of them (Ig M or Ig G) is not an adequate criterion to define the time of possible contact. Furthermore, there is insufficient evidence to ensure that the detected antibodies are actually protective or for how long they could be. The use of serology in these cases will be for research purposes or to determine seroprevalence in a given population, but they should not be used as the sole diagnostic criterion.

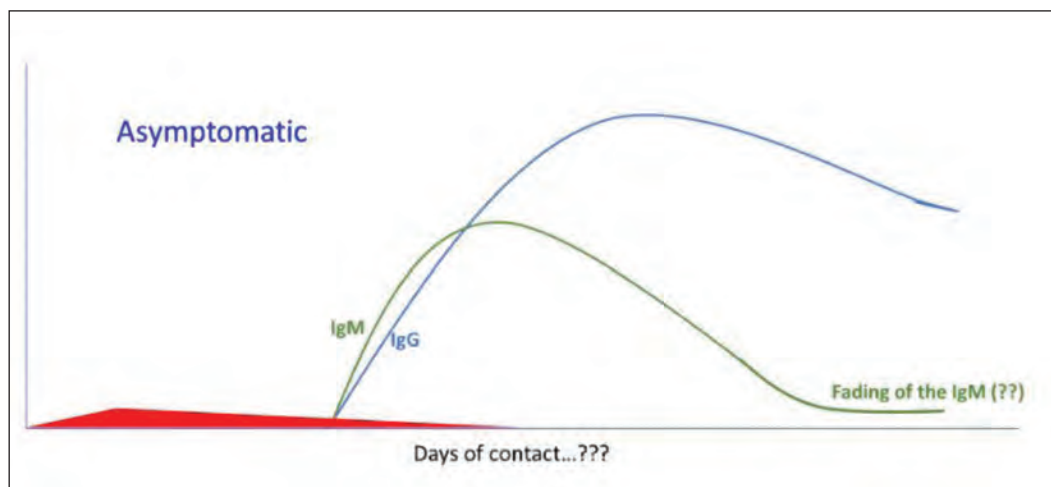


Figure. 4

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## Central Nervous System (CNS) infections

Myanmar Neurological Society

### Bacterial infections

- Meningitis
- Tuberculosis
- Suppurative encephalitis
- Neurosyphilis
- Brain abscess
- Paravertebral (epidural abscess)

### Viral infections

- Meningitis
- Encephalitis
- Myelitis
- Progressive multifocal leucoencephalopathy
- Poliomyelitis
- Subacute sclerosing pan encephalitis (late sequel)
- Rabies
- HIV infection

### Prion diseases

- Creutzfeldt-Jakob disease (CJD)
- Kuru

### Protozoal infections

- Malaria
- Toxoplasmosis (in immune-suppressed)
- Trypanosomiasis
- Amoebic abscess

### Helminthic infections

- Schistosomiasis
- Gnathostomiasis
- Cysticercosis
- Hydatid disease
- Strongyloidiasis

### Fungal infections

- *Candida* meningitis or brain abscess
- Cryptococcal meningitis



Here, common CNS infections will be discussed as follows:

### (1) Bacterial meningitis

**Aetiology:** *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Listeria monocytogenes* (if age > 50 years and those with brainstem signs, immune suppression, diabetes, alcoholism).

**Diagnosis:** Acute onset of fever, headache, neck stiffness with/without altered conscious level, focal neurological deficits and CSF findings suggestive of bacterial meningitis (Table 1).

**Investigations:** Blood culture, full blood count (FBC), C-reactive protein (CRP), urea, creatinine, electrolytes, liver function tests and clotting screen, Meningococcal and Pneumococcal PCR, serology, Cerebrospinal fluid (CSF) for RE (routine examination), polymerase chain reaction (PCR), gram stain or antigen testing, culture, Imaging (Chest X-ray (CXR), contrast enhanced CT head scan).

**LP should be delayed if any of the following features are present**

- Signs of severe sepsis or rapidly evolving rash
- Respiratory or cardiac compromise
- Anticoagulant therapy / known thrombocytopenia
- Infection at the site of LP
- Focal neurological signs
- Presence of papilloedema
- Continuous or uncontrolled seizures

**Indications of CT (head) before LP**

- Focal neurological signs
- Presence of papilloedema
- Continuous or uncontrolled seizures
- GCS  $\leq$  12

**First line therapy:** IV Ceftriaxone 2 g 12 hourly or IV Cefotaxime 2 g 6 hourly for 14 days.

If *Listeria meningitis* is suspected, add IV Ampicillin/Amoxicillin 2 g 4 hourly for 21 days.

**Second line therapy:** IV Meropenem 2 g 8 hourly for 14 days.

**In severe beta-lactam allergy:** IV Vancomycin 15-20 mg/kg 8-12 hr and IV Moxifloxacin 400 mg OD.

**Role of steroids:** If pneumococcal meningitis is confirmed, or thought probable based on clinical, epidemiological and CSF parameters, IV dexamethasone 10 mg 6 hourly should be started either shortly before or simultaneously with antibiotics or until 12 hr after the first dose of antibiotics and continued for 4 days. If another cause of meningitis is confirmed, or thought probable, dexamethasone should be stopped.



### (2) Brain abscess

**Aetiology:** Aerobic, anaerobic and microaerophilic streptococci, Anaerobic Gram-negative bacilli (i.e. *Prevotella* spp., *Bacteroides* spp.), *Staphylococcus aureus*, Enterobacteriaceae, *Pseudomonas aeruginosa*, *Actinomyces*, *Nocardia*; In immunocompromised state - aerobic Gram-negative bacilli, *Toxoplasma gondii*, *Nocardia* spp., *Mycobacterium* spp., *Listeria monocytogenes*, *Cryptococcus neoformans*, *Aspergillus* spp., *Coccidioides immitis*, *Candida* spp., Mucorales.

**Diagnosis:** Fever, headache, drowsiness, seizures, raised ICP, focal neurological signs, in alone or combination with CT/MRI features suggestive of brain abscess.

**Investigations:** Blood culture, FBC, CRP, urea, creatinine, CXR, contrast enhanced CT or MRI scan.

**Empirical first line therapy:** IV Ceftriaxone 2 g 12 hourly or IV Cefotaxime 2 g 6 hourly and IV metronidazole 1 g followed by 500 mg 8 hourly.

**Brain abscess arising from oral, otogenic or sinus source:** IV Ceftriaxone 2 g 12 hourly or IV Cefotaxime 2 g 6 hourly and IV metronidazole 1 g followed by 500 mg 8 hourly.

**Brain abscess following penetrating trauma or haematogenous source (bacteraemia, endocarditis with multiple abscesses in middle cerebral artery distribution, post-neurosurgery or congenital heart disease):** IV Vancomycin 15-20 mg/kg 8-12 hourly and IV Ceftriaxone 2 g 12 hourly or IV Cefotaxime 2 g 6 hourly.

**Brain abscess of unknown source:** IV Vancomycin 15-20 mg/kg 8-12 hourly and IV Ceftriaxone 2 g 12 hourly or IV Cefotaxime 2 g 6 hourly and IV metronidazole 1 g followed by 500 mg 8 hourly for 4-8 weeks.

**Second line therapy:** IV Meropenem 2 g 8 hr for 4-8 weeks.

If a microorganism is identified, therapy can be adjusted accordingly.

**Duration of antibiotics:** Patients with cerebritis can be treated with a shorter course (4-6 weeks). However, those with an encapsulated abscess, tissue necrosis, undrained abscess(s), multi-loculated abscess(s), lesions in vital locations, and the immunocompromised, need 6-8 weeks or longer, depending on initial size, causative pathogen(s), and treatment response. The initial course is intravenously, often followed by a 2-6 months of oral therapy. A shorter course (3-4 weeks) may be adequate in patients who had surgical drainage.

Emergency intervention (aspiration or excision) should be performed for a single abscess > 2.5 cm. In cases of multiple abscesses or in abscesses in essential areas, repeated aspirations are preferred.

Corticosteroids, mannitol and hyperventilation may be indicated where there is increased intracranial pressure. Routine use of corticosteroids in the absence of increased intracranial pressure is not recommended.

**(3) Tuberculous meningitis (TBM)**

**Aetiology:** Mycobacterium tuberculosis

**Diagnosis:** Insidious onset of fever, appetite loss, weight loss, irritability/lethargy, neck stiffness, headache, vomiting, seizures, confusion/coma, cranial nerve palsies, hemiparesis, evidence of tuberculous infection elsewhere and CSF findings suggestive of TBM (Table 1).

Feature strongly suggestive of TBM (> 5 days of symptoms, WBC in blood < 15 x 10<sup>9</sup>, CSF neutrophils < 90% plasma, Imaging evidence of basal meningeal enhancement, hydrocephalus, cerebral infarction).

**Investigations:** FBC, urea, creatinine, liver function, CRP, ESR, blood culture, HIV test, CXR, CSF for RE, microscopy, culture and sensitivity, smear and culture for AFB, PCR for mycobacteria, test for Cryptococcus if HIV positive, CT (Head) with contrast (hydrocephalus, basal contrast enhancing exudates). Magnetic resonance imaging (MRI) provides high definition of infra-tentorial lesions and the early features of CNS tuberculosis.

**Therapy:** 2 HRZE + 10 HR (total of at least 12 months) (H - Isoniazid, R - Rifampicin, Z - Pyrazinamide, E - Ethambutol) (Isoniazid 300 mg); Rifampicin 450 mg (< 50 kg), 600 mg (> 50 kg); Pyrazinamide 1.5 g (< 50 kg), 2 g (> 50 kg); Ethambutol 15 mg/kg with Dexamethasone 0.4 mg/kg/24 hr with a reducing course over 6 to 8 weeks.

**(4) Cryptococcal meningitis**

**Aetiology:** Cryptococcus neoformans, Cryptococcus gattii

**Diagnosis:** Subacute onset of fever, headache, neck stiffness with/without altered conscious level and CSF findings suggestive of fungal meningitis (Table 1). Diagnosis can be made by CSF culture with Indian Ink staining and serum cryptococcal polysaccharide antigen (CRAG) test. It is a major life-threatening fungal infection in patients with severe HIV infection and may also complicate organ transplantation, reticulo-endothelial malignancy, corticosteroid treatment, or sarcoidosis.

**First line therapy:**

Induction therapy: IV Liposomal Amphotericin B 3-4 mg/kg od and/or PO Flucytosine 25 mg/kg qds for 4-6 weeks

Consolidation therapy: PO Fluconazole 400-800 mg od for 8 weeks

Maintenance therapy: PO Fluconazole 200-400 mg od for 12 months

**Second line therapy:**

IV Amphotericin B 0.7-1 mg/kg q 24 hr for 2 weeks and/or PO Flucytosine 25 mg/kg qds for 2 weeks followed by PO Fluconazole 400 mg od for a minimum of 8-10 weeks.

In patients intolerant of Amphotericin B: PO Fluconazole 800-1200 mg/day and Flucytosine 100 mg/kg/day for at least 6 weeks.

**(5) Viral Encephalitis**

**Common viral aetiology:** Enterovirus, Arbovirus, Measles, Mumps, Herpes family virus, Flavi viruses.

**Diagnosis:** Acute onset fever, headache, drowsiness, nausea, vomiting, altered conscious level, disorientation, behavioural changes, seizures with CSF findings suggestive of viral encephalitis supported by EEG and neuro imaging findings.

**Investigations:** CSF RE and PCR test for HSV (1 and 2), VZV and enteroviruses, Japanese B encephalitis (JE), blood serology tests including Chikungunya viruses, JE, HIV test, electroencephalogram (EEG), CT or MRI (Brain).

**Therapy:** IV acyclovir 10 mg/kg 8 hourly for 14-21 days. If patient is unaffordable, PO Valaciclovir 1 g 8 hourly for 14-21 days.

The risks of nephropathy can be reduced by maintaining adequate hydration and monitoring renal function. The dose of acyclovir should be reduced in patients with pre-existing renal impairment.

**(6) Neurosyphilis****Diagnosis**

**Verified:** Reactive non-treponemal test and Reactive treponemal test with both

- Clinical symptoms or signs consistent with neurosyphilis without other causes, AND
- A reactive VDRL in CSF in the absence of grossly bloody contamination of the CSF.

**Likely:** Reactive non-treponemal test and Reactive treponemal test with both of

- Clinical symptoms or signs consistent with neurosyphilis without other causes, AND
- Elevated CSF protein (> 50 mg/dL) or leukocyte count (> 5 WBC/cubic millimeter CSF) in the absence of other causes.

**Possible:** Reactive non-treponemal test and reactive treponemal test and clinical symptoms or signs consistent with neurosyphilis without other causes.

**Clinical symptoms or signs consistent with neurosyphilis:**

Early neurologic clinical manifestations (i.e., cranial nerve dysfunction, meningitis, stroke, acute altered mental status, and auditory or ophthalmic abnormalities) usually present within the first few months or years of infection.

Late neurologic manifestations (i.e., tabes dorsalis and general paresis) occur 10-30 years after infection.

**Therapy:** IV Benzyl penicillin 4 million units every 4 hours for 10-14 days followed by IM Benzathine penicillin 2.4 million units once per week for up to 3 weeks.



If penicillin allergy, IV Ceftriaxone 1-2 g daily for 10-14 days or PO Doxycycline 200 mg twice a day for 28 days.

**Second line therapy:** IV Ceftriaxone 1-2 g daily for 10-14 days or IM Procaine penicillin 1.2-2.4 million units daily and PO probenecid 500 mg four times daily, both for 10-14 days.

Follow-up examination of cerebrospinal fluid should be performed 6 weeks to 6 months after treatment of neurosyphilis. Treatment failure is defined as recurrent or persistent symptoms or a sustained fourfold increase in non-treponemal test titers despite appropriate treatment. Re-treatment should also be considered if the CSF white blood cell count does not decline after six months or not completely normalize after two years.

**Table 1. CSF features of different causes of meningitis**

	Normal	Acute bacterial meningitis	Viral meningitis	Tuberculous meningitis	Fungal meningitis
<b>Pressure</b>		Normal/Increased	Normal	Normal/Increased	Increased
<b>Colour</b>	Clear	Cloudy	Clear	Clear/cloudy	Clear
<b>Red cell count (x 10<sup>6</sup>/L)</b>	Normal	Normal	Normal	Normal	Normal
<b>White cell count (x 10<sup>6</sup>/L)</b>	0-5 lymphocytes	100-5000 polymorphs	10-300 lymphocytes	50-500 lymphocytes	10-200 lymphocytes
<b>Glucose (mg/dl)</b>	50-75	Decreased	Normal	Decreased	Decreased
<b>Protein (mg/dl)</b>	15-40	Increased > 100	Normal/ slightly increased	Increased > 100	Increased 50-200
<b>Microbiology</b>	Normal	Organisms on Gram stain and/or culture	Sterile/ Virus detected	Ziehl-Nielsen stain or tuberculosis PCR or culture positive	India ink stain, Cryptococcal antigen positive, culture

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## Reproductive Tract Infections (RTIs)

Myanmar Obstetrical and Gynaecological Society

### Introduction

Reproductive tract infection (RTI) is defined as the infection of the female genital tract which causes the loss of healthy life among sexually active women of reproductive age<sup>1</sup>. Women in the reproductive age group are at risk of RTI during natural events in their life such as menstruation, pregnancy and child birth<sup>2</sup>.

Reproductive tract infections (RTIs) include (1) Sexually transmitted diseases (STDs), such as Chlamydia, Gonorrhea, Syphilis, Trichomonas, Herpes simplex virus, Human papilloma virus (HPV) and Human immunodeficiency virus (HIV) (2) Endogenous infections, which are caused by overgrowth of organisms normally present in the genital tract of healthy women, such as bacterial vaginosis or vulvovaginal candidiasis; and (3) Iatrogenic infections, which are associated with unsafe abortion or poor delivery practices. Infact, RTIs are preventable and most of them are treatable.

RTI has a profound impact on sexual and reproductive health worldwide. More than 1 million STIs are acquired every day. In 2016, WHO estimated 376 million new infections with 1 of 4 STIs: Chlamydia (127 million), Gonorrhoea (87 million), Syphilis (6.3 million) and Trichomoniasis (156 million). More than 500 million people are living with Genital herpes infection and an estimated 300 million women have an HPV infection, the primary cause of cervical cancer (STIs Fact Sheet, 2019)<sup>3</sup>.

Moreover, RTI can have serious consequences beyond the immediate impact of the infection itself. Herpes and Syphilis can increase the risk of HIV acquisition three-fold or more, mother-to-child transmission of STIs can result in stillbirth, neonatal death, low-birth-weight and prematurity, sepsis, pneumonia, neonatal conjunctivitis, and congenital deformities. Approximately 1 million pregnant women were estimated to have active syphilis in 2016, resulting in over 350,000 adverse birth outcomes of which 200,000 occurred as stillbirth or neonatal death<sup>4</sup>.

RTIs are caused by bacterial, parasitic, and viral pathogens. Generally, the pathogens causing RTIs enter the body through the mucous membranes during unprotected vaginal, anal, or oral intercourse with an infected partner.

### Clinical Manifestations of RTIs

Female RTI usually originate in the lower genital tract, such as vaginitis or cervicitis and can produce symptoms such as abnormal vaginal discharge, genital pain, genital ulcers, burning feeling with urination, abdominal pain and irregular menstrual cycle.



## Transmission of RTIs

Major route of transmissions of RIT are sexual contact with infected partners. Vertical transmission can occur through haematogenous spread to the fetus and perinatal transmission can occur during vaginal delivery. Endogenous infection like Candida infection and Bacterial Vaginosis are not sexually transmitted and symptoms may occur when overgrowth of organisms happened.

