CHAPTER 1
ALIMENTARY TRACT

1.1 GASTROINTESTINAL DISORDERS

1.1.1 BOWEL PREPARATIONS

DESCRIPTION
Bowel preparation is essential for colonoscopy. LoE:IIa[i]

GENERAL MEASURES
Health care professionals should provide both oral and written patient education instructions and emphasise the importance of adherence to the bowel preparation.

MEDICINE TREATMENT
Start bowel preparation as a split-dose regimen the day before the scheduled procedure: half the dose the night before and half the dose on the day of colonoscopy.
Commence a low residue diet the day before.

Preparations containing ingredients such as polyethylene glycol (PEG) and sodium sulphate are adequate for bowel cleansing. LoE:II[ii]

- PEG/sodium sulphate oral, solution:
  - Prescribe 2 litres the night before the procedure and 2 litres the following morning, two hours prior to the procedure. LoE:I[iii]

Note:
Routine use of adjunctive agents (e.g. bisacodyl, senna, prokinetics) for bowel cleansing before colonoscopy is not recommended. LoE:III[iv]

1.1.2 DIVERTICULOSIS
K57.0-5/K57.8-9

DESCRIPTION
Colonic diverticulosis becomes increasingly common with age. Acute diverticulitis is suspected in patients with lower abdominal pain (typically in the left lower quadrant). The pain is usually constant and is often present for several days prior to presentation. Nausea and vomiting are often present due to a bowel obstruction or an ileus as a result of peritoneal irritation. This may be associated with changes in bowel habits.

Diverticulosis can be complicated by haemorrhage or diverticulitis. Acute diverticulitis is inflammation of diverticulae and may, uncommonly, be

accompanied by polymicrobial infection. Acute diverticulitis is defined as complicated in the presence of bowel obstruction, abscess, fistula, or perforation.

GENERAL MEASURES
Increase dietary fibre intake.

MEDICINE TREATMENT
Not all patients require antibiotics. If antibiotic treatment is required, the total duration is ten days depending on clinical response.

Uncomplicated diverticulitis:
- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly.

If unable to tolerate oral therapy: *LoE:III[v]*
- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly.
  - Switch to oral therapy once able to tolerate.

REFERRAL
» Acute diverticulitis with clinical deterioration or failure to improve on medical therapy.
» Peritonitis.
» Complicated diverticulitis (to a centre which can perform colonic surgery).
» Massive haemorrhage.

1.1.3 GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) AND DYSPEPSIA
K21.0/K21.9/K22.7/K30

DESCRIPTION
GORD is a disorder which develops as a consequence of the reflux of gastric and duodenal contents into the oesophagus. It is usually characterised by heartburn and regurgitation.

Dyspepsia is the sensation of epigastric discomfort. It may be a feature of potentially severe diseases such as peptic ulcer disease or gastric cancer. It may also be a symptom of *H. pylori* gastritis or NSAID gastritis.

Intermittent indigestion, heartburn or dyspepsia may be associated with:
» use of NSAIDs e.g. aspirin, ibuprofen, pain powders.
» spicy food, alcohol, carbonated drinks.
» smoking.

Complications that may develop in severe GORD are strictures, ulceration, Barrett's oesophagus and adenocarcinoma of the oesophagus. Two thirds of patients have a normal endoscopy which is termed non-erosive reflux disease

(NERD) or non-ulcer dyspepsia (NUD) depending on the predominant symptom.

GENERAL MEASURES

LoE:IIIb[vi]

» Stop smoking.
» Limit alcohol intake.
» Eat small frequent meals.
» Avoid late night meals.
» Avoid fatty meals.
» Avoid carbonated beverages.
» Lose weight if overweight.
» Sleep with upper body elevated.
» Sleep on the left side.
» Avoid excessive exercise.
» Stop the use of potential ulcerogenic medicines, e.g. NSAIDs.
» If pale, check haemoglobin, and refer if anaemic.

All patients with alarm symptoms, i.e. weight loss, haematemesis or melaena, dysphagia, or anaemia, chest pain, or patients older than 60 years of age with new onset dyspepsia should have an endoscopy.

LoE:IVb[vii]

MEDICINE TREATMENT

New onset symptoms

Empiric therapy with a proton pump inhibitor (PPI) may be initiated **in the absence of alarm symptoms** (see referral section). Improvement of symptoms confirms acid-related disease.

- PPI, e.g.: LoE:I[viii]
- Pantoprazole, oral, 40 mg daily for 4 weeks. LoE:I[ix]
  - Ensure adherence to promote healing.

Recurrence of symptoms

<u>After endoscopic confirmation of disease:</u>

- PPI, e.g.:
- Pantoprazole, oral, 40 mg daily.
  - Decrease dose of PPI after 4 weeks, e.g: pantoprazole, oral, 20 mg daily except for severe endoscopic GORD (Grade C or D LA classification) and Barret's oesophagus or specific advice from the endoscopist.

Barrett's oesophagus K22.7

- Restart PPI, e.g.:
- Pantoprazole, oral, 40 mg daily.

<u>Note:</u>

» Patients with Barrett's oesophagus usually need maintenance PPI therapy.
» There is no convincing evidence that long-term treatment of Barrett's oesophagus with PPIs reduces dysplasia or progression to malignancy.

REFERRAL

Discuss the following with a specialist:

» young patients who are PPI dependent and will require life-long therapy;
» patients unable to take PPIs;
» patients requiring high doses of PPIs;
» patients with large hiatus hernias and “volume reflux”;
» a rolling hiatus hernia with obstructive symptoms – requires surgery;
» All patients with alarm symptoms:
  – Evidence of gastrointestinal bleeding,
  – Iron deficiency anaemia,
  – Anorexia,
  – Unexplained weight loss,
  – Dysphagia,
  – Odynophagia (painful swallowing),
  – Persistent vomiting, haematemesis, and/or melaena
  – Gastrointestinal cancer in a first-degree relative.