### Sequelae of RTIs

RTIs and their sequelae have widespread effects on the health of people and in each year, thousands of women die from the sequelae of undiagnosed or untreated RTIs including cervical cancer, ectopic pregnancy, puerperal infections and acute and chronic pelvic infections. Other sequelae include infertility, low birth weight, infant blindness, neonatal pneumonia, mental retardation and fetal loss.

### Laboratory Diagnosis

Detection of *Treponema pallidum* by dark-field microscopy and direct fluorescent antibody test are the direct methods for diagnosis of **syphilis**. Serologic tests for syphilis divide into two categories: non Treponemal tests for screening including Venereal Disease Research Laboratory (VDRL), Rapid Plasma Reagin (RPR), and Treponemal tests for confirmation which include T. pallidum particle agglutination (TP-PA), fluorescent Treponemal antibody absorption (FTA-ABS), and various enzyme immunoassays (EIAs).

Nucleic acid amplification tests (NAAT) are the recommended test for diagnosis of Gonorrhea and Chlamydia infection. Gram's stain and bacterial culture are not as sensitive as NAAT for the diagnosis of gonorrhea infection. Non-amplification molecular tests and cell culture for Chlamydia infection have significantly lower sensitivity than NAAT.

Most cases of anogenital warts caused by **Herpes Papilloma Virus (HPV)** are diagnosed clinically. The Papanicolaou test is a useful screening method for cervical cytologic abnormalities and HPV tests detect different high-risk types of HPV DNA.

The polymerase chain reaction (PCR) assays are the preferred test to diagnose herpes simplex virus infection. Previously, viral culture was the gold standard.

**Bacterial Vaginosis (BV)** can be diagnosed by the use of clinical criteria (i.e., Amsel's Diagnostic Criteria) or Gram stain. Clinical criteria require three of the following symptoms or signs: homogeneous, thin, white discharge that smoothly coats the vaginal walls, clue cells (e.g., vaginal epithelial cells studded with adherent coccobacilli) on microscopic examination, pH of vaginal fluid > 4.5 or fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test). Culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific.



Recent research stated that recurrence of BV is explained by formation of Biofilm, adherent bacteria are extracellular polymeric matrix. It serves as a reservoir for regrowth of pathogens towards high rate of recurrence.

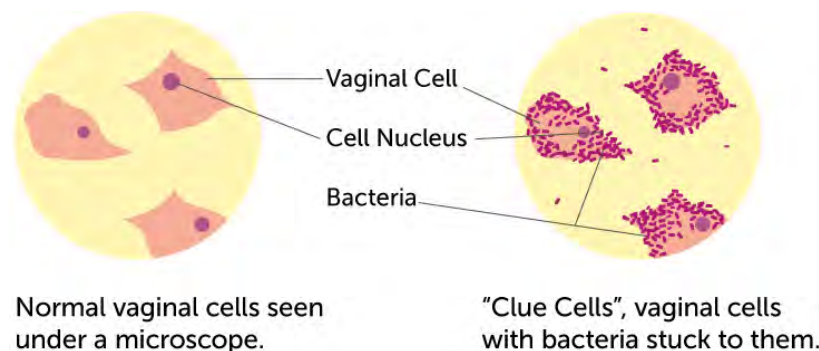


Figure 1. "Clue Cells" in Bacteria Vaginosis

A diagnosis of **Candida** infection is done clinically by the presence of external dysuria and vulvar pruritus, pain, swelling, and fissures. Thick white curdy or "cottage cheese" like adherent to walls of vagina may be present. Vagina PH is less than 4.5 and wet mount preparation using KOH will show yeasts, pseudohyphae and spores. Cultures can be performed. Positive cultures and Candida found on pap smears in asymptomatic women need not be treated (10-20% harbor Candida albicans).

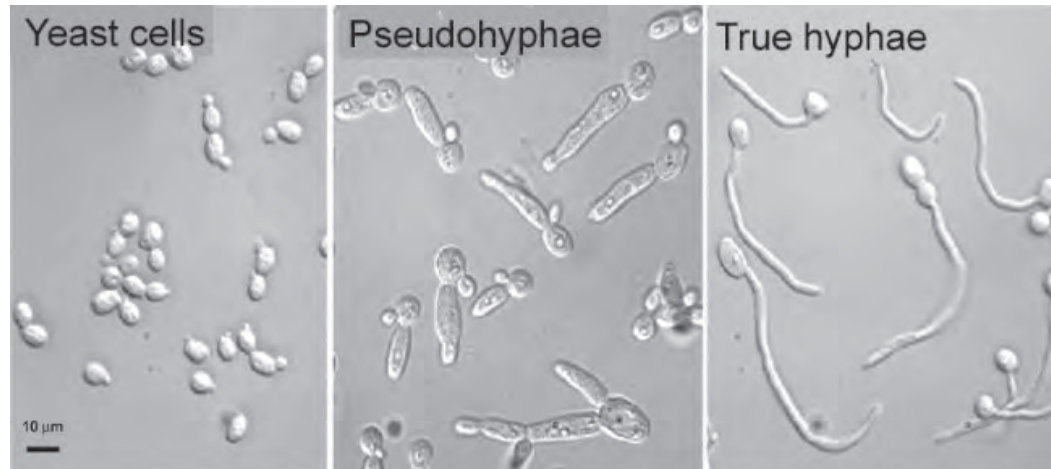


Figure 2. Yeast cells and pseudohyphae in Candidiasis

Diagnosis of **Trichomonas vaginalis**; Vaginal pH > 4.5, direct observation of the motile protozoa by a wet saline preparation (sensitivity 40-70%), microscopy for *T. vaginalis* should be performed immediately and culture media are available and diagnose up to 95% cases. Nucleic acid amplification tests (NAATs) have been developed; sensitivities and specificities approaching 100%.

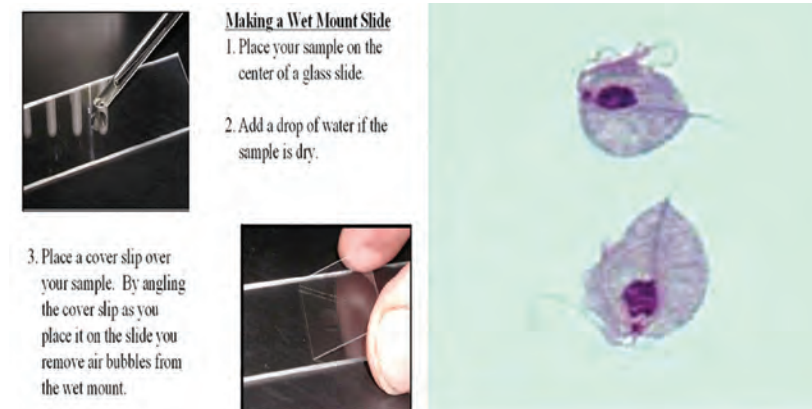


Figure 3. Wet Mount Preparation and *Trichomonas Vaginalis*

#### Treatment

Disease	Recommended	Dose/Route	Alternative Rx
<b>Syphilis</b> - Primary, secondary, or early latent  - Latent > 1 year, latent of unknown duration - In Pregnancy	Benzathine penicillin G  Benzathine penicillin G  Benzathine penicillin G	2.4 million units IM in a single dose  2.4 million units IM in 3 doses each at 1 week intervals  2.4 million units IM in a single dose	Doxycycline 100 mg 2x/day for 14 days or Tetracycline 500 mg 4x/day for 14 days  Doxycycline 100 mg 2x/day for 14 days or Tetracycline 500 mg orally 4x/day for 14 days  Amoxicillin 500 mg and Probenacid 500 mg 4x/days for 14 days <sup>5</sup>
<b>Gonorrhoea</b> - Gonococcal Infections	Ceftriazone plus Azithromycin	250 mg IM 1 G orally in single dose	If Ceftrizone is not available, Cefixime 400 mg orally in a single dose plus Azithromycin 1 G orally in single dose <sup>6</sup>
<b>Chlamydial Infection</b> - Adult and Adolescents  - Pregnancy	Azithromycin or Doxycycline  Azithromycin	1 G oral single dose 100 mg 2x/ for 7 days  1 G oral single dose	Erythromycin base 500 mg orally 4x/day for 7 days Levofloxacin 500 mg 1x/day for 7 days Amoxicillin 500 mg 3x/day for 7 days <sup>7</sup>



<b>Genital Warts</b> (Human Papillo-mavirus)	- apply imiquimod 3.75% or 5% cream or Podofilox 0.5% solution or gel - Provider-Administered - Cryotherapy - Trichloroacetic acid or bichloro-acetic acid 80-90%		Podophyllin resin 10%-25% in compound tincture of benzoin may be considered for provider-administered for strict adherence to recommendations for application <sup>8</sup>
<b>Genital Herpes Simplex Infections</b> - First clinical episode of genital herpes  - Episodic therapy for recurrent genital herpes	- Acyclovir or - Valacyclovir or - Famiclovir  - Acyclovir or - Valacyclovir or - Famiclovir	400 mg 3x/day for 7-10 days 1 G orally 2x/days for 7-10 days 250 mg 3x/days for 7-10 days  400 mg 3x/day for 5 days 1 G orally 2x/days for 5 days 250 mg 3x/days for 5 days <sup>9</sup>	
<b>Bacterial vaginosis</b>	- Metronidazole or  - Metonidazole gel 0.75% or  - Clindamycin cream 2%	500 mg orally twice a day for 7 days one full applicator (5 g) intravaginally once a day for 5 days one full applicator (5 g) intravaginally at bedtime for 7 days	- Tinidazole 2 g orally 1x/day for 2 days or  - Clindamycin 300 mg orally 2x/day for 7 days or  - Clindamycin ovules 100 mg intravaginally at bedtime for 3 days <sup>10</sup> <b>Non antibiotic treatment</b> ❖ Vaginal lactic acid ❖ Doughing with lactic acid ❖ Acid Buffering gel, boric acid ❖ Biofilms



<b>Vulvovaginal Candidiasis</b>	- Clotrimazole 1% cream or - Clotrimazole 2% cream or - Miconazole 2% cream	- 5 g intravaginally daily for 7-14 days - 5 g intravaginally for 3 days - 5 g intravaginally daily for 7 days	- Miconazole 100 mg vaginal suppository daily for 7 days or - Ticonazole 6.5% ointment 5 g intravaginally in a single application <sup>11</sup>
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### Conclusion

Although some RTIs are not curable, all are preventable. Prevention of RTIs is an important issue, including for women at low risk. Primary prevention involves avoiding infection in the first place; the most effective way to prevent sexual transmission of RTIs is to avoid sexual intercourse with infected partners. Secondary prevention reduces the likelihood of complications and sequelae of RTIs. Prevention goals require that people adopt preventive behaviors (such as avoiding unprotected intercourse with infected partners) and that clinicians diagnose and treat existing infections effectively. Training and education session needs to be carried out to identify the early symptoms of RTI. Awareness about marriage and pregnancy, sex education, delivery at Health Institution by experienced health personnel, menstrual and personnel hygiene, and use of the condom are essential for prevention of RTI<sup>12</sup>.

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## Childhood TB

Myanmar Pediatric Society

Tuberculosis is a major challenge to public health in Myanmar. TB in children is often overlooked due to non-specific symptoms and difficulties in diagnosis. Moreover, insufficient knowledge on childhood TB coupled with inappropriate and incorrect treatment gives rise to the emergence of multidrug-resistant tuberculosis (MDR-TB).

Children are usually infected with tuberculosis by an adult or an older child with bacteriologically confirmed PTB, often a family member. Less commonly, they may be infected by contact with clinically confirmed (often culture-positive) cases. The best way to prevent childhood TB is therefore by proper identification and treatment of infectious patients. Case notifications of childhood TB usually represent 6-20% of all TB cases registered with the NTP.

Children can present with TB at any age, but the most common age is between 1 and 4 years. The frequency of childhood TB depends on the intensity of the epidemic, the age structure of the population, the available diagnostic tools and whether contact tracing is routinely undertaken. The ratio of PTB : EPTB in children is usually around 1 : 3 but varies depending on factors such as age, ability to examine contacts and possibly genetic factors.

### Risk factors for Developing Childhood Tuberculosis

*Presence of one or more of the following risk factors*

- Close contact (household, close relatives, caregiver, neighbour and teacher) with a newly diagnosed smear-positive case as well as smear negative-culture positive case
- Age < 5 years of age
- HIV infection
- Severe malnutrition, measles and immunosuppressive drugs or illnesses
- Absence of BCG vaccination
- Failure to thrive or weight loss (documented)

### Criteria to Identify TB Suspect in Children

The child can be considered as a TB-suspect if 2 out of 3 following features are present.

- Fever (38°C) for more than 2 weeks and/or cough for more than 2 weeks
- Failure to gain weight (Weight loss if known/consult weight chart)
- History of contact with suspected or diagnosed TB patient

### Symptom suggestive of childhood TB

- Cough for more than 2 weeks which is not improving with full course of antibiotic and /or bronchodilators



- Fever (> 38°C) for > 2 weeks after exclusion of common causes of fever (e.g. malaria)
- Failure to gain weight (Weight loss if known/see weight chart)
- Unexplained loss of appetite

*MDR TB should be suspected in a child with TB-related symptoms who has:*

- History of previous treatment for TB within the past 12 months
- Close contact with a person known to have MDR-TB
- Close contact with TB case that has died, failed TB treatment or is non-adherent to TB treatment
- Failure to improve clinically - persistence of symptoms, failure to gain weight after 2 to 3 months of first-line TB treatment, including persistence of positive smear or culture

### Signs suggestive of childhood TB

#### ***Pulmonary tuberculosis:***

Signs of persistent pneumonia after full course of appropriate antibiotics (ATB)

#### ***Highly suggestive Extra-pulmonary tuberculosis (EPTB):***

- Pleural effusion
- Acute vertebral gibbus
- Non-painful glands with draining sinus

#### ***Suggestive EPTB***

- Meningitis not responding to antibiotics
- Pericardial effusion
- Swollen non-painful joints
- Significant enlarged lymph glands more than 2 cm in diameter and more than 2 in number with no known local cause and not responding to usual antibiotics
- Distended abdomen with ascites
- Clinical features indicative of Tuberculin hypersensitivity (e.g. erythema nodosum phlyctenular conjunctivitis)

### Diagnosis

- Diagnosis is very difficult in children due to non-specific features and the radiological features are not as easy to interpret as in the adult.
- However, in children with risk factors who have suspicious clinical criteria, more definitive diagnosis can be made if appropriate investigations are done.

#### **Diagnosis to be based on a combination of**

- History of contact
- Risk factors
- Clinical presentation
- Bacteriological confirmation (Sputum / CSF / Biopsy examination wherever possible)



- Imaging - Chest X-ray / CT
- Immunological evidence of TB infection Mantoux test (Positive if induration > 10 mm after 48-72 hours) (not a strong factor to be considered for diagnosis of active TB disease)

### Diagnostic Tests

#### **Bacteriological confirmation**

A definitive diagnosis of TB can be achieved only by the demonstration of presence of *Mycobacterium bacillus* in the lesion or its product. The main laboratory methods used to detect *Mycobacterium tuberculosis* in a sample from a child suspected of having TB are smear for acid-fast bacilli, Xpert MTB/RIF assay (using real-time PCR) or mycobacterial culture. Xpert MTB/RIF (and culture if available) is recommended in all children that are suspected of having MDR-TB.

#### • **Sputum examination**

- ❖ Indicated in children older than 8 years or in any younger children who is able to provide a good quality sputum
- ❖ Sputum should be collected spot, early morning and spot strategy

• **Gastric lavage (aspiration)** - Indicated in children less than 8 years or in children who is unable to produce sputum (Should be carried out after 4 hours of not eating or drinking).

#### **Chest X-ray**

- ❖ No specific radiological signs
- ❖ Features suggestive in the diagnosis of TB
  - Unequivocal hilar lymph gland enlargement with or without parenchyma opacification
  - Miliary mottling (especially in HIV non-infected host)
  - Large pleural effusion ( $\geq \frac{1}{3}$  of pleural cavity) in children > 5 years
  - Apical opacification with cavitation (adult type disease; very rare in children, common in adolescents)

#### **Tuberculin skin tests (TST)**

Tuberculin skin tests are useful in the diagnosis of TB infection in young children for contact tracing. It is also useful as an adjunct test where the diagnosis of TB is uncertain. TB should never be ruled out in children based on a negative TST result.