1.1.4 HIATUS HERNIA

K44.0/K44.1/K44.9

GENERAL MEASURES

Manage GORD. See Section 1.1.3: Gastro-Oesophageal Reflux Disease (GORD) and dyspepsia.

1.1.5 INFLAMMATORY BOWEL DISEASE

K50.0-1/K50.8-9/K51.0-5/K51.8-9/K52.0-3/K52.8-9

DESCRIPTION

Inflammatory bowel disease is a chronic inflammatory disorder of the gastrointestinal tract that includes both Crohn’s disease (CD) and ulcerative colitis. Abdominal pain, rectal bleeding, diarrhoea and weight loss characterise both CD and ulcerative colitis.

REFERRAL

Discuss all patients with a potential diagnosis of Crohn’s disease or ulcerative colitis with a specialist.

1.1.6 PANCREATITIS, ACUTE

K85.0-3/K85.8-9

DESCRIPTION

Acute inflammatory condition of the pancreas.

Acute pancreatitis is based on the fulfilment of ‘2 out of 3’ of the following criteria:

» clinical (upper abdominal pain),

» laboratory (serum amylase or lipase >3x upper limit of normal), and/or
» imaging (CT, MRI, ultrasonography) criteria.

Intense local inflammation results in pain, and local as well as systemic, complications. Disseminated intravascular coagulopathy (DIC), metabolic derangements and shock may occur.
Measurement of renal function and electrolytes measurements (including calcium) can be used to determine severity.

GENERAL MEASURES

» Parenteral fluid replacement to correct metabolic and electrolyte disturbances.
» Parenteral nutrition is associated with adverse outcomes and should only be considered in patients that cannot receive or tolerate nasogastric or enteral nutrition.
» Drainage of abscess/pseudocyst, if required.

MEDICINE TREATMENT

Pain:

- Morphine, IV, to a total maximum dose of 10 mg (See Appendix II, for individual dosing and monitoring for response and toxicity).

Acute symptomatic hypocalcaemia: E83.5

- Calcium gluconate 10%, IV infusion, 10 mL as a bolus over 10 minutes.
  - Follow with 60–120 mL diluted in 1 L sodium chloride 0.9%, administered over 12–24 hours. *LoE:III*
  - Monitor serum calcium at least 12 hourly.

<u>If serum magnesium <0.5 mmol/L:</u>
ADD

- Magnesium sulfate, IV infusion, 25–50 mmol in 12–24 hours.
  - 1 mL magnesium sulfate 50% = 2 mmol magnesium.

Antimicrobial therapy
Routine administration of prophylactic antibiotics are not necessary.

<u>For infected necrosis of the pancreas:</u>
Broad spectrum IV antibiotics: *LoE:III*[x]

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly for 10 days, depending on clinical response.

REFERRAL

Severe complications, e.g. necrosis; haemorrhagic or systemic complications; or infective pancreatitis.

1.1.7 PANCREATITIS, CHRONIC

K86.0-3/K86.8-9

DESCRIPTION

Chronic inflammatory condition of the pancreas with severe abdominal pain, which results in functional and structural damage. In most patients, this is a chronic, progressive disease that leads to exocrine and/or endocrine insufficiency.

GENERAL MEASURES

» Abstinence from alcohol reduces abdominal pain in the early stages of the disease.
» Stop smoking.
» Small frequent meals and restricted fat intake reduces pancreatic secretion and pain.
» When weight loss is not responding to exogenous enzymes and diet, consider supplementation with medium chain triglycerides.
» There is a risk of developing cancer of the pancreas. Consider this in patients who develop worsening pain, new onset diabetes or deterioration in exocrine function.
» Dietary advice by dietician.

MEDICINE TREATMENT

Treatment is aimed at:
» pain,
» exocrine dysfunction (malabsorption, and diarrhoea),
» endocrine function. See section 8.5.2: Type 1 Diabetes mellitus.

Analgesia

See Section 26.1: Pain, chronic.

Note: Pancreatic enzymes may reduce pain by negative feedback on pancreatic secretion.

Malabsorption

Supplementation of fat-soluble vitamins may be indicated.

- Pancreatic enzyme replacement e.g. Lipase, oral, equivalent to lipase 30 000 units per day, in divided doses with meals and/or snacks.
  - Titrate pancreatic enzyme replacement therapy until symptom control has been achieved.

REFFERAL

» Presence of pseudocyst for surgical intervention.
» Autoimmune chronic pancreatitis.

1.1.8 PEPTIC ULCER

K25.0-7/K25.9/K26.0-7/K26.9/K27.0-7/K27.9

DESCRIPTION

Ulcer in the stomach mucosa (gastric ulcer: GU) or first few centimetres of the duodenum (duodenal ulcer: DU), which penetrates into, or through the muscularis mucosa. Diagnosis is made after endoscopy as all GUs require biopsy to exclude malignancy.

GENERAL MEASURES

» Advise patient to avoid ulcerogenic medications, e.g. NSAIDs.
» Advise patient to stop smoking and drinking alcohol.
» Dietary advice by dietician.
» Patients with GUs and complicated DUs, those that have bled, perforated or are recurrent, must be rescoped at appropriate intervals until the ulcer has healed. *H. pylori* can be assessed at scope by rapid urease testing (RUT) or biopsy.

MEDICINE TREATMENT

***H. pylori* positive:**

The vast majority of GUs and DUs are associated with *H. pylori* infection and eradication therapy is indicated if infection is present. This will greatly reduce the rate of recurrent ulceration. Empiric eradication of *H. pylori* **is not recommended**.

H. pylori eradication: K25.0-7/K25.9/K26.0-7/K26.9/K27.0-7/K27.9 + (B98.0)

- Amoxicillin, oral, 1 g 12 hourly for 14 days. *LoE:Ib*[xi]

OR

For severe penicillin allergy: (Z88.0)

- Azithromycin, oral, 500 mg daily for 3 days.

AND

- Metronidazole, oral, 400 mg 12 hourly for 14 days.

Proton pump inhibitors (PPIs):

- PPI, e.g.:
- Pantoprazole, oral, 40 mg 12 hourly for 14 days.

Continue with PPI therapy as follows: *LoE:IIIb*[xii]

- PPI, e.g.:
- Pantoprazole, oral, 40 mg daily.
  - Duodenal ulcer: for up to 2 weeks
  - Gastric ulcer: for up to 6 weeks

***H. pylori* negative:**
» These are usually a consequence of NSAID use.
» Stop NSAID until ulcer has healed.
» If patient is unable to stop NSAID, refer to specialist for guidance.

- PPI, e.g.:
- Pantoprazole, oral, 40 mg daily.
  - Duodenal ulcer: for up to 4 weeks
  - Gastric ulcer: for up to 8 weeks.

LoE:IIIb[xiii]

Resistant disease
» Ulcer not healing.
» High-risk patients, i.e. poor surgical risk and the elderly or concomitant disease.

Maintenance therapy:

LoE:III[xiv]

- PPIs, e.g.:
- Pantoprazole, oral, 40 mg daily. Specialist initiated.

REFERRAL
» Failure of *H. pylori* eradication: Discuss with specialist.

1.2 HEPATIC DISORDERS

DESCRIPTION
Hepatitis (inflammation of the liver) may be infectious (caused by viral, bacterial, fungal, and parasitic organisms) or non-infectious (triggered by alcohol, drugs, autoimmune diseases, and metabolic diseases).

Causes of hepatitis includes idiosyncratic drug reactions, viral hepatitis (A, B, C, D, E), alcoholic hepatitis, non-alcoholic fatty liver disease, autoimmune hepatitis, Wilson's disease, ischaemic hepatopathy, Budd-Chiari syndrome, veno-occlusive disease, acute fatty liver of pregnancy/HELLP syndrome, malignant infiltration, partial hepatectomy, toxin exposure, including mushroom poisoning, sepsis, heat stroke or haemophagocytic lymphohistiocytosis.

1.2.1 HEPATITIS, NON-VIRAL
K70.1/K71.0-9/K73.0-2/K73.8-9/K75.4
* Notifiable medical condition if caused by agricultural chemicals or insecticides.

DESCRIPTION
Any form of hepatitis not caused by the common hepatotropic viruses.

Liver biopsy is indicated if hepatitis persists or diagnosis is unclear.

GENERAL MEASURES

» Diet: If no hepatic encephalopathy, then normal protein intake is appropriate. With clinical monitoring of hepatic encephalopathy, maintain 1 to 1.5 g/kg daily protein intake.
» Avoid alcohol and other hepatotoxic agents.
» Monitor blood glucose regularly given potential risk of hypoglycaemia.

MEDICINE TREATMENT

If the patient is jaundiced with a prolonged INR (INR>2)

- Vitamin K1, IV, 10 mg
  - Administer as a slow IV injection.
  - Do not dilute or mix with other injectables.

LoE:IVb

If the patient is bleeding, give

LoE:IIb[xv]

- Lyophilised plasma, IV, 15mL/kg over 20-30 minutes.

OR

- Fresh Frozen Plasma, IV, 15mL/kg over 20-30 minutes.

AND

Discuss further management with a specialist.

Hepatitis due to infections

Antibiotic therapy based on culture, serology or suspected aetiology e.g. leptospirosis.

Alcohol-induced hepatitis

- Thiamine, oral, 300 mg daily.

Other vitamins if indicated.

Drug-induced hepatitis

Stop all potentially hepatotoxic medication immediately, in consultation with a specialist.

Auto-immune hepatitis K75.4

Patients with persistent hepatitis, negative viral markers and no hepatotoxins. Biopsy and/or various parameters are required to make the diagnosis.

<u>If autoimmune hepatitis:</u>

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 0.5 mg/kg daily.
  - Taper dose to a suitable maintenance dose. (Refer to Appendix II for an example of a dose reduction regimen).

AND (in consultation with gastroenterologist or hepatologist)

- Azathioprine, oral, 0.5 mg/kg daily, titrated up to 1 mg/kg daily depending on response and WCC.

REFERRAL
» Where patients cannot be managed locally or biopsy cannot be done, i.e. diagnosis is unclear.
» Non-resolving hepatitis.

Note: Refer timeously before extensive liver damage occurs.

1.2.2 LIVER FAILURE, ACUTE
K72.0/K72.9

DESCRIPTION
Acute liver failure refers to the development of severe acute liver injury with encephalopathy and impaired synthetic function (INR of ≥1.5) in a patient without cirrhosis or pre-existing liver disease. There are many causes, but the commonest are viral hepatitis, alcohol, drug-induced liver injury, toxins or ischaemic hepatitis.

GENERAL MEASURES
» Patient education.
» Avoid hepatotoxic drugs and alcohol.
» Rest and reduce physical activity.
» Protein restriction is indicated for encephalopathy, however, severe protein restriction may accentuate catabolism. Use increments of 20 g protein per day, aiming for 1 g/kg/day as tolerated.
» Monitor blood glucose regularly because hypoglycaemia is common.
» Correct electrolyte disturbances.
» Exclude GI bleed and infection.
» Avoid factors (especially medications) that may worsen or precipitate functional deterioration.
» Avoid vigorous paracentesis.
» If the patient is bleeding, check INR and correct coagulopathy with FFP or lyophilised plasma.

MEDICINE TREATMENT
- Lactulose, oral, 10–30 mL 8 hourly, titrated to attain 2–3 soft stools per day.

Note: Do not give antibiotics unless there is evidence of bacterial sepsis.

REFERRAL
» All cases of severe acute liver failure should be discussed with a specialist.

1.2.3 PORTAL HYPERTENSION AND CIRRHOSIS
R18/K72.9/K74.6+(I98.2*/I98.3*)

DESCRIPTION
The complications of portal hypertension include:

» variceal bleeds,
» ascites,
» hepatic encephalopathy (HE),
» splenomegaly with hypersplenism,
» hepatorenal syndrome,
» hepato-pulmonary syndrome or porto-pulmonary hypertension.