- Induration > 10 mm is considered positive irrespective of whether BCG has been administered (not a strong factor to be considered for diagnosis of active TB disease)
- Induration > 5 mm is considered positive in HIV positive children
- Negative TST never rule out TB in children



**Interferon-gamma release assays (IGRAs)** should not replace the tuberculin skin test (TST) in low- and middle-income countries for the diagnosis of latent TB infection in children or for the diagnostic work-up of children (irrespective of HIV status) suspected of TB disease in these settings. *Commercial sero-diagnostics should not be used in children suspected of active pulmonary or extra-pulmonary TB, irrespective of their HIV status.*

#### Diagnostic tests for other extra-pulmonary TB

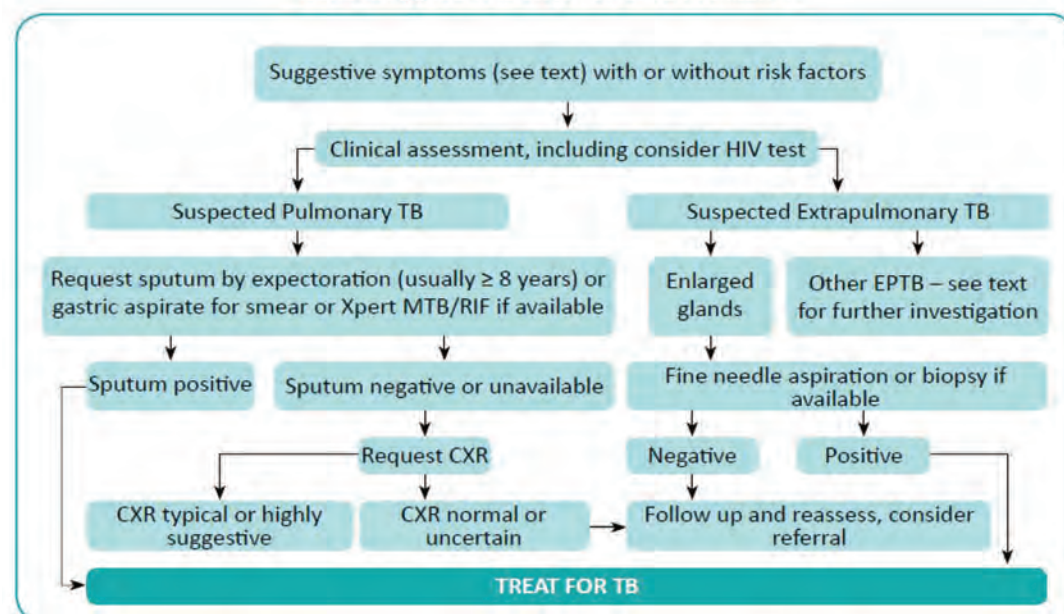
Disease	Special investigation
Cervical / other lymph glands	Biopsy / Fine needle aspiration (FNA)
TB Meningitis	lumbar puncture (LP), Computerized Tomography (CT) of brain
TB Arthritis	Aspiration, biopsy
TB Abdomen / ascites	Ultrasound (US), Analysis of Aspiration
TB Vertebra	Vertebral X-ray; CT / MRI of vertebral column
TB pleural Effusion	Pleural tap for cytology

#### TB/HIV co-infection

Recommendation for HIV testing in

- Miliary TB
- Severe acute malnutrition
- Clinical signs suggestive of HIV
- Mother known to be HIV positive or either parents suspected of being HIV infected
- Relapse or treatment failure

#### General Approach to diagnosis of TB in children



#### TREATMENT OF TB IN CHILDREN

Effective management of TB relies on

- Rapid diagnosis of TB
- Rapid detection of drug resistance
- Rapid initiation of effective treatment regime

The main objectives of anti-TB treatment are to:

- Cure the patient with TB (by rapidly eliminating most of the bacilli);
- Prevent death from active TB or its late effects;
- Prevent relapse of TB (by eliminating the dormant bacilli);
- Prevent the development of drug resistance (by using a combination of drugs);
- Decrease TB transmission to others (smear-positive cases)

#### Recommended treatment regimens for children in each TB diagnostic category

Type of TB Patient	TB cases	Regimen	
		Intensive phase	Continuation phase
New case	Children < 8 years of age (exceptions: see below)	2HRZ	4HR
	• Children ≥ 8 years of age • Children < 8 years of age with severe forms of pulmonary / extra pulmonary TB or who are HIV-infected	2HRZE	4HR
	• Meningitis /disseminated TB disease • Osteoarticular TB	2HRZE	10HR
Previously treated case	• Relapse • Treatment after failure • Treatment after loss to follow-up	3HRZE	5HRE
MDR-TB	Specially designed standardized or individualized regimens (refer to Myanmar National guidelines on Management of MDR-TB)		

#### Recommended doses of first line anti-TB drug

Drug	Recommended daily dosing	
	Dose and range (mg/kg)	Maximum (mg)
Isoniazid (H)	10 (7-15)	300
Rifampicin (R)	15 (10-20)	600
Pyrazinamide (Z)	35 (30-40)	
Ethambutol (E)	20 (15-25)	

## Indications for Hospitalization

- TB meningitis
- Miliary TB
- Respiratory distress in any form of TB
- Spinal TB
- Severe adverse events (e.g. hepatotoxicity)

## Follow up

Ideally, each child should be assessed at least at the following intervals: 2 weeks after treatment initiation, and at two, five and six-month. The assessment should include as a minimum; symptom assessment, assessment of treatment adherence, enquiry about any adverse events and weight measurement. Medication dosages should be adjusted to account for any weight gain. Adherence should be assessed by reviewing the treatment card, and pill count or blister pack count. A follow-up sputum sample for smear microscopy at 2, 5 and 6 months after treatment initiation should be obtained for any child who was smear-positive at diagnosis.

Follow up chest radiographs

- Not routinely required in children
- Indications for follow up CXR
  - ❖ Extensive pulmonary involvement
  - ❖ Continued symptoms
  - ❖ Treatment failure regardless of smear positivity

## CONTACT TRACING AND MANAGEMENT

Young children living in close contact with a source case of smear-positive pulmonary TB are at particular risk of TB infection and disease. The risk of infection is greatest if the contact is close and prolonged such as the contact an infant or toddler has with a mother or other caregivers in the household and especially so if the index case is not treated.

### The main purposes of child contact screening are to

- Identify symptomatic children (e.g. children of any age with undiagnosed TB disease);
- Provide preventive therapy for susceptible individuals (e.g. asymptomatic children of < 5 years of age in close contact with a smear-positive pulmonary TB case)

### Definitions

**Source case** - A case of pulmonary TB (usually sputum smear positive) which results in infection or disease among contacts

**Contacts for screening** - All close contacts of a source case of any age, including young children < 5 years, should be screened for symptoms suggestive of TB.

**Close contact** - Living in the same household as a source case or in frequent contact with a source case (e.g. caregiver, grandparents, relatives)

**Strategy for Contact Tracing** - Contact tracing should be reinforced in two ways:

- Through index adult case (Detection of TB in close contacts of usually adult source case particularly sputum smear positive cases) (downstream tracing)
- Through close contacts of childhood TB cases (Detection of source case for a paediatric TB patient, also known as reverse contact tracing) (upstream tracing)
- Parents and caregivers are to be strongly encouraged to bring children for contact screening to health centre (passive contact screening). Alternatively, if the child is found with TB disease, his / her family members and neighbours should also undergo TB screening.

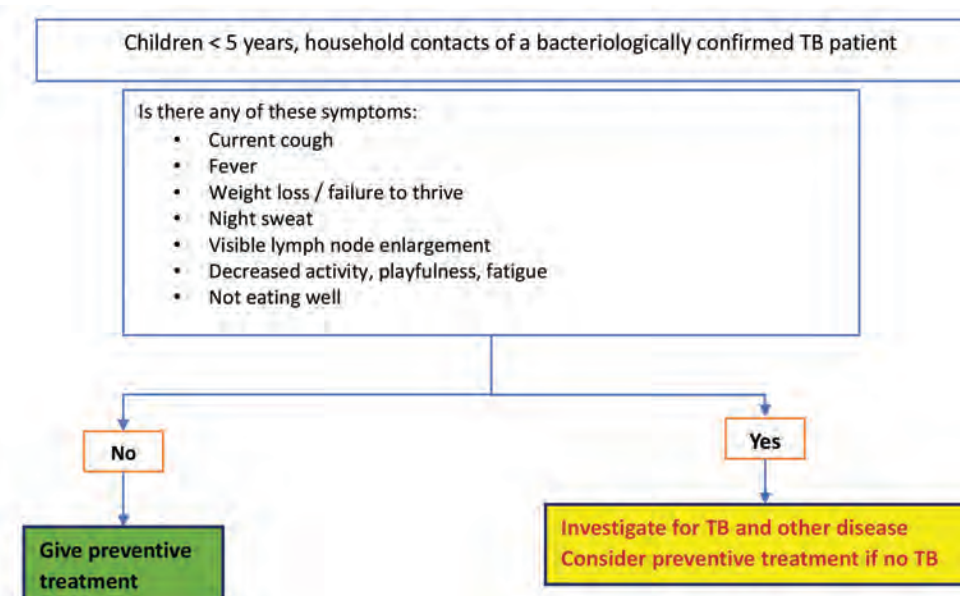
**Approach to Contact screening** - Three main steps used for contact screening

- clinical screening: symptoms assessment of all contacts of any age, including children
- clinical evaluation for TB: any contact with symptoms suggestive of TB should be further evaluated for TB, e.g. sputum, Chest X-ray etc.
- contacts who are younger than 5 years of age or HIV-infected of any age, and do not have active TB should be offered preventive therapy.

## Tuberculosis Preventive Treatment (TPT)

Asymptomatic children under 5 years of age after exclusion of active TB, exposed to an adult with infectious (smear positive) TB from the same household, will be given 6 months of Isoniazid (10 mg/kg daily) or daily Rifampicin (15 mg/kg) / Isoniazid (10 mg/kg) for 3 months.

### Algorithm for screening HIV negative infants and children less than 5 years household contacts of people with TB



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**Evaluation of a patient with Jaundice****Myanmar Surgical Society****Definition**

Jaundice is a yellow discoloration of body tissues usually observed in the skin, sclera and mucus membranes secondary to excess bilirubin in the serum (hyperbilirubinemia). Serum bilirubin levels accumulate when its production exceeds its metabolism and excretion. Imbalance between production and clearance may result either from excess release of bilirubin into the bloodstream or from processes that impair uptake, metabolism or excretion. The normal range for serum bilirubin is 5-17 mmol/L (0.3-1 mg/dl). When the serum bilirubin exceeds 50 mmol/L (3 mg/dl), jaundice is visible.

**Pathophysiology of jaundice**

Jaundice occurs due to imbalance between bilirubin production and clearance. Approximately 80% of bilirubin is produced from breakdown of senescent red blood cells by reticuloendothelial (RE) cells in the spleen and liver when they reach the end of their life span of approximately 120 days. The other 15-20% of bilirubin comes from ineffective erythropoiesis resulting in destruction of maturing erythroid cells in the bone marrow and a smaller proportion from metabolism of other (non-haemoglobin) haem containing proteins in the liver.

On breakdown of haemoglobin, haem is released that is further broken down to porphyrin and biliverdin. Biliverdin, on oxidation within RE cells, forms bilirubin. This bilirubin is unconjugated and water insoluble. This is bound to albumin and transported in the circulation. When unconjugated bilirubin reaches the sinusoidal space of Disse within the liver, it separates from albumin.

Bilirubin molecules are taken up by hepatocytes with the help of bilirubin transporter protein. Within the hepatocyte (endoplasmic reticulum), bilirubin undergoes a two-step conjugation to bilirubin mono- and di-glucuronide catalyzed by an enzyme, uridine diphospho-glucuronosyl transferase (UDPG).

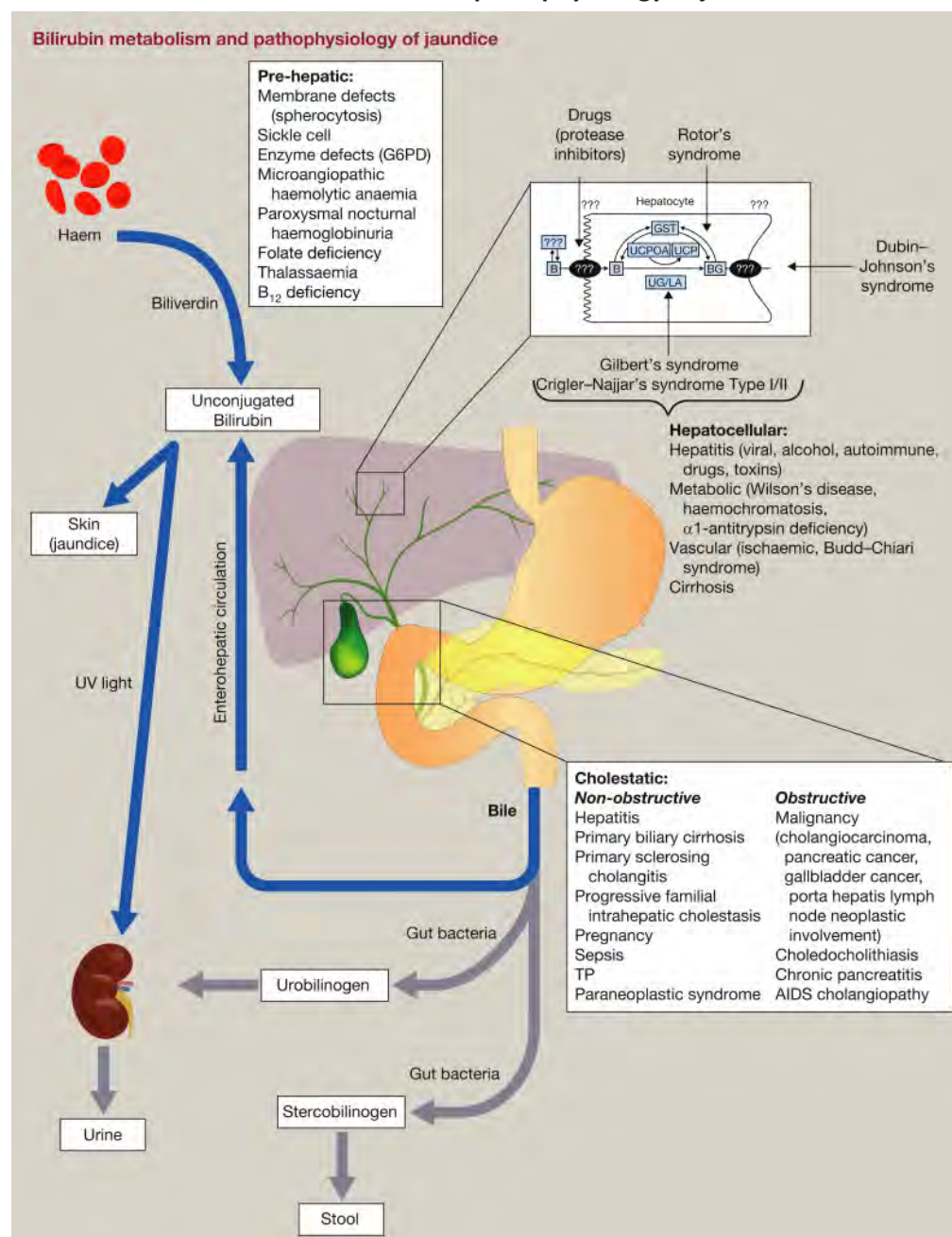
Over 90% of serum bilirubin is in the unconjugated form and a smaller proportion is in conjugated water-soluble form. Bilirubin excretion from hepatocytes into biliary canaliculi is an energy dependent process facilitated by multi-resistant drug protein (MRP2). Conjugated bilirubin is excreted in bile as one of its components and stored in the gall bladder. This bile is concentrated ten fold in the gall bladder and excreted into second part of the duodenum.

Conjugated bilirubin is not reabsorbed by the intestinal mucosa. It is further metabolized by small and large intestinal bacteria to urobilinogen and stercobilinogen. Urobilinogen can be reabsorbed from the intestine. Some of the reabsorbed urobilinogen is taken up by the liver and re-excreted into the bile and the remainder bypasses the hepatocytes and is excreted by the kidneys. Thus, urine contains small amount of urobilinogen (< 4 mg/24 hr).



When the production of bilirubin is greatly increased (e.g., with haemolysis) or the hepatic uptake of urobilinogen is impaired (e.g., hepatitis), urinary urobilinogen will increase significantly. On the contrary, if there is intra- or extrahepatic biliary obstruction, with interference of the intestinal phase of bilirubin metabolism, there is a resulting significant reduction in production and urinary excretion of urobilinogen. Absence of urinary urobilinogen is very useful to differentiate obstructive jaundice from other causes of jaundice.

### Bilirubin metabolism and pathophysiology of jaundice



### Types of jaundice

Understanding the pathophysiology of bilirubin helps to classify jaundice into three main types:

- prehepatic (secondary to increased pigment production);
- hepatic (due to reduced hepatic uptake or conjugation of bilirubin); and
- post-hepatic or obstructive or cholestatic (secondary to decreased excretion of the conjugated bilirubin into bile).

The first two types are associated with predominantly unconjugated hyperbilirubinaemia and the third group is associated with predominantly conjugated hyperbilirubinaemia. Cholestasis represents impairment of flow of bile from the liver to the duodenum.

### Post-hepatic or obstructive or cholestatic jaundice

Post-hepatic jaundice or cholestasis results in impairment of bile formation and/or bile flow which may clinically present with fatigue, pruritus and in its most overt form, jaundice due to retention of bilirubin and bile salts. This can be further divided into intrahepatic cholestasis (IHC - due to impaired bilirubin excretion by hepatocytes) and extrahepatic cholestasis (EHC - due to extrahepatic biliary obstruction).

There are several possible mechanisms that can account for impaired excretion of conjugated bilirubin in IHC, including canalicular obstruction by swollen hepatocytes, inspissated bile, infiltration by inflammatory cells, change in hepatocyte membrane permeability resulting in re-uptake of excreted pigment and possible inhibition of membrane transport proteins.

### Intrahepatic cholestasis

Causes of intrahepatic cholestasis include dose dependent and idiosyncratic drug-induced hepatocyte injury, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), alcoholic hepatitis, autoimmune hepatitis, intrahepatic cholestasis of pregnancy, benign recurrent intrahepatic cholestasis and total parental nutrition (TPN).

### Extrahepatic cholestasis

Extrahepatic cholestasis occurs due to obstruction of extrahepatic bile ducts resulting in predominant rise in serum conjugated bilirubin, dark urine and pale stools.

This can be due to lesions **within the lumen of the bile duct** (e.g., common bile duct stones), **with the wall of the duct** (e.g., biliary trauma, bile duct cancer, PSC), or from **external compression** (e.g., pancreatic tumour, acute and chronic pancreatitis with scarring).

The functional reserve of the liver is such that localized occlusion of the intrahepatic ducts do not produce jaundice, unless the drainage from 75% of the liver parenchymal segments are obstructed or the liver is extensively replaced with primary or secondary cancer.