GENERAL MEASURES

» Ascites: Perform diagnostic paracentesis if indicated. Restrict sodium intake, i.e. ≤ 2 g/day or ≤ 88 mmol/day.
» Monitor weight regularly.
» Encephalopathy: with acute HE, protein restrict (ideally under advice of dietician), otherwise 1–1.5 g/kg protein per day.
» Exclude infection, high protein load, occult bleed, sedatives, electrolyte disturbances and hepatocellular carcinoma.
» Variceal bleeding: endoscopic variceal ligation and/or immediate referral for advanced management.

MEDICINE TREATMENT

Ascites R18

- Spironolactone, oral, 100 mg daily.
  AND
- Furosemide, oral, 40 mg daily.

For spironolactone and furosemide:

- Increase spironolactone and furosemide dose by 100 mg and 40 mg, respectively, every 3–5 days, to a maximum dose of 400 mg spironolactone and 160 mg of furosemide depending on serum Na^+, K^+, urea and creatinine.
- Spironolactone may cause hyperkalaemia.
- Rapid fluid shifts may precipitate acute liver and/or renal failure.

Monitoring of sodium, potassium and renal function is essential in patients taking spironolactone. Avoid spironolactone if eGFR <30 mL/minute.
LoE:III[xvi]

Measure response to diuretics by weighing patient daily. Aim for maximal weight loss of:

» Patients without oedema: 500 g/day
» Patients with oedema: 1 000 g/day

Tense ascites R18

Albumin replacement must be given if ≥5 L of fluid is drained by paracentesis, or if there is pre-existing renal dysfunction:

- Albumin, IV, 40 g (20%), as an infusion. LoE:II[xvii]
  - Refer to specialist unit to consider transjugular intrahepatic portosystemic (TIP) shunt or potential transplant.
- Introduce diuretics and titrate doses as necessary to prevent recurrence of ascites (see above).

Note:
» Avoid NSAIDS and ACE-inhibitors.
» Exclude spontaneous bacterial peritonitis in patients with new onset ascites.

Refractory ascites R18
Defined as:
» No response to optimal diuretic therapy despite sufficient sodium restriction (≤2 g/day or ≤88 mmol/day) and avoidance of NSAIDs.
» Ascites that recurs rapidly following therapeutic paracentesis.

Perform serial large volume paracentesis, as an outpatient, usually not more frequently than every 2 weeks.
Haemodynamic collapse is more likely in patients who have intravascular volume depletion. Check renal function before paracentesis.

Albumin replacement must be given if ≥5 L of fluid is removed by paracentesis:
- Albumin, IV, 40 g (20%), as an infusion. LoE:II[xviii]

Encephalopathy
- Lactulose, oral, 10–30 mL 8 hourly, depending on stool number and consistency (aim for 2 soft stools/day).

Look for precipitating factors: Sepsis, protein load, GIT bleed, over diuresis, sedation.

Oesophageal varices I85.0/I85.9
To reduce the risk of bleeding:
- Beta-blocker, e.g.: LoE:III[xix]
- Propranolol, oral, 20–40 mg 12 hourly. Titrate to resting pulse rate of 50–60 beats per minute. Monitor pulse and BP.

REFERRAL
Refer to specialist unit to consider TIP shunt, endoscopic variceal ligation or potential transplant.

1.2.4 HEPATITIS, VIRAL

*Notifiable medical condition.

DESCRIPTION

Hepatitis caused by one of the hepatotropic viruses, hepatitis A, B, C, D and E.

1.2.4.1 HEPATITIS B, ACUTE

B16.0-2/B16.9

GENERAL MEASURES

» Bed-rest until acute phase has resolved.
» Avoid alcohol during the illness and for ≥ 6 months after clinical recovery.
» Screen sexual contacts of patients with acute hepatitis B. Non-immune contacts (negative for hepatitis B surface antibodies) should receive hepatitis B active immunisation (see Section 9.2: Adult vaccination).

MEDICINE TREATMENT

For nausea and vomiting: (R11)

- Metoclopramide, IV/oral, 10 mg 8 hourly as required.

Hepatitis B virus: prophylaxis following exposure e.g. needle stick injury
S61.0 + (W46.22+Z20.5+Z29.8)

» Persons at risk can be protected by passive immunisation with hyper immune serum globulin prepared from blood containing anti-HBs.
» It is essential that all categories of healthcare workers (HCW) at risk of contact with bodily fluids, including cleaning staff and home-based or family caregivers, are screened and fully vaccinated against hepatitis B if nonimmune.
» All occupational exposure incidents must be adequately documented for possible subsequent compensation.
» Recommended post-exposure management for HCW exposed to infectious material from patients with infectious hepatitis B (either surface antigen or e antigen positive).

Check vaccination status and antibody response of HCW (See table below for management depending on immunity):

Vaccination status and antibody response status of HCW	Source patient status & treatment		
	HBsAg positive	HBsAg negative	HBsAg unknown
Unvaccinated **OR** vaccination incomplete	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)	• Initiate Hep B vaccination (month 0, 1 and 6)	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)
Vaccinated **AND** HBsAb ≥10 units/mL[#]	No treatment	No treatment	No treatment
Vaccinated **AND** HBsAb <10 units/mL	• HBIG, IM, 500 units* • Repeat Hep B vaccine (3 doses at monthly intervals)	• Initiate Hep B vaccination (month 0, 1 and 6)	• HBIG, IM, 500 units* • Repeat Hep B vaccine (3 doses at monthly intervals)

* HBIG and first dose of vaccine to be given simultaneously, but at different sites.
[#] If the delay in obtaining HBsAb results is more than 24 hours initiate treatment as for vaccinated AND HBsAb <10 units/mL.
Table 1.1: Prophylaxis following Hepatitis B exposure

1.2.4.2 HEPATITIS B, CHRONIC (NON-HIV COINFECTION)

B18.0-2/B18.8-9

Consult the most recent Hepatitis Guidelines from the National Department of Health for comprehensive monitoring recommendations.