## Evaluation of a patient with jaundice

The initial workup of jaundice should focus on the history and physical examination to help clarify the diagnosis.

**History** details should include

- determination of length of symptoms,
- including presence of abdominal pain, pruritus, fever,
- change in bowel habit,
- loss of weight, appetite,
- 'flu'-like symptoms,
- dark urine and pale or clay color stools.

**Previous history** of blood transfusion, IV drug use, alcohol intake, indiscriminate sexual activity, family history of liver diseases, are relevant.

**Detailed history on medications** including oral contraceptives or other hormonal drugs used for physical enhancement (e.g., anabolic steroids) in young males are important.

**History of foreign travel** to countries where endemic enteric transmission of hepatitis A and E are prevalent should be explored.

Jaundice, in a background of known gall stones, may indicate passage of stones that subsequently obstruct the common bile duct.

Appearance of jaundice in someone with a pre-existing medical condition, may indicate a diagnosis involving the liver or bile ducts (e.g., ulcerative colitis and PSC, pregnancy and intrahepatic cholestasis of pregnancy, right heart failure and cholestasis).

**Physical examination** should include measurement of height, weight and calculation of Body Mass Index (BMI).

Jaundiced patients should be examined for the **stigmata of chronic liver disease**, such as palmar erythema, Dupuytren's contracture, asterix (coarse flapping tremor), clubbing, bruising, spider naevi, gynaecomastia, caput medusa, ascites and ankle swelling. Grey or bronze skin discolouration is associated with haemochromatosis and Kayser-Fleischer rings in the eyes with Wilson's disease.

The presence of **peripheral lymphadenopathy** should be noted, in particular an enlarged left supraclavicular lymph node (Virchow's node or Troisier's sign) is often associated with an upper gastrointestinal malignancy.

**Trousseau's sign of migratory thrombophlebitis** is reported in 7% of patients with pancreatic cancer.

**The abdomen** should be carefully examined for **masses and hepato-splenomegaly**.

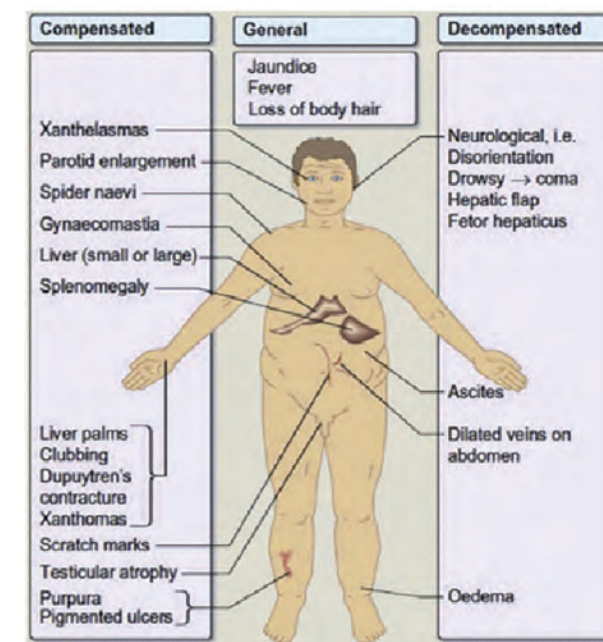
**Localized abdominal tenderness in the right hypochondrium** on inspiration (Murphy's sign) may indicate acute cholecystitis.

In a jaundiced patient, if the gall bladder is distended and palpable, it is likely that the cause of the jaundice is not a stone (**Courvoisier's law**).

An exception to this law is a patient with Mirizzi's syndrome, where a stone impacted in the neck of the gall bladder causes distension of the gall bladder and jaundice due to extrinsic compression of the common hepatic/common bile duct.

**Sudden onset of a triad of symptoms including jaundice, right upper quadrant pain and rigors (Charcot's triad)** indicates acute cholangitis.

**Stigmata of compensated and decompensated chronic liver disease.** (From Kumar & Clark's Clinical Medicine, 8<sup>th</sup> edition, 2012. Elsevier, with permission.)



## Blood Tests Investigations

**Full blood count** along with red cell indices including reticulocyte counts are useful in identifying the presence and type of anaemia (secondary to haemolysis, haemoglobinopathies) and thrombocytopenia (secondary to portal hypertension).

**Liver blood tests** are readily available but the spectrum of standard tests vary from hospital to hospital. They have historically been referred to as liver function test (LFTs), yet the predominant abnormality does not relate to liver dysfunction.

**Hepatobiliary enzymes**, when interpreted in isolation convey information on the level of ongoing injury, whereas **bilirubin, albumin and INR** convey information on liver function, with platelets conveying information on the level of fibrosis.

Most laboratories will routinely report total bilirubin, which comprises unconjugated and conjugated fractions. Elevations of either fraction will therefore lead to a rise in the measured total bilirubin concentration. The most common cause of an isolated elevated bilirubin concentration is Gilbert's syndrome.



**Albumin** is a protein that is produced only in the liver and has multiple biological actions, including maintenance of oncotic pressure, binding of other substances (such as fatty acids, bilirubin, thyroid hormone and drugs), metabolism of compounds, including lipids, and antioxidant properties. **As albumin is only produced by the liver, the serum albumin concentration is often considered as a marker of the synthetic function of the liver.**

Albumin concentrations are reduced in many clinical situations, including sepsis, systemic inflammatory disorders, nephrotic syndrome, malabsorption, postoperative period and gastrointestinal protein loss.

**Prothrombin time (PT) and INR** are assessments of blood clotting, which are used to measure liver function, as the underlying protein clotting factors (II, V, VII, IX and X) are made in the liver. If there is significant insult to the liver, this results in a reduction in clotting factor production and subsequent coagulopathy, as confirmed by a prolonged PT or INR. While a prolonged PT/INR can indicate either acute or chronic liver dysfunction it can also be caused by vitamin K deficiency as seen in fat malabsorption and chronic cholestasis.

**Alkaline phosphatase (ALP)** is produced mainly in the liver (from the biliary epithelium) but is also found in abundance in bone and in smaller quantities in the intestines, kidneys and white blood cells. Levels are physiologically higher in childhood, associated with bone growth, and in pregnancy due to placental production.

Pathologically increased levels occur mainly in bone disease (e.g., metastatic bone disease and bone fractures) and cholestatic liver disease, for example, primary biliary cholangitis, primary sclerosing cholangitis, common bile duct obstruction, intrahepatic duct obstruction (metastases) and drug-induced cholestasis.

Furthermore, hepatic congestion secondary to right-sided heart failure can also lead to cholestasis (elevated ALP levels and/or bilirubin).

**When ALP is elevated in isolation, the measurement of g-glutamyl transferase (gGT) can indicate whether the ALP is of hepatic or non-hepatic origin.**

**Aspartate transaminase (AST) and alanine transaminase (ALT)** are enzymes present in hepatocytes and are released into the blood stream in response to hepatocyte injury. Elevations in either of these enzymes are the most common abnormality seen on liver blood test profiles.

Both enzymes are present in many differing types of tissue, but **ALT is considered more liver-specific** since it is present in low concentrations in non-hepatic tissue, and non-liver related elevations are uncommon.

However, AST is abundantly present in skeletal, cardiac and smooth muscle and so may be elevated in patients with myocardial infarction or myositis. Although ALT is considered a more specific indicator of liver disease, the concentration of AST may be a more sensitive indicator of liver injury in conditions such as alcohol-related liver disease and in some cases of autoimmune hepatitis.



**$\gamma$  Glutamyl transferase ( $\gamma$  GT)** is abundant in the liver and also present in the kidney, intestine, prostate and pancreas but not in bone; therefore, it can be useful in confirming that an elevated ALP is of liver and not bony origin.  $\gamma$  GT is most commonly elevated as a result of obesity, excess alcohol consumption or may be induced by drugs.

Although an elevated  $\gamma$  GT has a low specificity for liver disease, it is one of the best predictors of liver mortality. It is particularly useful in children to establish the likelihood of biliary disease when ALP is not a reliable indicator.

Predominant causes of cholestasis in children include congenital abnormalities of the biliary tract and genetic disorders affecting bile synthesis and excretion.

**Renal function** should also be assessed due to the association of renal dysfunction with jaundice, and to assess for electrolyte disturbances, particularly hyponatraemia, found in patients with chronic liver disease.

A more detailed liver screen is done to identify the aetiology of the underlying liver disease. This will include **viral hepatitis serology (A, B, C, D, E)**, cytomegalo virus, Epstein Barr virus serology, serum iron studies for haemochromatosis, anti-mitochondrial antibody (found over 90% of patients with PBC), anti-neutrophil cytoplasmic antibodies (found over 80% of patients with PSC), anti-nuclear antibody, anti-smooth muscle antibodies (for PSC and autoimmune hepatitis) and in younger patients serum copper, caeruloplasmin for Wilson's disease and  $\alpha$ -1-antitrypsin level to diagnose rare causes.

**Tumour markers** are measured if a mass lesion is identified in the liver or pancreas on investigation of jaundice. Alpha fetoprotein (AFP), carcino embryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are the common tumour markers used. They are used in conjunction with clinical presentation and cross-sectional imaging in hepatocellular carcinoma (AFP), colorectal liver secondaries (CEA), intrahepatic cholangiocarcinoma (CA 19-9) or pancreatic ductal adenocarcinoma (CA 19-9) in diagnosis and in some cases to predict the prognosis.

### Imaging

**Ultrasound** is the initial imaging investigation of choice in the jaundiced patient, being relatively inexpensive, reproducible, non-invasive and readily available. Features of note would be intra- or extrahepatic biliary dilatation, whether the gall bladder was distended or contracted, the presence or absence of gall stones within the gall bladder or biliary tree and evidence of a peri-ampullary mass. Furthermore, the sonographer would be expected to comment on the echo texture of the liver parenchyma, whether there was increased echogenicity, indicating a fatty liver (steatosis) and whether there were any focal solid or cystic liver lesions and their location. Ultrasound may also detect features of portal hypertension such as ascites and splenomegaly.



**Limitations of ultrasound** are that it is operator dependent and good views may not be obtained in the obese patient, or if there is overlying bowel gas. Contrast-enhanced ultrasound consists of an intravenously administered suspension of gas-filled micro bubbles, slightly smaller than red blood cells, which remain within the intravascular space and travel through the smallest blood vessels bursting. Following intravenous injection, they remain within the circulation for about 5 minutes. They resonate in an ultrasound field at the frequencies used in diagnostic sonography. Three phases of enhancement following administration of an intravenous bolus are seen (i.e. arterial, portal venous and a late phase).

This technique can be used to help characterize specific liver lesions such as complex cysts, haemangiomas, focal nodular hyperplasia, focal fatty sparing and focal fatty change.

**Ultrasound with transient elastography (Fibroscan)** can be used to measure liver stiffness, indicating tissue resistance to deformation under mechanical stress. A greater stiffness corresponds to a higher tissue resistance and is elevated in steatosis, steatohepatitis and fibrosis. The Fibroscan works by measuring shear wave velocity (the velocity of a sound wave passing through the liver), which is then converted into liver stiffness, measured in kilo pascals. This has the advantage over a liver biopsy in that it is non-invasive, easily reproducible and the whole liver can be assessed, rather than a small core of tissue, which may represent a sample error.

**Endoscopic ultrasound (EUS)** is used for staging of periampullary malignancies (for example the extent of portal or superior mesenteric vein involvement in a head of pancreas cancer) and can allow fine needle aspiration for tissue diagnosis prior to surgery and chemotherapy.

#### Cross-sectional imaging:

**Computed tomography (CT)** with oral and intravenous contrast agents may demonstrate liver, biliary and pancreatic tumours, portal lymphadenopathy and tumour spread beyond the organ of origin. It can show biliary dilatation and the level of obstruction. It may demonstrate a cirrhotic liver, with a nodular or fine cobble stone appearance of the margin, liver lobar asymmetry, caudate hypertrophy and features of portal hypertension such as varices, splenomegaly and ascites.

Risks associated with CT include radiation exposure and contrast-induced nephropathy. Furthermore, only 10% of gall stones are visible on CT. Thus, ultrasound remains the preferred initial investigation in the jaundiced patient.

**Magnetic resonance imaging (MRI)** with different contrast agents and diffusion-weighted imaging can allow assessment of the quality of the liver parenchyma and characterization of liver lesions. MRI has more advantages compared to ultrasound, CT, positron emission tomography (PET), or any other imaging modality in diagnosing focal hepatic masses. With a combination of basic T1- and T2-weighted sequences, in and out of phase chemical shift imaging, diffusion weighted imaging, extracellular (Gadolinium) and liver specific (gadoxetic acid or Primovist, Bayer Schering Pharma AG, Berlin, Germany) contrast



agents, most liver lesions can be adequately diagnosed. Benign lesions, such as cyst, haemangioma, focal nodular hyperplasia (FNH) or adenoma, can be distinguished from malignant lesions. Advantages of MRI include the lack of ionizing radiation. Disadvantages include the risk of contrast-induced nephropathy, patient intolerance due to the noise, claustrophobia and the length of time required to acquire the different sequences.

#### Imaging of the biliary tree:

**Magnetic resonance cholangiopancreatography (MRCP)**, using T2 weighted sequences, is a non-invasive, non-contrast method of obtaining an accurate 'road map' of the biliary tree and has now superseded diagnostic endoscopic retrograde cholangiopancreatography (ERCP).

**ERCP with a side viewing duodenoscope** is widely considered to be the gold standard for investigation of biliary and pancreatic duct pathology. It permits direct examination and biopsy of the ampulla in cases of suspected ampullary carcinoma. Cannulation of the ampulla, injection of water-soluble contrast agents and real-time screening permits diagnostic and therapeutic maneuvers such as endoscopic sphincterotomy, gall stone extraction, biliary brushing for cytology and insertion of plastic or metal endo biliary or pancreatic duct stents.

Complications of ERCP include haemorrhage, pancreatitis, cholangitis and retro-duodenal perforation, with an overall mortality rate of less than 1%.

**The Spy Glass system (Boston Scientific)** is a single use flexible catheter which can be inserted through the 4.2 mm working channel of a duodeno scope. It has three ports, one for the Spy Probe which is a fibre optic probe to provide direct visualization of the biliary tree, one for water flushing/aspiration and one to allow the passage of specialized biopsy forceps. The system allows users to visually examine the biliary ducts, take biopsy samples and treat large biliary stones by either electro hydraulic or laser lithotripsy. Spy Glass is currently used in approximately 5% of all ERCP procedures. Its main indications are for the treatment of difficult intraductal stones and the assessment of indeterminate biliary strictures.

**Percutaneous trans hepatic cholangiography (PTC)** involves percutaneous puncture of a peripheral bile duct within the liver and injection of water-soluble contrast agents to obtain a cholangiogram. Similar to ERCP, biliary brushing may be obtained and stents placed. It is particularly useful for managing hilar strictures or biliary strictures post-hepatectomy, or if the ampulla is not readily accessible, for example if the patient has had a Billroth II gastrectomy or a gastric bypass. It is facilitated by the presence of dilated intrahepatic bile ducts. Complications of PTC include bile leak, bleeding and cholangitis.

**Functional imaging: techniques** may be used in the further evaluation of the jaundiced patient. For example, PET used in conjunction with CT and various radio labelled tracers, the most common being 18F-fluoro-2-deoxy-D-glucose (FDG), is a useful adjunct in the staging of hepato-pancreato-biliary cancers.



Furthermore, somatostatin receptor scintigraphy using indium-111 radio labelled octreotide (Octreo Scan) can be used for the investigation and staging of neuroendocrine tumours.

### Liver biopsy

A liver biopsy may be required to achieve a diagnosis in a jaundiced patient, particularly with hepatocellular jaundice or intrahepatic cholestasis. It is generally not recommended to biopsy a liver tumour if the patient has resectable disease, due to the risk of disease dissemination and such a biopsy should only be performed after multi-disciplinary team discussion.

### Laparoscopy

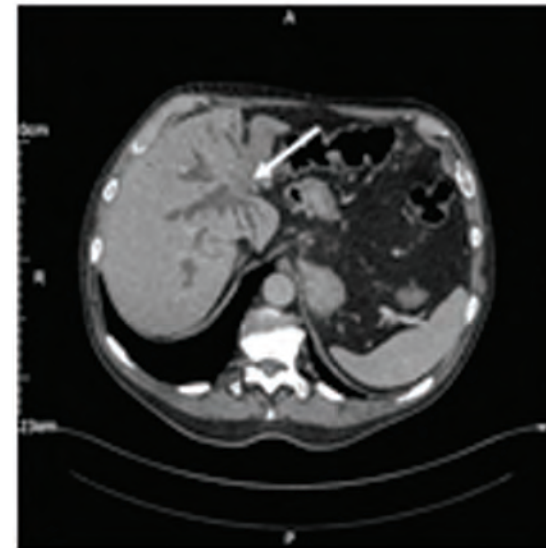
Laparoscopy is used selectively in the staging of hepatico-pancreatico-biliary malignancies, in particular looking for small-volume peritoneal disease, not seen on cross-sectional imaging, which might preclude a major resection.

### Summary

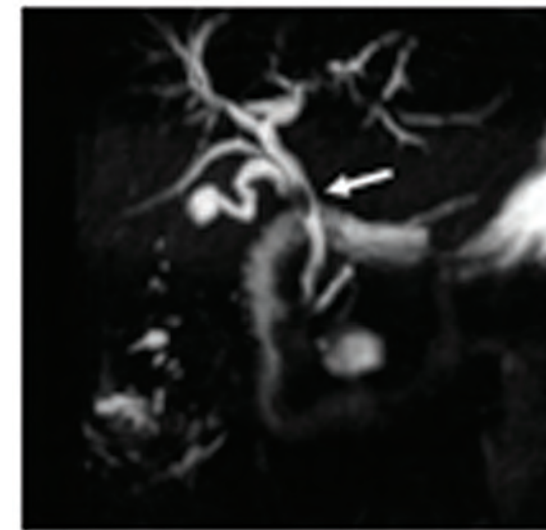
When patients present with jaundice a careful history, clinical examination, blood tests and urine dipstick for urobilinogen will usually differentiate obstructive jaundice from non-obstructive jaundice. This could be further clarified with an ultrasound scan. All patients need to be assessed for sepsis, pre-existing dehydration and clotting abnormality so that these issues can be addressed prior to instituting further more invasive investigations and treatment depending on the underlying pathology by a multidisciplinary team of specialists including surgeons, gastroenterologists, haematologists, oncologists, radiologists and pathologists.

#### Presentation of jaundice

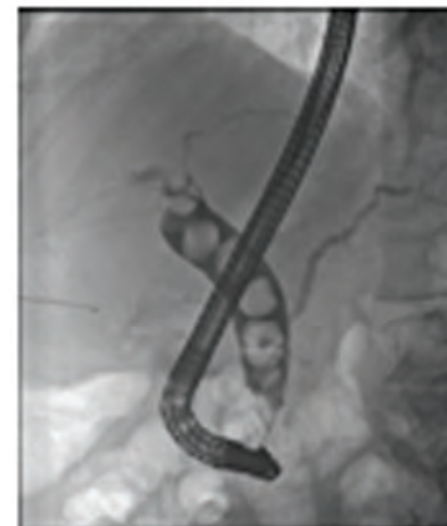
	Stones in common bile duct	Malignancy	Drug-induced cholestasis	Acute viral hepatitis
<b>History</b>	Dyspepsia, biliary colic	Nil	Drug history (present and last 6/12 months)	Transfusions, injections, contacts
<b>Pain</b>	Colic, epigastric to back (episodic), none	Epigastric to back (constant), none	None	Discomfort in right upper quadrant, none
<b>Weight loss</b>	Slight±	Remorseless, none	Slight±	Slight±
<b>Pruritis</b>	±	+	+	Transient
<b>Investigations</b>				
Bilirubin (serum; mmol/l)	50-150	Steady rise to >200	Variable	Variable
Urobilinogen (urine)	+	-	-early	-early (+late)
Alkaline phosphatase (serum; × normal)	>3×	>3×	>3×	<3×
Aspartate aminotransferase (serum; × normal)	<5×	<5×	>5×	>10×
White cell count (differential)	1/Normal (1/polymorphs)	1/Normal	Normal	1(l/lymphocytes)
Ultrasound	Gallstones ± dilated ducts	Dilated ducts ± mass/stricture	Normal	Splenomegaly



CT of a patient who presented with painless obstructive jaundice. The image shows bilateral biliary dilatation secondary to a hilar cholangiocarcinoma (arrowed).



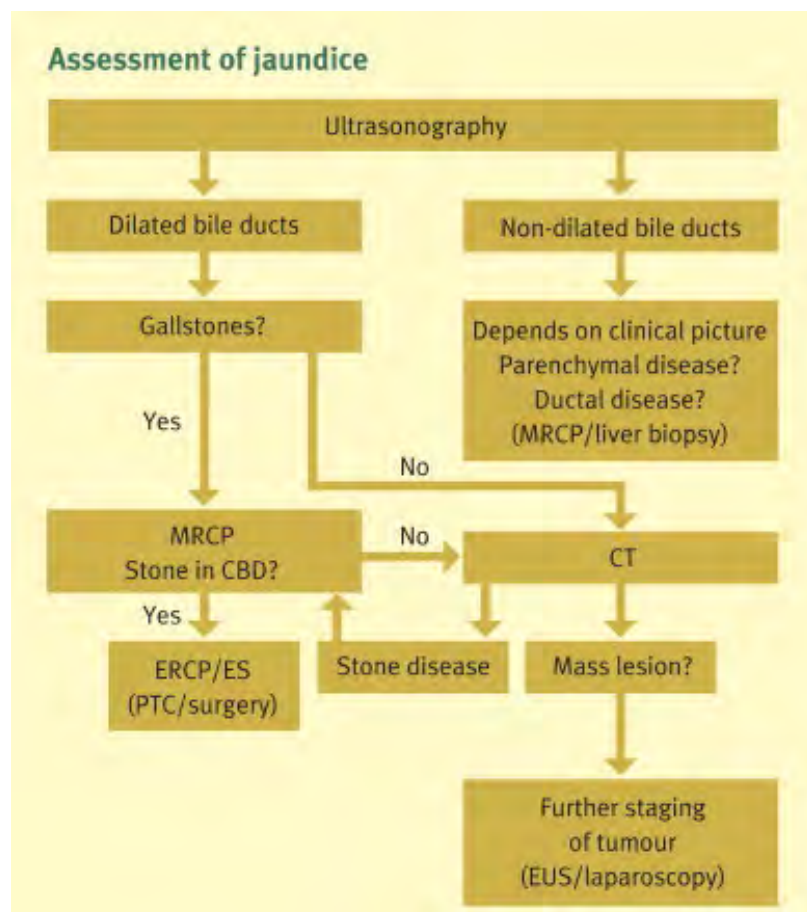
**Magnetic resonance cholangiopancreatography** image to show a gall stone impacted at the common hepatic/cystic duct confluence (arrowed). Endoscopic retrograde cholangiopancreatography failed to extract this and it was eventually removed via laparoscopic choledochotomy.



A 'steinstrasse' (German word for 'stone street') of common bile duct stones shown at endoscopic retrograde cholangiopancreatography in a patient who presented with cholangitis. A wire has been passed into the intrahepatic biliary tree to facilitate endobiliary stenting.



## Assessment of jaundice



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## Clinical Experience on use of TDF in treating HIV-infected patients

Myanmar Society of HIV Medicine

## Introduction

Tenofovir Disoproxil Fumarate (TDF) is a nucleotide analogue reverse-transcriptase inhibitor (NRTI), which is highly effective for treating both HIV and hepatitis B virus infections. TDF has a long intracellular half-life, allowing once-daily dosing and encouraging treatment adherence, and is commonly recommended as a first-line therapy by many HIV treatment guidelines. TDF was first approved to treat HIV infection in 2001 in US. It has been available in Myanmar since 2010 and TDF/3TC/EFV combination, as first line ART regimen was included in the National AIDS Program since 2013. In Myanmar more than 90% of HIV-infected patients who start ART are prescribed TDF-based first-line ART regimens (TDF/3TC/EFV or TDF/3TC/DTG). If people taking TDF for treatment of chronic HBV infection are to be counted, there is a significant number of people taking TDF. It was enthusiastically welcomed when first introduced, since it was believed to be a relatively safe drug, compared to its older counterparts like D4T (which can cause lipodystrophy, peripheral neuropathy) and AZT (which is commonly associated with severe anemia). But as more and more experience is gained with the use of this drug, it is being increasingly recognized that, it is not as safe as formerly thought. It is true that overall, TDF has a good safety profile but in some patients it can give rise to disabling and life-threatening complications. Renal tubular toxicity is a well-recognized complication of TDF therapy and can present with various clinical manifestations. The attending clinician may fail to recognize the presentations if not familiar with the side effects of the drug or not vigilant enough with monitoring. Since the magnitude of the complications can vary from biochemical changes, mild bone pain or muscle weakness, to death (due to acute renal failure), every clinician prescribing the drug should know its side effects and how to diagnose them.

## Pharmacology and pathogenesis

TDF is a prodrug of tenofovir (TFV). It is cleared by the kidneys through glomerular filtration and active proximal renal tubular secretion. TDF enters tubular cells from the basolateral membrane through organic anion transporters (OAT) 1 and 3 and is secreted into the tubular lumen through multi-drug resistance proteins (MRP) 2 and 4. Intracellular accumulation can occur due to increased uptake by OAT or reduced efflux from MRP (e.g., inhibition by Ritonavir). Proximal tubules reabsorb a variety of solutes (glucose, phosphate, urate, potassium, etc) across the apical membrane through sodium-mediated co-transport, which is driven by the Na<sup>+</sup> gradients generated by the activity of the basolateral adenosine triphosphatase sodium-potassium pump (Na<sup>+</sup>-K<sup>+</sup>-ATPase). Proximal tubules contain a high density of mitochondria. DNA polymerase  $\gamma$ , the enzyme responsible for replication of



mitochondrial DNA (mtDNA) is inhibited by TDF (and all other NRTI). And mitochondrial toxicity is the major mechanism of TDF-associated nephrotoxicity. The proximal tubule is intrinsically vulnerable to mitochondrial dysfunction because of limited anaerobic ATP-generating capacity. Mitochondrial injury, swelling and depletion impairs molecular transport (leading to wasting of glucose, phosphate, bicarbonate, amino acids), vitamin D activation, and urinary acidification. These effects can cause various clinical syndromes including acute/chronic renal failure, Fanconi's syndrome and osteomalacia.

### Incidence

The incidence of clinically significant renal toxicity due to TDF in randomized controlled trials done in America, Europe and Africa is quite different from the real world situation in our population. Data from 17 studies (about 9,000 patients) concluded that patients treated with TDF experienced a small but significant loss of kidney function during the course of treatment compared with controls<sup>1</sup> (mean difference in eGFRs, 3.9 mL/min; risk difference of acute renal failure, 0.7%). In a cohort study of more than 10,000 patients starting TDF treatment, increases in serum creatinine levels > 0.5 or > 2 mg/dL were observed in 2.2% and 0.6% of patients, respectively<sup>2</sup>. In a study done in 12 countries in Asia-Pacific region (2,425 patients), renal dysfunction on TDF occurred in 103 patients over 5,368 person-years of TDF use (4.2%; incidence 1.75 per 100 person-years)<sup>3</sup>. In a study done in Thailand in 2010, 19.3% of patients out of 405, had a 25% decrease in GFR after an average of 16 months of treatment<sup>4</sup>. One hospital cohort data from Specialist Hospital Mingalardon in 2019 showed that out of 8,553 patients who had ever started TDF, 457 (5.3%) needed to be switched to other regimens due to renal problem.

The incidence of Fanconi's syndrome in these studies is low<sup>2</sup> (< 0.1%). An observational study showed that 21 of 1,375 (0.85%) had osteomalacia<sup>5</sup>. Many of the OM cases are described by case series.

Incidence of acute renal failure requiring hemodialysis is rarely reported. Risk factors associated with TDF nephrotoxicity are: increased age, low body weight, pre-existing decreased renal function, and concomitant use of nephrotoxic drugs and pharmacological boosters (e.g., ritonavir or cobicistat). But TDF-associated nephrotoxicity can occur in individuals without obvious risk factors and at highly variable times after the initiation of therapy.

Although WHO allowed TDF use in children older than 3 year (8 mg/kg/d), its use in Myanmar, it is very low due to concern about bone problem in the growing age.

### Clinical presentations

Four clinical presentations of proximal tubulopathy are listed which in fact is different presentations of the same problem which differ only in degree of severity, rapidity of onset and organ preferentially affected.



**(1) Fanconi's syndrome:** It is the proximal renal tubulopathy (PRT), characterized by tubular proteinuria, amino aciduria, phosphaturia, glycosuria, and bicarbonate wasting leading to metabolic acidosis. It is the earliest presentation and is a laboratory diagnosis. If the disease progresses, it is dominated by clinical syndromes. The effect of TDF on glomerular function appears to be mild. Therefore, measuring eGFR and/or dipstick testing of urine for albuminuria is unlikely to be sufficiently sensitive to detect early nephrotoxicity. A well-equipped laboratory is needed to diagnose this condition. Better tests are Urine protein creatinine ration (Up/c) and fractional excretion of phosphate; and the best test is urinary Retinol binding protein creatinine ratio to detect early PRT. But the only easy test that can be done at ART clinics is urine dipstick which can detect glycosuria in the presence of normal blood glucose. In our practice, potassium leakage and hypokalemia is also a big problem and measurement of serum electrolyte is a useful test for monitoring and diagnosis. Patients can present with fatigue and muscle weakness, which is different from the weakness caused by osteomalacia and low vitamin D by the absence of bone or muscle pain. Patients who develop subclinical tubular dysfunction with TDF probably could be left on the drug treatment safely, but kept under regular follow-up to evaluate the longer term effects on kidney function and bone health. TDF should be stopped if significant abnormalities occur in the setting of normal eGFR or if eGFR is reduced. TDF-induced PRT seems to be reversible. If eGFR declines below < 50 mL/min, one of the following 3 approaches can be considered.

- reduction in dose of TDF (e.g., TDF/3TC given every 48 hr, but EFV or DTG maintained at original dose). This approach needs frequent visits and close monitoring, and is often not successful after a few months, since renal failure progresses.
- changing to TAF (Tenofovir alafenamide, a newer generation of TDF) which can be given until eGFR is 30 mL/min or
- changing to ABC/3TC/DTG. This is the most commonly taken action if eGFR is < 30 mL/min. Even at eGFR between 30-50 mL/min, this is the action taken at public hospitals/ART clinics where close monitoring is not feasible.

**(2) Acute renal failure:** This is the most dramatic presentation. The patient abruptly presents with some or all the full-blown pictures of ARF like oliguria/anuria, acute pulmonary oedema, uremic encephalopathy, metabolic acidosis, hyper or hypokalemia and GI bleeding. It can occur as early as a few weeks after initiation. If unrecognized and untreated, it is fatal. It can be mistaken for PCP (rapid respiration due to metabolic acidosis) or meningitis (decreased conscious level due to uremic encephalopathy), unless the astute clinician orders the creatinine and electrolytes. The drug has to be stopped immediately. It is of vital importance that anybody who first sees the patient must recognize the problem and stop the culprit drug immediately without waiting for specialist consultation. Since this is an emergency situation, 3 drugs (TDF/3TC/EFV), which is contained in one tablet, is stopped altogether. The treatment is acute renal replacement therapy like haemodialysis or peritoneal dialysis, but the availability of these services is limited. The clinical recovery



is usually very quick and the patient may need only 3 or 4 sessions of HD, but some may require 6 or 8 sessions. Nowadays, many regional and state hospitals have dialysis machines. Administrators and clinicians should not be reluctant to start acute HD to an HIV patient on the ground of infection being transmitted to others by HD machine, since many studies have proved that HIV cannot be transmitted by HD machine if the dialyser is single-used. Although the biochemical recovery (reduction of creatinine level) is slower, most patients have normal or near normal creatinine within 3 months. Some patients who do not meet criteria for acute HD recover spontaneously after cessation of the drug. Serum Cr values as high as 25 mg/dl has been seen to fall back to normal within 3 months without intervention. Three to four weeks after ARF or when serum Cr value falls around 3 mg/dl, non-TDF ART (usually ABC/3TC/ DTG at full dose) can be restarted. If even after 3 months, Cr values remain high, the dose of 3TC should be adjusted according to the eGFR (ABC and DTG are not excreted by kidneys and dose adjustment is not necessary).

**(3) Chronic renal failure:** This is seen in patients who are taking ART but failed to continue regular follow-up with their care providers, and thus Cr is not monitored for a long time. Cr creeps up gradually for years until some time when renal function is assessed for some other reasons: either a routine medical check-up, as a pre-op screening or simply due to vague symptoms like fatigue. TDF is stopped and the regimen changed accordingly. Cr value decreases but usually not back to normal level.

**(4) TDF-induced osteomalacia:** This is the least known complication and the diagnosis is often missed. Patients hopped from one specialist to another. They would consult orthopedic surgeons, rheumatologists or physiotherapists for bone and muscle pain. Usually HIV infection and ART history is not disclosed to them. As a result, a long time elapsed before the true culprit is known. It occurs more frequently in females after a variable duration on ART (usually after 2 or more years). Since the onset is insidious, patients often ascribe weakness to part and parcel of HIV infection. Patients have muscle pain, proximal myopathy and bone pain especially in the spine and hips. They find progressively difficult to do daily activities. They go out less and ART is collected by their family members, or if they do come for it, they come in wheel chairs. If anybody who is not paraplegic comes to ART clinic on wheelchair, the possibility of TDF-induced osteomalacia should come to mind immediately. Those patients with poor family support cannot visit the clinic and defaulted ART. Finally they can only move a few steps in the room and are confined to bed. In extreme circumstances, bone deformities occur, analogous to rickets of childhood vitamin deficiency, but morphologically different. The height is shortened, the upper sternum is depressed and the ribs are flared and deformed, leading to a very miserable condition. Diagnosis requires strong clinical suspicion, laboratory tests and imaging. There is phosphaturia and low serum phosphate, glycosuria, decreased vitamin D level, raised alkaline phosphate (ALP), loosers zone or multiple pseudofractures in bone X-rays. If above tests are costly, raised ALP level (usually > 500, upper limit of normal = 300) together with a compatible clinical picture, is a very useful and practical test to make



the diagnosis. TDF is substituted by ABC. If 25 (OH) vitamin D is deficient, a loading dose of e.g., 10,000 IU vitamin D daily (or 60,000 IU vitamin D weekly) for 8-10 weeks is usually given followed by maintenance with 800-2,000 IU vitamin D daily. The principal goal is to achieve a serum vitamin D level > 20 ng/mL (50 nmol/L) and to maintain normal serum PTH levels. The condition can be reversible but clinical recovery may take months or years.