DESCRIPTION

» HBV is most commonly transmitted horizontally in children <5 years of age. Vertical mother to child transmission and adult transmission, sexually or through a parenteral route, can also occur.
» Acute infection may be asymptomatic or present as acute hepatitis.
» A proportion of patients develop chronic hepatitis (defined as abnormalities listed in the table below persisting for >6 months), which can result in cirrhosis and hepatocellular carcinoma.
» It is essential to know the HIV status of all patients with chronic hepatitis B before considering therapy.
» Antiviral therapy is not indicated for acute hepatitis B infection.

There are 5 potential phases of chronic hepatitis B infection which determine the need for treatment:

Phase	Serology	Viral load (HBV DNA) IU/mL	ALT	Management *LoE:III*[px]
1. HBeAg-positive chronic HBV infection *Immune Tolerant*	» HBsAg positive » HBeAg positive	>20 000 (usually >200 000)	Normal	» Treatment not routinely needed, but should be followed up. » Treat only if on immunosuppressive therapy to prevent hepatitis B flares.
2. HBeAg-positive chronic hepatitis B *Immune clearance*	» HBsAg positive » HBeAg positive	>20 000	Elevated	» Treatment required.
3. HBeAg-negative chronic HBV infection *Immune Control*	» HBsAg positive » HBeAg negative	<2 000	Normal	» Treatment not routinely needed, but should be followed up. » Treat only if on immunosuppressive therapy to prevent hepatitis B flares.
4. HBeAg-negative chronic hepatitis B *Immune Escape*	» HBsAg positive » HBeAg negative	>2 000	Elevated	» Treatment required.
5. Occult hepatitis B	» HBsAg negative » HBsAb negative » HB IgG core Ab positive	<200	-	» No follow-up required. » Treat only if on immunosuppressive therapy to prevent hepatitis B flares.

HBsAg: hepatitis B surface antigen; *HBsAb:* hepatitis B surface antibody; *HBIG:* hepatitis B immunoglobulin

Table 1.2: Phases of Chronic Hepatitis B infection

Treat all patients with cirrhosis regardless of ALT level, HBeAg status and HBV viral load, to prevent hepatitis B flares that will lead to decompensation. Screen all categories of healthcare workers (HCW) at risk of contact with bodily fluids, including cleaning staff, home-based or family caregivers and vaccinate against hepatitis B if not immune (see Section 24.1.5: Management of close contacts of patients with hepatocellular carcinoma).

MEDICINE TREATMENT

<u>If eGFR > 50mL/min:</u>

- Tenofovir disoproxil fumarate (TDF), oral, 300 mg daily.

LoE:III[pxi]

<u>If eGFR 15-50mL/min (or on haemodialysis):</u>

- Tenofovir alafenamide (TAF), oral, 25 mg daily.

LoE:IIb[pxii]

Aims of treatment

HBeAg-positive disease:

» Sustained HBsAg loss off therapy, with/without the development of anti-HBs, **and**
» Suppression of HBV DNA to undetectable or low (<2000 IU/mL) levels, **and**
» Normalisation of ALT, **and**
» Sustained HBeAg loss and seroconversion to anti-HBe.

HBeAg-negative disease:

» Sustained HBsAg loss off therapy, with/without the development of anti-HBs, **and**
» Suppression of HBV DNA to undetectable or low (<2000 IU/mL), **and**
» Normalisation of ALT.

Monitoring whilst on tenofovir

Monitoring test	When to perform test
Serum phosphate and urine protein	Baseline
INR	Baseline, Week 4
Serum creatinine	All patients: Baseline Patients on TDF: Week 4, then 3 months, 6 months, and 12 months after initiation; then, every 12 months thereafter.
ALT	Baseline, Week 4, and every 12 weeks thereafter
FBC+Diff	Baseline, Week 4, and every 12 weeks thereafter
HBeAg and Anti-HBe	HBeAg-positive patients: Every 12 months
HBsAg	HBeAg-positive patients: HBsAg every 6 months after anti-HBe seroconversion HBeAg-negative patients: HBsAg every 6 months with persistently undetectable HBV DNA
HBV DNA levels	HBeAg-positive patients: 12 months after HBeAg seroconversion

Table 1.3: Monitoring tests whilst on tenofovir

Adapted from: National Department of Health, National guidelines for the management of viral hepatitis, 2019. Available at www.health.gov.za

Duration of tenofovir treatment:

» HBeAg-positive patients: discontinue 12 months after HBeAg seroconversion and in association with persistently normal ALT levels and undetectable HBV DNA levels.
» HBeAg-negative patients: Long-term therapy unless HBsAg

seroconversion is achieved.
» Cirrhotic patients: Lifelong treatment.

REFERRAL
Failure of, or contraindications to, tenofovir disoproxil fumarate and tenofovir alafenamide.

1.2.4.3 HEPATITIS B, CHRONIC (HIV CO-INFECTION)
See chapter 10: HIV and AIDS.

1.2.4.4 HEPATITIS C, CHRONIC
Consult a specialist.

1.2.5 LIVER ABSCESS, PYOGENIC
K75.0

DESCRIPTION
Focal bacterial infection, usually polymicrobial, of the liver with pus. Multiple abscesses are not uncommon.

GENERAL MEASURES
Drainage is essential in all cases. This should preferably be done percutaneously by inserting a catheter under ultrasound guidance.

MEDICINE TREATMENT
Empiric antibiotic therapy
- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly.

If unable to tolerate oral therapy:
- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly.

Duration of antibiotic therapy is ill defined, but may need to be for as long as 12 weeks in cases of multiple abscesses. Continue until drainage is complete and CRP has returned to normal values. Monitoring response to therapy by ultrasound is not useful due to slow resolution of abscesses on imaging.

1.2.6 LIVER ABSCESS, AMOEBIC
A06.4

DESCRIPTION
Focal hepatic infection due to *E. histolytica*. Only about a third of cases have concomitant amoebic colitis. Diagnosis can be excluded if the serological test is negative. It is essential to exclude pyogenic infection (a diagnostic aspirate should be taken under ultrasound guidance in all cases where there is doubt).

GENERAL MEASURES
Drainage is recommended for abscesses that are large (i.e. >10 cm diameter), involve the left lobe, or are near the surface of the liver. Drainage can be achieved by percutaneous aspiration under ultrasound guidance.

MEDICINE TREATMENT
- Metronidazole, oral, 800 mg 8 hourly for 10 days. *LoE:III*[xxiii]

1.2.7 CHOLECYSTITIS, ACUTE AND CHOLANGITIS, ACUTE
K81.0/K83.0

GENERAL MEASURES
Surgical drainage/cholecystectomy according to indication and/or patient's condition.

MEDICINE TREATMENT
Acute cholecystitis
Mild and asymptomatic cases without risk factors may not require antibiotic treatment. If signs of infection present and/or risk factors for severe disease are present, such as:
» Elderly patients (>60 years of age)
» Co-morbid conditions
» Immune compromised

Acute cholecystitis and acute cholangitis
- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly.

<u>If unable to tolerate oral therapy:</u>
- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly.

REFERRAL
» Clinical deterioration or failure to improve.
» Fistulae or perforation.
» Need for complicated surgery.

1.3 DIARRHOEA

1.3.1 CHOLERA
A00.0-1/A00.9
*Notifiable medical condition.

DESCRIPTION
Diarrhoea due to *Vibrio cholerae*, often in outbreaks.

GENERAL MEASURES

Rehydration is the cornerstone of management. Oral rehydration is preferred.

MEDICINE TREATMENT

- Oral rehydration solution (ORS) by mouth or nasogastric tube.
  - If enteral administration not possible, e.g., patient is vomiting, profoundly dehydrated, or stuporous:

IV treatment if unable to tolerate oral rehydration: *LoE:IVb*[xxiv]

- Ringers lactate, IV (preferred).

OR

- Sodium chloride, 0.9%, IV.

AND

Antibiotic therapy: *LoE:III*[xxv]

- Ciprofloxacin, oral, 1 g as a single dose.
  - Adjust antibiotic choice, according to the sensitivity of the isolate responsible for the local epidemic.

CAUTION

Dextrose 5% should not be used for fluid replacement in patients with cholera as it does not contain electrolytes, which are required to ensure adequate fluid resuscitation.

1.3.2 DYSENTERY (ACUTE INFLAMMATORY DIARRHOEA)

A02.0/A02.9/A03.0-3/A03.8-9/A04.2/A04.5/A04.8-9

DESCRIPTION

Diarrhoea with neutrophils, blood and/or mucus.

GENERAL MEASURES

» Rehydration is the cornerstone of management. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated.
» Perform a stool culture.

MEDICINE TREATMENT

CAUTION

Loperamide is contraindicated as it may result in toxic megacolon.

Antibiotic therapy

Consider in patients with signs of sepsis, severe cases, or significant underlying disease:

- Ceftriaxone, IV 1 g daily.

Switch antibiotic when clinically appropriate:
- Ciprofloxacin, oral, 500 mg 12 hourly, ideally based on culture and sensitivity if available.

For uncomplicated dysentery in patients with no co-morbidity:
- Ciprofloxacin, oral, 500 mg 12 hourly for 3 days.
  - Extend treatment duration to 7 days in patients with significant co-morbidity, e.g. immunocompromised patients.

REFERRAL
Persistent diarrhoea with blood and mucus for longer than 2 weeks.

1.3.3 DIARRHOEA, ACUTE NON-INFLAMMATORY
A04.1

DESCRIPTION
Diarrhoea without macroscopic blood or mucus, or neutrophils on microscopy. Common causes include viruses and enterotoxigenic strains of *E. coli*.
Note: Neutropenic patients may have inflammatory diarrhoea in the absence of neutrophils.

GENERAL MEASURES
Rehydration is the cornerstone of management. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated.

MEDICINE TREATMENT
- Loperamide, oral, 4 mg immediately, followed by 2 mg after each loose stool. *LoE:III*[xxvi]
  - Maximum dose: refer to dose table below

Weight band	Maximum daily dose (equivalent maximum number of 2 mg tablets per day)
34-39 kg	10 mg (5 tablets)
40-46 kg	12 mg (6 tablets)
47-53 kg	14 mg (7 tablets)
≥ 54 kg	16 mg (8 tablets)

1.3.4 CLOSTRIDUM DIFFICILE (*CLOSTRIDIOIDES DIFFICILE*) DIARRHOEA
A04.7
*Notifiable medical condition.

DESCRIPTION
» Diarrhoea caused by altered bowel flora due to antibiotic exposure.

» *Clostridium difficile* (*Clostridioides difficile*) infection may result in severe disease and/or the development of pseudomembranous colitis.
» Diagnosis is confirmed in the laboratory on a stool sample. Patients with unexplained and new-onset diarrhoea of more than 3 unformed stools in 24 hours should be tested. Repeat testing (within 7 days) is not recommended.

GENERAL MEASURES

» The most important aspect of management is discontinuation of antibiotics.
» Rehydration may be necessary. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated.
» Patients with known or suspected *Clostridium difficile* infection should be placed on contact precaution according to institutional infection control and prevention measures.
» Contact precautions should be maintained for at least 48 hours after diarrhoea has resolved.
» Healthcare workers and all close contacts should perform regular handwashing with soap and water. Alcohol-based hand sanitizer does not kill spores.

MEDICINE TREATMENT

CAUTION
Loperamide is contraindicated as it may result in toxic megacolon.

Mild to moderate infection
Laboratory results confirm toxigenic *Clostridium difficile* infection but diarrhoea does not settle on antibiotic withdrawal:

- Metronidazole, oral, 400 mg 8 hourly for 10 days.

Severe infection
Laboratory results confirm toxigenic *Clostridium difficile* infection, WCC >15 $x10^9$/L or serum creatinine >132 micromol/L, or other risk predictors of severity (immunodeficiency, intensive care admission, serious comorbidity, age >65 years of age).

- Vancomycin, oral, 125 mg 6 hourly (give parenteral formulation orally) for 10 days.