**Figure 1 A. patient severely affected by TDF-induced OM. Note depression of the upper sternum**

### Prevention and monitoring

Most guidelines recommend to avoid TDF in patients with eGFR < 50 ml/min. All patients on TDF should be regularly screened for renal toxicity with Up/c every six months (more frequently in patients with risk factors), and if detected further tests for PT dysfunction should be done. European AIDS Clinical Society (EACS) recommends monitoring of serum phosphorus and ALP, in addition to Up/c and Creatinine. Alternatively, tenofovir alafenamide (TAF), a newer prodrug of TDF should be used if there is a strong indication to use TDF (like HBV co-infection). TAF is not a substrate of OAT. When compared to TDF, its concentration is 90% less in proximal tubular cells but > 4-fold higher in its target cells (i.e. lymphocytes). Accordingly, renal/bone side effects are less common while antiviral efficacy is similar or increased compared to TDF. It can be used until eGFR falls to 30 ml/min. If TDF is used in combination with atazanavir/ritonavir, more caution should be exercised as TDF concentration is increased. In patients who are to take aminoglycosides for a long term (e.g., MDR-TB patients), it is better to avoid use of TDF.

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## Glycemic Control in Patients with Diabetic Kidney Disease

### Myanmar Endocrinology & Metabolism Society

Diabetic Kidney Disease (DKD) is identified clinically by persistently high urinary albumin-to-creatinine ratio  $\geq 30$  mg/g and/or sustained reduction in eGFR  $< 60$  ml/min per  $1.73 \text{ m}^2$ . DKD typically develops after duration of 10 years in type 1 diabetes but may be present at diagnosis of type 2 diabetes. And so, screening for DKD should be performed annually for patients with type 1 DM beginning 5 years after diagnosis and annually for all patients with type 2 DM beginning at the time of diagnosis. In patients with albuminuria, the presence of diabetic retinopathy is strongly suggestive of DKD.

The preferred test for albuminuria is a urinary albumin-to-creatinine ratio performed on a spot sample, preferably in the morning. The eGFR is calculated from the serum creatinine concentration. Although the CKD-EPI equation is more accurate, particularly at eGFR levels in the normal or near-normal range, the MDRD equation is typically reported by clinical laboratories. Confirmation of albuminuria or low eGFR requires two abnormal measurements at least 3 months apart.

If features atypical of DKD are present, then other causes of kidney disease should be considered. Atypical features include sudden onset of low eGFR or rapidly decreasing eGFR, abrupt increase in albuminuria or development of nephrotic or nephritic syndrome, refractory hypertension, signs or symptoms of another systemic disease, and 30% eGFR decline within 2-3 months of initiation of a renin-angiotensin system inhibitor.

DKD can progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation and is the leading cause of ESRD. In addition, among people with type 1 or 2 diabetes, the presence of CKD markedly increases cardiovascular risk and health care costs. DKD occurs in about 20-40% of patients with diabetes.

### Glycemic Monitoring in Patients with DKD

HbA1c is recommended to monitor glycemic control in patients with diabetes and CKD. In CKD, HbA1c has limitations including underestimation or overestimation of the actual degree of glycemic control. Accuracy and precision of HbA1c measurement declines with advanced CKD (G4-G5), particularly among patients treated by dialysis, in whom HbA1c measurements have low reliability.

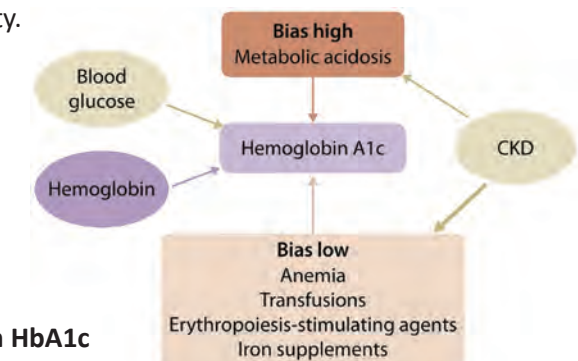


Fig (1). Effects of CKD-related factors on HbA1c

Source: Kidney International (2020) 98, S1-S115

Glycated albumin and fructosamine have been proposed as candidates for alternative long-term glycemic monitoring. These biomarkers reflect glycemia in a briefer time-frame (2-4 weeks) than HbA1c due to their shorter survival time in blood. However, the glycated albumin assay is biased by hypoalbuminemia, a common condition in patients with CKD due to protein losses in the urine, malnutrition, or peritoneal dialysis.

Advanced CKD substantially increases the risk of hypoglycemia in patients with diabetes treated by many oral agents and insulin. Daily glycemic monitoring with self-monitoring of blood glucose (SMBG) improves the safety of anti-hyperglycemic therapy by identifying fluctuations in glucose as a means to avoid hypoglycemia.

#### Self-monitoring of blood glucose (SMBG)

Self-sampling of blood via fingerstick for capillary glucose measurement using glucometers  
Since sampling is performed intermittently, episodes of hypoglycemia or hyperglycemia are often harder to detect

#### Continuous glucose monitoring (CGM)

Minimally invasive subcutaneous sensors which sample interstitial glucose at regular intervals (e.g., every 5–15 min)  
There are three categories of CGMs:

##### (a) Retrospective CGM

Glucose levels are not visible while the device is worn. Instead, a report is generated for evaluation after the CGM is removed

##### (b) Real-time CGM (rtCGM)



Refers to sensors transmitting and/or displaying the data automatically throughout the day, so that the patient can review glucose levels and adjust treatment as needed

##### (c) Intermittently scanned CGM



Also known as 'flash' CGM or FGM for short. Glucose levels can be seen while the device is worn when they are queried

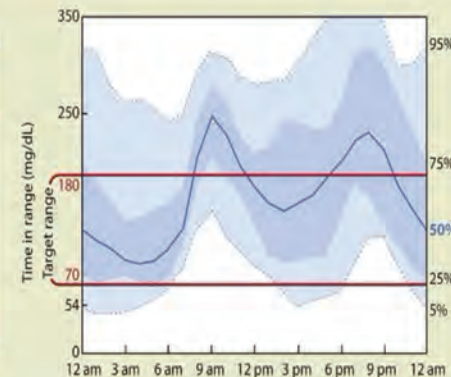
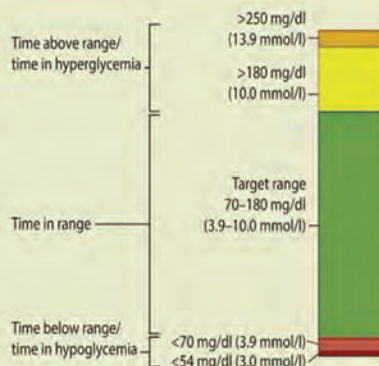
#### Glucose management indicator (GMI)

Provides a measure of average blood glucose levels calculated from CGM readings, expressed in units of A1C (%), that can be used to gauge whether clinical A1C levels are falsely high or low

#### Time in range (TIR)

This is a metric of glycemic control that assesses the percentage of CGM readings within a certain range

Commonly accepted ranges are 70–180 mg/dl (3.9–10.0 mmol/l) at >70% of readings; time per day



Source: Kidney International (2020) 98, S1-S115

Fig (2). SMBG and CGM

Continuous glucose monitoring (CGM) yield direct measurements of glucose in interstitial fluid. The glucose management indicator (GMI) is a measure of average blood glucose that is calculated from CGM and expressed in the units of HbA1c (%), facilitating interpretation of the HbA1c values. For example, if HbA1c is lower than a concurrent measure of GMI, the HbA1c can be interpreted to underestimate average blood glucose by the difference in measurements, allowing adjustment of A1c targets accordingly. GMI may be useful for patients with advanced CKD, including those treated with dialysis, for whom reliability of HbA1c is low.

Although there are burdens and expenses, daily glycemic monitoring to achieve targets while avoiding hypoglycemia is prudent.

Monitoring HbA1c twice per year is reasonable for patients with diabetes. HbA1c may be measured as often as 4 times per year if the glycemic target is not met or after a change in anti-hyperglycemic therapy.

Population	HbA1c			GMI
	Measure	Frequency	Reliability	
CKD G1–G3b	Yes	<ul style="list-style-type: none"> <li>Twice per year</li> <li>Up to 4 times per year if not achieving target or change in therapy</li> </ul>	High	Occasionally useful
CKD G4–G5 including treatment by dialysis or kidney transplant	Yes	<ul style="list-style-type: none"> <li>Twice per year</li> <li>Up to 4 times per year if not achieving target or change in therapy</li> </ul>	Low	Likely useful

Source: Kidney International (2020) 98, S1-S115

Fig (3). Frequency of HbA1c measurement and use of GMI in CKD

G1-G3b: estimated glomerular filtration rate  $\geq 30$  ml/min per  $1.73 \text{ m}^2$

G4-G5: eGFR  $< 30$  ml/min per  $1.73 \text{ m}^2$ , GMI: glucose management indicator

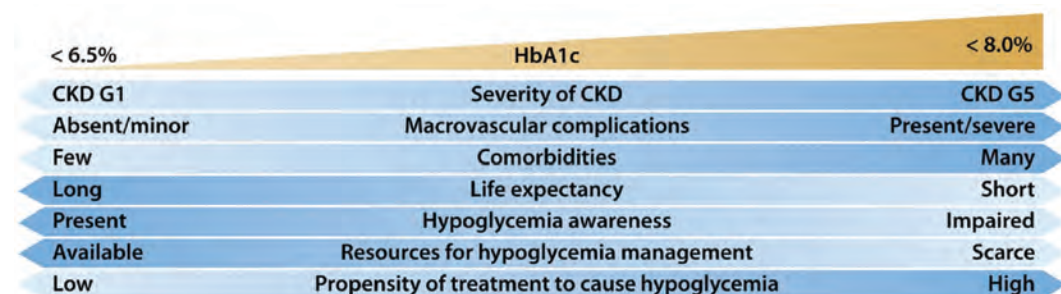
#### Glycemic Target

HbA1c targets are central to guide anti-hyperglycemic treatment. Among patients with diabetes and CKD, a U-shaped association of HbA1c with adverse health outcomes has been observed, suggesting risks with both inadequately controlled blood glucose and excessively lowered blood glucose. More-stringent glycemic control compared with less-stringent glycemic control increases risk of hypoglycemia. A flexible approach allows each patient to optimize these trade-offs, whereas a “one-size-fits-all” single HbA1c target may offer insufficient long-term organ protection for some patients and place others at undue risk of hypoglycemia.

An individualized HbA1c target ranging from  $< 6.5\%$  to  $< 8.0\%$  in patients with diabetes and CKD not treated with dialysis is recommended. For patients for whom prevention of complications is the key goal, a lower HbA1c target (e.g.,  $< 6.5\%$  or  $< 7.0\%$ ) might be



preferred. For those with multiple co-morbidities or increased burden of hypoglycemia, a higher HbA1c target (e.g.,  $< 7.5\%$  or  $< 8.0\%$ ) might be preferred.



Source: Kidney International (2020) 98, S1-S115

Fig (4). Factors guiding decisions on individual HbA1c targets

### Lifestyle interventions in patients with diabetes and CKD

Lifestyle therapy is the cornerstone of management for patients with DKD.

### Nutrition Intake

Patients with DKD should consume an individualized diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages.

KDIGO guideline recommends maintaining a protein intake of 0.8 g protein/kg (weight)/d for those with DKD not treated with dialysis. Patients treated with hemodialysis, and particularly peritoneal dialysis, should consume between 1.0 and 1.2 g protein/kg (weight)/d.

Sodium intake should be  $< 2$  g of sodium per day (or  $< 90$  mmol of sodium per day, or  $< 5$  g of sodium chloride per day) in patients with DKD.

### Physical Activity

Patients with DKD should be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. Recommendations for physical activity should consider age, presence of other co-morbidities, and access to resources. Patients should be advised to avoid sedentary behavior. For patients at higher risk of falls, health care providers should provide advice on the intensity of physical activity (low, moderate, or vigorous) and the type of exercises (aerobic vs. resistance, or both).

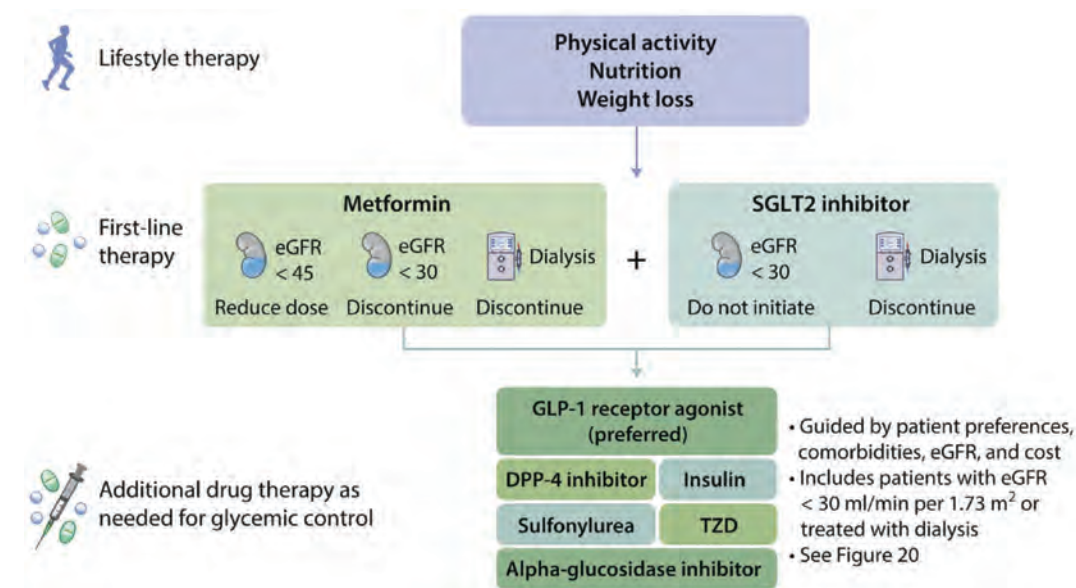
Physicians should consider advising/encouraging patients with obesity, diabetes, and CKD to lose weight, particularly patients with  $\text{eGFR} \geq 30$  ml/min per  $1.73 \text{ m}^2$ .



### Anti-hyperglycemic therapies in patients with DKD

Treatment of hyperglycemia in patients with DKD represents a major challenge, which may impose avoidance/discontinuation or dose adjustment of certain anti-hyperglycemic drugs.

Glycemic management for patients with T2D and CKD should include lifestyle therapy, first-line treatment with metformin and a sodium-glucose cotransporter-2 inhibitor (SGLT2i), and additional drug therapy as needed for glycemic control. Additional anti-hyperglycemic drugs can be added to this base drug therapy as needed to achieve glycemic targets, with GLP-1 RA generally preferred because of their demonstrated cardiovascular benefits, particularly among patients with established ASCVD, and possible kidney benefits.

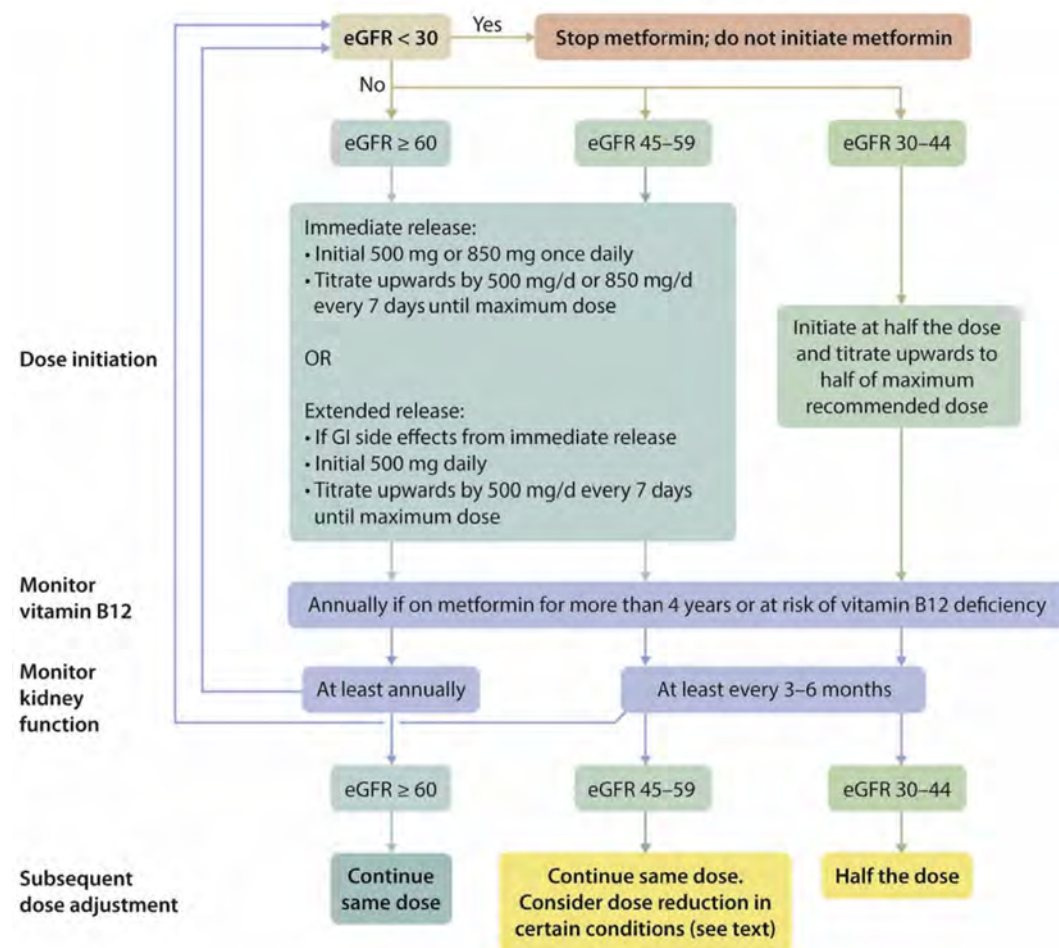


Source: Kidney International (2020) 98, S1-S115

Fig (5). Treatment algorithm for selecting anti-hyperglycemic drugs for patients with T2D and CKD ( $\text{eGFR}$ ; ml/min per  $1.73 \text{ m}^2$ )

For patients with T2D, CKD, and  $\text{eGFR} > 30$  ml/min per  $1.73 \text{ m}^2$ , not currently treated with anti-hyperglycemic drugs (i.e., “drug naïve” patients), initiate metformin first for most patients.