Fulminant infection
<u>If ileus or toxic megacolon or hypotension/shock:</u>

- Vancomycin, oral, 125 mg 6 hourly (give parenteral formulation orally) for 10 days.

AND

- Metronidazole, IV, 500 mg 8 hourly for 10 days.

Switch to oral metronidazole, if/when possible, to complete 10 day course.

Recurrence
If metronidazole was used during the first episode:
- Vancomycin, oral, 125 mg 6 hourly (give parenteral formulation orally) for 10 days.

If vancomycin was used during the first episode, administer oral vancomycin as a tapered and pulsed regimen:
- Vancomycin, oral, 125 mg (give parenteral formulation orally) as follows:
  - 6 hourly for 10 days, then
  - 12 hourly for 7 days, then
  - once daily for 7 days, then
  - every 2nd or 3rd day for 2 to 8 weeks.

LoE:I[xxvii]

REFERRAL
» Surgical consult should be obtained in all patients with complicated *Clostridium difficile* infection (e.g. bowel perforation, hypotension requiring vasopressor therapy, clinical signs of sepsis).
» Failure to improve on medical therapy after 5 days.

1.3.5 AMOEBIC DYSENTERY
A06.0-1

DESCRIPTION
Diarrhoea with blood and/or mucus due to *E. histolytica*. Organism must be demonstrated on a warm stool specimen with microscopy.

GENERAL MEASURES
» Rehydration may be necessary. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated.
» Surgery for bowel perforation.

MEDICINE TREATMENT
LoE:III[xxviii]
- Metronidazole, oral, 800 mg 8 hourly for 10 days.

CAUTION
Loperamide is contraindicated as it may result in toxic megacolon.

1.3.6 GIARDIASIS
A07.1

DESCRIPTION
Infection with the protozoan parasite, *G. lamblia* which colonises the proximal small intestine. Does not typically present with acute diarrhoea.

GENERAL MEASURES
Fluid and electrolyte replacement in severe diarrhoea.

MEDICINE TREATMENT

- Metronidazole, oral, 2 g daily for 3 days.

1.3.7 TYPHOID

See section 9.11: Typhoid fever.

1.3.8 BACTERIAL PERITONITIS

K65.0/K65.8-9

DESCRIPTION

Infection of the peritoneum, usually secondary to a surgical cause such as perforated bowel. In this setting polymicrobial infection with anaerobes, Gram-positive cocci, and Enterobacteriaceae are usually found. Primary or spontaneous bacterial peritonitis is much less common and usually complicates ascites in patients with portal hypertension. This is not usually polymicrobial but due generally to Enterobacteriaceae such as *E. coli*. Spontaneous bacterial peritonitis is often culture-negative but is diagnosed by ascitic neutrophil count >0.25 x 10^9/L (250 cells/mm^3).

GENERAL MEASURES

Secondary peritonitis

» Intravenous fluids and nasogastric suction.
» Prompt surgical intervention is essential.

MEDICINE TREATMENT

Empiric antibiotic therapy

For surgical causes of peritonitis:

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly.

As soon as patient can tolerate oral medication:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly.

For spontaneous bacterial peritonitis:

- Ceftriaxone, IV, 1 g daily.
  - Patients not responding to ceftriaxone after 48 hours, consult a specialist.

Switch to oral therapy when clinically appropriate according to culture or treat with:

- Ciprofloxacin, oral, 500 mg 12 hourly.
  - Total duration of therapy: 14 days.

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SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 1: ALIMENTARY TRACT
NEMLC RECOMMEDATIONS FOR MEDICINE AMENDMENTS (2020-4 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

A: MEDICINE AMENDMENTS

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED/RETAINED
1.1 Gastrointestinal disorders		
1.1.1 Bowel Preparations	Description - dietary restrictions	Guidance amended
1.1.2 Diverticulosis	Description	Amended
	Use of antibiotics	Guidance amended
1.1.3 Gastro-oesophageal reflux disease (GORD)	Title and description	Editorial amendment - dyspepsia added
	General measures	Amended
	Medicine treatment	Editorial amendments
	Medicine treatment - lansoprazole	Deleted
	Medicine treatment - pantoprazole	Added
	Referral	Editorial amendments
1.1.6 Pancreatitis, acute	General measures	Editorial amendments
	Antimicrobial therapy	Editorial amendments
	Co-amoxiclav	Retained for empirical treatment of infected necrosis of the pancreas
1.1.7 Pancreatitis, chronic	General measures	Editorial amendments
	Medicine treatment	Editorial amendments
1.1.8 Peptic ulcer	Medicine treatment	PPI doses and duration amended
	Azithromycin	Treatment duration of three days retained for H.pylori eradication
	Medicine treatment - lansoprazole	Deleted
	Medicine treatment - pantoprazole	Added
1.2 Hepatic Disorders	Description	Editorial amendments
1.2.1 Hepatitis, non-viral	General measures	Editorial amendments
	Medicine treatment - Lyophilised plasma	Guidance added
	Medicine treatment – Fresh frozen plasma:	Guidance added
	Medicine treatment – Vitamin K, IV	Guidance added
1.2.2 Liver failure, acute	General measures	Editorial amendments
	Antiviral therapy – acute treatment	Not added
1.2.3 Portal hypertension and cirrhosis	General measures	Editorial amendments
	Variceal bleeding - octreotide	Not added
	Medicine treatment - ascites	Editorial amendments
	Medicine treatment – tense ascites	Editorial amendments
	Medicine treatment – refractory ascites	Editorial amendments
	Medicine treatment – oesophageal varices	Carvedilol – not added – on therapeutic interchange database
	Referral	Editorial amendments
1.2.4 Hepatitis, viral	Description	Editorial amendments
-1.2.4.1 Hepatitis B, acute	General measures	Editorial amendments
	General measures	Add cross-reference to Hep B vaccination
	Hepatitis B virus prophylaxis following exposure	Amended
-1.2.4.2 Hepatitis B, chronic (Non-HIV coinfection)	Hepatitis B virus prophylaxis following exposure	Amended
	Tenofovir disoproxil furmarate (TDF) eGFR > 50mL/min	Retained
	Tenofovir alafenamide (TAF) eGFR >50mL/min	Added to TI database
	Tenofovir alafenamide (TAF) – 15-50mL/min (or on haemodialysis)	Added