Metformin has been proven to be a safe, effective, and inexpensive foundation for glycemic control in T2D with modest long-term benefits for the prevention of diabetes complications.



Source: Kidney International (2020) 98, S1-S115

**Fig (6). Metformin use in patients with DKD**

Metformin should not be initiated in patients with an eGFR < 30 ml/min per 1.73 m<sup>2</sup> and it should be discontinued when eGFR is below of 30 ml/min per 1.73 m<sup>2</sup>.

SGLT2i are recommended for patients with T2D, CKD, and eGFR > 30 ml/min per 1.73 m<sup>2</sup> because of their high value on the renoprotective and cardioprotective effects clearly shown in cardiovascular and kidney outcome trials.

An SGLT2i can be added to other anti-hyperglycemic medications for patients whose glycemic targets are not currently met. Even when glycemic targets are achieved on metformin, an SGLT2i should be added in these patients for the beneficial effect on CKD progression and CVD, when education and monitoring for multiple potential adverse effects are feasible. The combination of metformin and an SGLT2i is logical because they have different mechanisms of action, and neither carries increased risk of hypoglycemia. Using low doses of both an SGLT2i and metformin may be a practical approach to manage



glycemia, receive the organ-protection benefits of an SGLT2i (which do not appear to be dose dependent), and minimize drug exposure.

For patients in whom additional glucose-lowering may increase risk for hypoglycemia (e.g., those treated with insulin or sulfonylureas and currently meeting glycemic targets), it may be necessary to stop or reduce the dose of an anti-hyperglycemic drug other than metformin to facilitate addition of an SGLT2i.

For patients with T2D, there is a small but increased risk of euglycemic diabetic ketoacidosis with SGLT2i. It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for keto-sis). If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy. For patients who initiate an SGLT2i at an eGFR > 30 ml/min per 1.73 m<sup>2</sup> and subsequently decline to an eGFR < 30 ml/min per 1.73 m<sup>2</sup>, the SGLT2i can be continued until initiation of kidney replacement therapy, in accordance with the approach studied in the CREDENCE trial.

SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients.

SGLT2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials	Dosing approved by the US FDA
Canagliflozin	100–300 mg once daily	CANVAS: eGFR ≥30 ml/min per 1.73 m <sup>2</sup> CREDENCE: eGFR 30–90 ml/min per 1.73 m <sup>2</sup>	No dose adjustment if eGFR >60 ml/min per 1.73 m <sup>2</sup> 100 mg daily if eGFR 30–59 ml/min per 1.73 m <sup>2</sup> Avoid initiation with eGFR <30 ml/min per 1.73 m <sup>2</sup> , discontinue when initiating dialysis
Dapagliflozin	5–10 mg once daily	DECLARE-TIMI 58: CrCl ≥60 ml/min DAPA-HF: eGFR ≥30 ml/min per 1.73 m <sup>2</sup> DAPA-CKD: eGFR 25–75 ml/min per 1.73 m <sup>2</sup>	No dose adjustment if eGFR ≥45 ml/min per 1.73 m <sup>2</sup> Not recommended with eGFR <45 ml/min per 1.73 m <sup>2</sup> Contraindicated with eGFR <30 ml/min per 1.73 m <sup>2</sup>
Empagliflozin	10–25 mg once daily	EMPA-REG: eGFR ≥30 ml/min per 1.73 m <sup>2</sup> EMPA-KIDNEY: eGFR 20–90 ml/min per 1.73 m <sup>2</sup> EMPEROR-Reduced: eGFR ≥20 ml/min per 1.73 m <sup>2</sup>	No dose adjustment if eGFR ≥45 ml/min per 1.73 m <sup>2</sup> Avoid use, discontinue with eGFR persistently <45 ml/min per 1.73 m <sup>2</sup>

Source: Kidney International (2020) 98, S1-S115

**Fig (7). SGLT2i with established kidney and cardiovascular benefits and dose adjustments as approved by the US FDA (take note of country-to-country variation)**

**Glucagon-like peptide-1 receptor agonists (GLP-1 RA)**

In patients with DKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, a long-acting GLP-1 RA is recommended. To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly.

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m <sup>2</sup>
Exenatide	10 µg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with CrCl >30 ml/min
Liraglutide	0.6 mg, 1.2 mg, and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 µg and 20 µg once daily	No dosage adjustment Limited data for severe CKD
Semaglutide (Injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

Source: Kidney International (2020) 98, S1-S115

**Fig (8). Dosing for available GLP-1 RA and dose modification for CKD**

Dipeptidyl peptidase 4 (DPP-4) inhibitors are becoming more popular for the treatment of hyperglycemia in patients with CKD because of their better tolerability and low risk of hypoglycemia. However, DPP-4 inhibitors have not been shown to improve kidney or cardiovascular outcomes and should not be used in combination with GLP-1 RA.

All the DPP-4 inhibitors are metabolized by the liver, though to a different extent, and are excreted by the kidney, with the exception of linagliptin, only ~ 5% of which is found in the urines. Therefore, while dosage of sitagliptin, vildagliptin, saxagliptin, and alogliptin should be reduced according to the level of eGFR, **linagliptin** requires no dose adjustment in patients with impaired renal function. However, all the DPP-4 inhibitors can be used safely in patients with renal dysfunction and, except saxagliptin, even in those on dialysis. The excellent safety profile of these agents, including the very low risk of hypoglycemia, makes them the first treatment option in elderly patients with reduced renal function and mild-to-moderate metabolic derangement who do not require specific cardiovascular protection.

**Sulfonylureas** stimulate endogenous insulin secretion by the  $\beta$ -cell in a glucose-independent manner. These drugs may potentially cause hypoglycemia, especially in high doses. Their use should be limited in patients with DKD.



Glipizide is metabolized by the liver into several inactive metabolites and its clearance and elimination half-life are not affected by a reduction in eGFR. Therefore, glipizide is the SU of choice in patients with DKD.

Gliclazide has inactive metabolites that are eliminated mainly in the urine (80%) and presents a lower risk of severe hypoglycemia than glibenclamide and glimepiride do. This drug can be considered in renal impairment if appropriate attention is paid to the dose. However, use should be avoided if the GFR falls to < 40 mL/min.

Glimepiride is metabolized by the liver into two main metabolites, one of which has hypoglycemic activity. In patients with renal impairment, these metabolites can accumulate. And so, glimepiride should be avoided or initiated conservatively at 1 mg daily in patients with reduced eGFR. Glibenclamide is contraindicated from stage 3 of CKD (eGFR < 60 mL/min).

**Meglitinide**

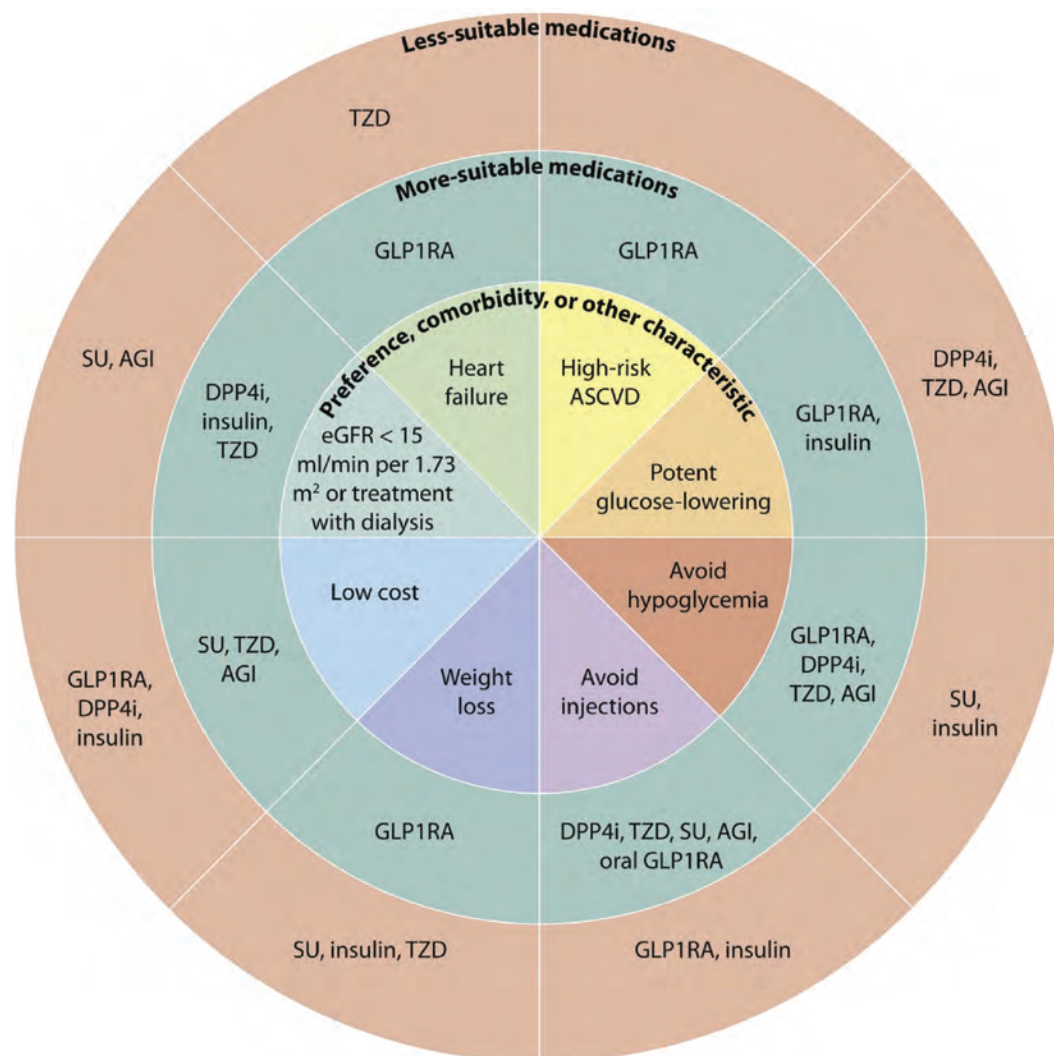
Repaglinide is a short-acting secretagogue that is also metabolized by the liver to inactive metabolites, which are excreted via the bile into the feces. Repaglinide is largely utilized across all eGFR categories, despite the increased risk of hypoglycemia. Repaglinide should be initiated conservatively at 0.5 mg and the dose should be adjusted in case of declining eGFR.

**Pioglitazone**, the only thiazolidinedione compound currently available for clinical use, activates peroxisome proliferator-activated receptor  $\gamma$ , a nuclear receptor regulating the transcription of genes involved in glucose and lipid metabolism, thus increasing insulin sensitivity. It is metabolized entirely by the liver and, hence, no dose adjustment is required according to the level of eGFR. However, caution is recommended in patients with advanced renal dysfunction, due to the increased risk of fluid retention, anemia, and bone fragility characterizing these individuals, which may be enhanced by the use of pioglitazone.

**Acarbose** is an inhibitor of  $\alpha$ -glycosidase. Acarbose should be avoided in individuals with an eGFR < 30 ml/min/1.73 m<sup>2</sup>.

**Insulin** treatment with both human preparations and insulin analogs is safe in all eGFR categories, though it may be necessary to reduce the dosage in patients with advanced renal dysfunction, especially for human insulins, which are metabolized by insulinase in both the liver and kidney. The reduction in insulin clearance has been estimated to range between 10% and 20% in patients with moderate-to-severe CKD.

Patient preferences, co-morbidities, eGFR, and cost should guide selection of additional drugs to manage glycemia. All anti-hyperglycemic medications should be selected and dosed according to eGFR.



Source: Kidney International (2020) 98, S1-S115

**Fig (9). Patient factors influencing the selection of glucose-lowering drugs other than SGLT2i and metformin in T2D and CKD**

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## New normal management of colorectal cancer in Covid era

### Myanmar Colorectal Surgeon Society (MCRSS)

Covid-19 is the global pandemic health problem which is causing a huge mortality around the world at the moment. Therefore, every country tries to control Covid outbreak by setting emergency plans which are suitable for each one. Dealing with Covid causes many adverse impacts, not only in health care sectors but also in social and economic sectors, globally. In Covid era, the burden on our health care providers in giving care for public is doubled in the view of Covid and Non-covid patients. Although Covid-19 contagiousness is important to be controlled, Non-covid patient are not to be neglected & should receive best possible care. However, there are delays for Non-covid patients in getting diagnosis, staging and treatment of their diseases.

Colorectal cancer (CRC) is the third most common internal malignancy and the second leading cause of carcinoma death (Gordon PH, 2019). It is a well-known fact that CRC are more common in elderly patients who may also have co-morbidities such as diabetes, hypertension, ischemic heart, and other immune suppressive conditions, like autoimmune disease, tuberculosis. They are not only prone to get Covid-19 but also likely to have serious unfortunate events if it happens. But on the other hand, there is also a high risk of cancer progression and death if not appropriately & timely treated. Therefore, great care should be undertaken on managing CRC patient, as well as health care personal when tackling with them.

### 1. Recommendation for medical checkup and screening

Although there is no national program for colorectal cancer screening in our country, some health-conscious people are doing medical checkup regularly. Basic medical checkup package does not include colorectal cancer screening. But some people may request to have colonoscopic examination in their medical checkup. In this situation, we should filter the patient step by step because colonoscopy is invasive procedure with risk of transmission of Covid-19 infection. It is well known that virus exists in the gastrointestinal tract and faeces besides respiratory tract (Zhang H, *et al.*, 2020). The study done by Xu Y, *et al* (2020) also found that virus RNA was found for prolonged duration in rectal swab even after clearance from respiratory tract.

Clinical examination is the most fundamental step so that it is recommended to do first with full personal protection. The next step is to order fecal occult blood test (FOBT). FOBT positive with clinically suspicious cases should only proceed to colonoscopic examination with full personal protective measure.

## 2. Recommendation for outpatient clinic

Covid-19 is the disease of high infectivity in crowded community, so that it is essential to reduce both exposure time and frequency of patient's visit to hospital. To control the spread of Covid-19 is important, but at the same time we need to give effective management for these patients. There will be two integral parts in outpatient management; administrative and clinical.

Administration is important part in outpatient management and its focus should be to reduce the total number of patients in OPD at a specific time, that is the patients and caregivers should not outnumber in the available space so that enough social distancing is achieved. Their other aim should be in minimizing the frequency of patients' visit to OPD. In order to do so, tele/online booking system should be incorporated.

In clinical part, only decision makers should see the patient. At the very first visit, the patient should be thoroughly examined and their findings recorded properly. Subsequent visit should be done via online consultation if no intervention is needed and if it is merely to review the results. Preparation for operation should also be done completely as outpatient. If some urgent matter (e.g., obstruction, bleeding etc.) is identified, the patient should be referred to emergency department for proper management. Patient should be admitted to hospital either only when they are ready to undergo operation or when it is an emergency.

## 3. Recommendations for emergency surgery

Emergency conditions of CRC are obstruction, bleeding and perforation of bowels. European Society for Medical Oncology (ESMO) recommends to prioritize the CRC patient and treat accordingly.

### Priorities for colorectal cancer (CRC): surgical oncology

#### High Priority

- ❖ Radiologically confirmed intestinal occlusion in newly diagnosed patients.
- ❖ Bowel perforation, peritonitis.
- ❖ Massive gastrointestinal bleeding.
- ❖ Postsurgical complications (perforation, anastomotic leak).
- ❖ Post-colonoscopy complications (perforation, bleeding).
- ❖ Post-interventional procedure such as liver and lung biopsies (perforation, organ damage, peritonitis, abscess, massive bleeding).
- ❖ Bone fractures with spinal cord compression due to metastasis.

#### Medium priority

- ❖ Clinical stage I, II and III colon cancer.
- ❖ Clinical stage I rectal cancer.
- ❖ Clinical stage II-III rectal cancer after neoadjuvant treatment.
- ❖ Resection of metastasis in oligometastatic patients with curative intent as front line or after neoadjuvant treatment.

#### Low priority

- ❖ Early-stage rectal cancer after complete radiological response following radiotherapy (watch-and-wait strategy).
- ❖ Prophylactic surgery - for familiar cases of CRC.
- ❖ Biopsy of metastatic lesions for molecular analysis for late-line treatments. Start last-line options and wait until the end of the COVID-19 pandemic for such evaluation. When possible, use liquid biopsies for such analyses rather than biopsies.

Emergency conditions are at high priority to do surgery even in Covid-era. It should be done by experienced surgeon with full personal protective equipment, as damage control surgery. ESMO also does not recommend bowel reconstruction in case of emergency CRC surgery. Some authors suggest that in case of obstruction due to CRC, the patient should undergo temporary stenting as a bridge to surgery (The Association of Coloproctology of Great Britain and Ireland, 2020). As for our country, stenting for obstructed bowel is not available and it is not feasible to do. Therefore, we have to proceed straightly into surgery in time. Any delay in emergency surgery may result in poor outcome.

## 4. Recommendations for elective surgery

Surgery is the only hope of cure for CRC and the time window to achieve this is also limited. If treatment is delayed in early stages, CRC may progress to un-curable stage and the advanced stages may need to be given neoadjuvant therapy so as to be resectable. Although there is some limitation in Covid-era, treatment should therefore, not be delayed in CRC patient. Elective surgery should be carried out according to local Covid protocol.

Definitive surgery of early and stage II and III CRC are recommended to perform. After surgery, adjuvant chemotherapy should be followed according to oncologic guideline. Advanced stage should be started with neoadjuvant therapy (Chemo ± radiotherapy), followed by surgery as usual. Chemo and radio therapy regime should be adjusted as oncologic guideline in Covid era (eg. Long course RT switch to short). But there should not be any delay in surgery for patient after downstaging. Right surgery at right time is important.



In routine practice, there will be two approaches; open and laparoscopic. Open approach is preferred in Covid era. There may be aerosol transmission in laparoscopic approach, therefore it should be avoided as much as possible. The Association of Coloproctology of Great Britain and Ireland also recommend to reduce the theater time. Consultant is proposed to operate the elective CRC cases and if possible, two consultants should be operating to reduce theatre time.

### 5. Recommendation for postoperative period

Postop care is not much different from usual time. But there should be great care, given that the patient may suffer covid at any time. Early mobilization, respiratory exercises, and ERAS protocol should be followed to get better recovery and shorten the hospital stay.

### Conclusion

Covid-19 will be around for certain period of time and we need to adapt to live with Covid. Social distancing, shortening the contact time, caring the patient with PPE and changing treatment strategy for patient without delay should be practiced. Though it is true that Covid infection is threatening everyone's life, Non-Covid people especially cancer patients are also endangered from their underlying progressive disease during Covid era. Therefore, they should not be forgotten in this chaotic period and should receive the best possible care.

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## Cervical lymphadenopathy

Myanmar ORL, Head and Neck Society

### Introduction

Enlarged lymph node or nodes in neck (cervical lymphadenopathy) is relatively common but can encompass a large range of potential pathologies. The role of clinician is to identify the patient with malignant disease with a minimum of delay. In most cases (if not all), primary management is critical towards a good outcome.

### Anatomical knowledge

First of all, it is important to differentiate the enlarged lymph node from other neck masses.

To consider differential diagnosis, the location of a neck mass is important. So, it is essential to know the anatomy.

### Triangles of the neck

The neck can be divided into anterior and posterior triangles by sternocleidomastoid muscle and each is subdivided into smaller triangles by the digastric and omohyoid muscle. Distribution of neck masses according to neck triangles are shown below.

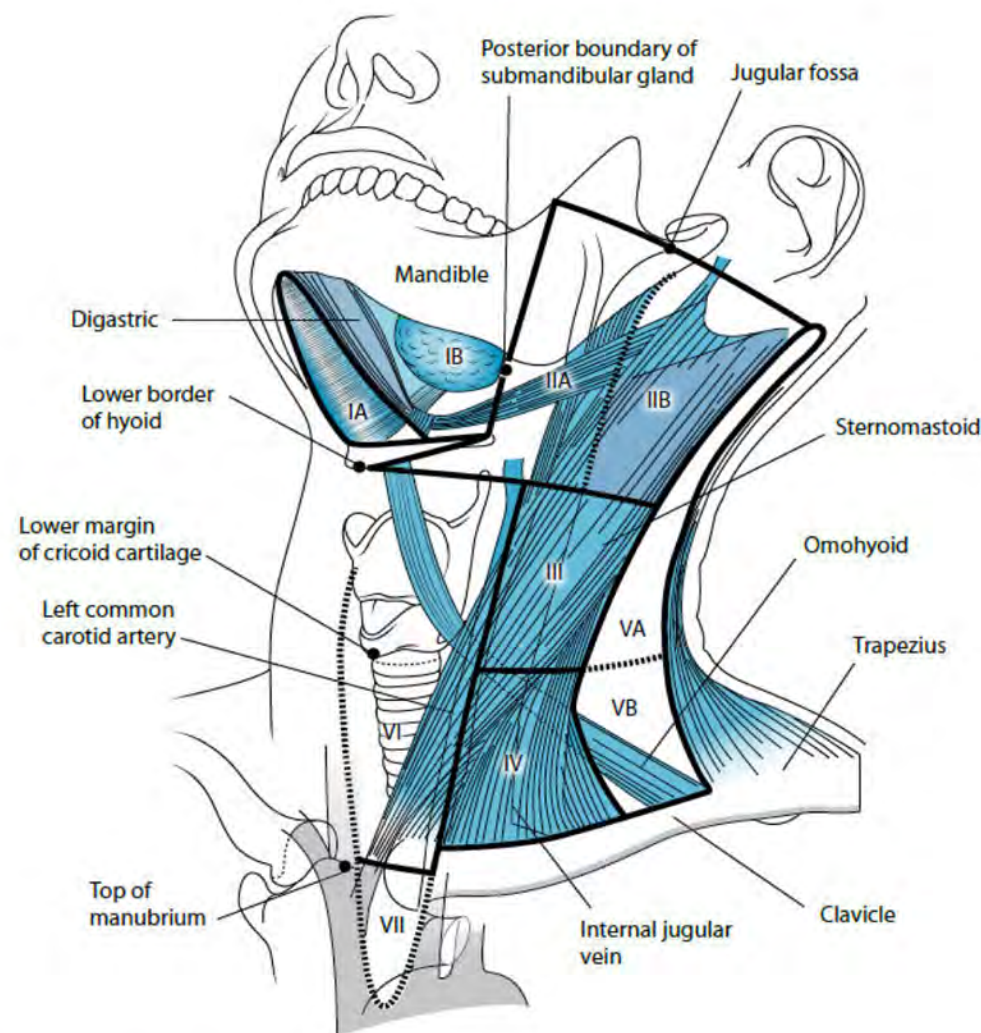
### Distribution of diseases categorized by location

Midline (Anterior neck)	Anterior triangle (Lateral neck)	Posterior triangle
<b>Congenital</b>		
Thyroglossal duct cyst	Branchial cyst	Lymphangioma
Dermoid	Thymic cyst	
<b>Inflammatory</b>		
Adenitis	Adenitis	Adenitis
- Bacterial	- Bacterial	- Bacterial
- Viral	- Viral	- Viral
- Granulomatous	- Granulomatous	- Granulomatous
<b>Neoplastic</b>		
Thyroid	Lymphoma	Lymphoma
Lymphoma	Primary salivary	
	Malignant adenopathy	Malignant adenopathy
	- Mucosal	- cutaneous
	- Cutaneous	- nasopharynx
	- Salivary	
	- thyroid	
	Primary vascular	Supraclavicular fossa
	- paragangliomas	- breast
		- lung
		- gastrointestinal tract
		- genitourinary tract



## Classification of cervical Lymph node groups

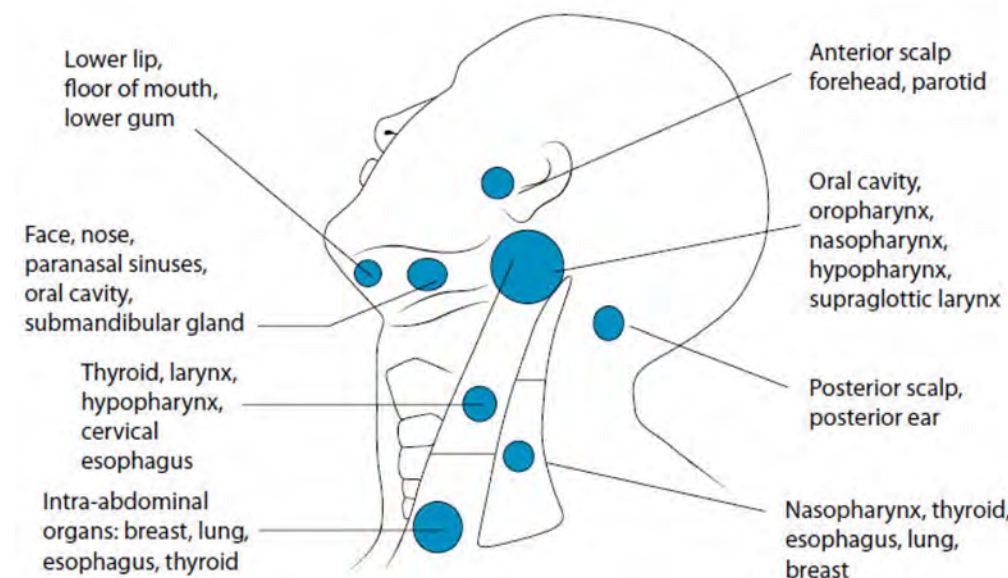
There are approximately 300 lymph nodes in head and neck region. They get drainage from structures of head and neck. The lymphatic drainage patterns are relatively constant and predictable. The American Academy of Otolaryngology Head and Neck Surgeons (AAO-HNS) developed a classification for cervical lymph node. Lymph nodes groups and anatomical boundaries are shown below.



### Levels of the neck.

### Drainage area of cervical lymph nodes groups

Knowledge of lymphatic drainage pattern is important. It can be predicted where is the primary lesion responsible for enlarge lymph node. These drainage sites related to enlarged lymph node should be carefully examine for any infection, inflammation or tumor.



Demonstration of the echelon node drainage for different potential primary tumour sites.

### Clinical feature

#### History

History is key to determining a differential diagnosis and properly investigating the patient.

#### Age

The patient's age is the prime consideration in the diagnosis. Three main groups should be considered: pediatric (< 15 years), young adult (16-40 years), and late adult (> 40 years). Order of occurrence in pediatric patients are inflammatory followed by congenital/developmental and finally neoplastic. The frequency of distribution is similar in the young adult group except the rate of neoplasm increases and the rate of congenital decreases. The first consideration in the late adult group always should be neoplasm. (Table. 2)

Table 2. Distribution of disease categories by age in order of frequency

Less than 15 years	16-40 years	More than 40 years
Inflammatory	Inflammatory	Neoplastic - benign/malignant
Congenital/developmental	Congenital/developmental	Inflammatory
Neoplastic - benign/malignant	Neoplastic - benign/malignant	Congenital/developmental

**Duration**

Duration of days may be considered infection or inflammation cause. Weeks or months suggest chronic infection (tuberculosis), chronic inflammation or neoplasia. In case of years has less chance to be a malignancy unless there is recent change.

**Progress**

Progression of size over 2 cm per month increase the likelihood of malignancy. Rapid growth over one or two weeks should concern of infection or inflammatory cause, but there is some risk of high-grade lymphoma or poorly differentiated malignancy.

**Associated symptoms*****Pain***

Malignant neck lumps are often painless but can cause referred pain. Infective lymphadenopathy is mostly painful. Taking history of upper aerodigestive tract symptoms of malignancy is important.

***Dysphagia***

It may suggestive malignant tumor involving the pharynx (mostly hypopharynx). Progressive dysphagia (i.e., first solid and progress to semisolid and liquid) is alarming symptom. Onset is usually insidious over months.

***Odynophagia (painful swallowing), sore throat, otalgia***

Acute inflammatory conditions like upper respiratory tract infections may manifest with these symptoms with lymph adenopathy.

***Change of voice or dysphonia***

In case of change of voice for more than two weeks especially in adult male raise the suspicion of tumor in the larynx.

***Skin and scalp lesion***

Infection or tumor of the skin of neck and scalp may be responsible or lymph node enlargement.

***Ulcer or lesion in the mouth/tongue***

Non-healing ulcer in oral cavity with cervical lymphadenopathy may be a malignant lesion.

***Nasal obstruction, Epistaxis/Blood stain mucus***

Lesion in nasopharynx and nose may present with nasal obstruction and blood stain mucus with cervical lymphadenopathy even in early stage.

***Diplopia and numbness of the cheek, Reduced hearing***

Nasopharyngeal carcinoma often causes palsy of 6<sup>th</sup> and 5<sup>th</sup> cranial nerve palsy resulting in diplopia and numbness in cheek. It may also cause eustachian tube dysfunction and otitis media with effusion.

**Constitutional symptoms**

These symptoms (fever, night sweat etc.) are suggestive of systemic disease or lymphoma.

**Risk factors**

- Smoking
- Alcohol drinking
- Previous head and neck cancer
- Immunosuppression

**Examination****Examination of a lump**

It includes site, size, shape, tenderness, consistency, mobility/fixation, skin changes.

**Features of neck lumps on examination that raise suspicion for malignancy**

Less suspicious	Suspicious
Small	Large
Soft/rubbery	Hard
Mobile	Fixed
Single	Multiple
No skin changes	Skin changes/breakdown
No neurology	Weak shoulder/face/ voice/tongue

**Lymphadenitis, chronic**

Young adult with no detectable primary lesion in neck = inflammatory cause

**CA PNS**

with secondary neck gland

**Bilateral L/N Enlargement**

An old male patient with lymph node enlargement must definitely undergo examination for a primary lesion in the head and neck region at the very least

**Examination of other neck nodes level**

It is important to systematic examination of neck looking for present of any other neck lump or enlarged lymph node. In TB lymphadenitis there may be more palpable matted lymph nodes nearby.

**Looking for generalized lymphadenopathy and abdominal examination**

Lymphoma may present with other enlarged lymph nodes in inguinal or axillary regions.

**Differential Diagnosis**

Differential Diagnosis for enlarged cervical lymph nodes includes:

**Infectious** (bacterial, viral, fungal, parasitic)

**Granulomatous** (TB, atypical mycobacteria, cat scratch)

**Neoplastic**

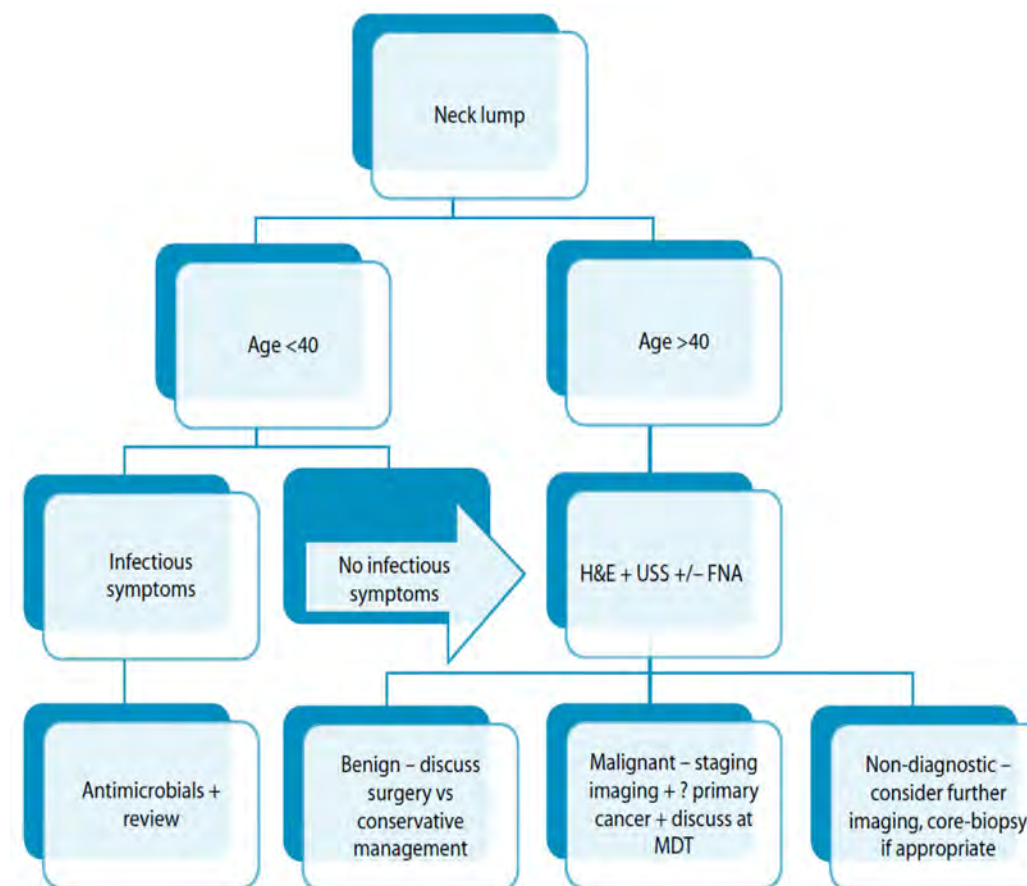
**Primary** - lymphoma

**Secondary**

- Metastatic carcinoma from lesion of upper aerodigestive tract and skin
- Metastatic thyroid and salivary gland cancer
- Metastasis from infra-clavicular primary cancer (lung, GI tract)

**Management**

Following history and examination, it may be apparent if the etiology of the neck lump is infective. In pediatric and young adult patients with a short history, a trial or observation and appropriate antimicrobials up to 2 weeks for improvement may be the most appropriate initial step. If the cause seems to be malignant (more the 40-year-old, risk factors + and firm node), refer to specialist center for further work up.



Flow Chart of work up of cervical lymphadenopathy (H & N - head and neck examination, USS/FNA - Ultrasound guided FNAC, MDT-multi-disciplinary team)

**Investigations**

After referral to specialist centers, following investigation can be done for further investigation.

- Complete upper aerodigestive examination (rigid and flexible nasoscopy/pharyngo-laryngoscope/bronchoscope) to look for primary lesion
- Panendoscopy and biopsy under GA for full survey of upper aerodigestive tract (especially in cases of metastatic neck node with unknown primary)
- USG guided Fine Needle Aspiration cytology (FNAC)



- Core biopsy
- Open lymph node biopsy is last court of appeal and should be done only when other previous investigation fails to yield a diagnosis. Excisional biopsy is better than incisional biopsy in such circumstance.
- Imaging
  - o CT scan
  - o MRI
  - o PET CT scan

### Conclusion

Cervical lymphadenopathy can be caused by infection, inflammation or malignancy. It is important to diagnose and manage the malignant case with minimal delay. Proper history taking and physical examination with background knowledge are keys to proper diagnosis and sound management. If there is any doubt, do not hesitate to specialist centers.

### References

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