	Monitoring whilst on tenofovir:	Editorial amendments
1.3 Diarrhoea		
1.3.1 Cholera	*Ciprofloxacin*	*Dose and duration of treatment amended*
	Ringers lactate	*Added*
1.3.2 Dysentry (acute inflammatory diarrhoea)	Antibiotic therapy	Editorial amendments
1.3.3 Diarrhoea, acute non-inflammatory	Medicine treatment –loperamide:	Dose amended
1.3.4 Clostridium difficile diarrhoea	Title	Editorial amendments
	Mild-moderate infection - vancomycin	Not added
	Fulminant infection – rectal vancomycin	Not added

1.1.1 BOWEL PREPARATIONS

Description – dietary restrictions: *Guidance amended*

The following editorial amendments were made in line with the European Society for Gastrointestinal Endoscopy (ESGE)[1] Bowel preparation for colonoscopy guidelines.

Bowel preparation is essential for colonoscopy.
Split-dose (half the dose the night before and half the dose on the day of colonoscopy) bowel cleanser ~~and no dietary restriction seems to provide better quality colon cleansing than single doses with a liquid diet on the day preceding colonoscopy. a low residue diet should be commenced the day before.~~ and a low residue diet should be commenced the day before.

1.1.2 DIVERTICULOSIS

Description: *Amended*

Medicine treatment – antibiotics: *Guidance amended*

External comment was received to consider less aggressive use of antibiotics for the management of mild diverticulitis. The Committee were of the view that the evidence is still evolving with regard to the appropriate patient cohorts for whom use of antibiotics is clearly indicated. Amendments were made to the guidance on medicine management as tabulated below. The Committee further recommended that the STG on the management of diverticulosis be prioritized for the next review cycle.

AMENDED FROM:
DESCRIPTION
Diverticulosis can be complicated by haemorrhage or diverticulitis. Acute diverticulitis is inflammation of diverticulae, usually accompanied by polymicrobial infection.

MEDICINE TREATMENT
Total duration of antibiotic therapy is 10 days, depending on clinical response.

AMENDED TO:
DESCRIPTION
Diverticulosis can be complicated by haemorrhage or diverticulitis. Acute diverticulitis is inflammation of diverticulae, uncommonly accompanied by polymicrobial infection.

MEDICINE TREATMENT
Not all patients require antibiotics, if antibiotic treatment is required, the total duration is ten days depending on clinical response.

1.1.3 GASTRO-OESOPHAGEAL REFLUX (GORD)

Title and description: *editorial amendment*

External comment received that the title for Section 1.1.3 should be amended to include dyspepsia and a general description for dyspepsia be included. The following editorial amendments have been made:

[1] Hassan C et al. Bowel preparation for colonoscopy: European Society for Gastrointestinal Endoscopy (ESGE)[1] guidelines: update 2029. DOI https://doi.org/10.1055/a-0959-0505. Published online: 2019 | Endoscopy

1.1.3 GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) AND DYSPEPSIA

K21.0/K21.9/K22.7, K30

DESCRIPTION

GORD is a disorder which develops as a consequence of the reflux of gastric and duodenal contents into the oesophagus. It is usually characterised by heartburn and regurgitation.

Dyspepsia is the sensation of epigastric discomfort. It may be a feature of potentially severe diseases such as peptic ulcer disease or gastric cancer. It may also be a symptom H pylori gastritis or NSAID gastritis.

Intermittent indigestion, heartburn or dyspepsia may be associated with:

- » use of NSAIDs e.g. aspirin, ibuprofen, pain powders
- » spicy food, alcohol, carbonated drinks
- » smoking

Complications that may develop in severe GORD ~~disease~~ are strictures, ulceration, Barrett's oesophagus and adenocarcinoma of the oesophagus. Two thirds of patients have a normal endoscopy which is termed non-erosive reflux disease (NERD) or non-ulcer dyspepsia (NUD) depending on the predominant symptom.

General measures: *amended*

The general measures have been aligned with the recommendations in Table 3 of the American College of Gastroenterology Clinical Guidelines[2]. Furthermore, the age threshold for referral for an endoscopy has been amended from older than 45 years to older than 60 years, in line with the ACG management of dyspepsia guidelines[3] and a local study by Cheddie et al.[4]

AMENDED FROM:	AMENDED TO:
GENERAL MEASURES » Stop smoking. » Limit alcohol intake. » Eat small frequent meals. » Avoid late night meals. » Check haemoglobin. » Stop the use of potential ulcerogenic medicines e.g. NSAIDs. All patients with alarm symptoms, i.e. weight loss, haematemesis or melaena, dysphagia, or anaemia, chest pain or older than 45 years of age should have an endoscopy.	**GENERAL MEASURES** » Stop smoking. » Limit alcohol intake. » Eat small frequent meals. » Avoid late night meals. » Avoid fatty meals. » Avoid carbonated beverages. » Lose weight if overweight. » Sleep with upper body elevated. » Sleep on the left side. » Avoid excessive exercise » Stop the use of potential ulcerogenic medicines e.g. NSAIDs. » If pale, check haemoglobin and refer if anaemic All patients with alarm symptoms, i.e. weight loss, haematemesis or melaena, dysphagia, or anaemia, chest pain or patients older than 60 years of age with new onset dyspepsia should have an endoscopy.

Medicine treatment – lansoprazole: Delete

Medicine treatment – pantoprazole: Added

Lansoprazole has been replaced with pantoprazole as the PPI of choice in line with the latest tender (Contract circular HP09-2023SD). Pantoprazole 40mg and 20mg is listed on the therapeutic interchange database as an alternative to lansoprazole 30mg and 15mg respectively.

Medicine treatment: *editorial amendments*

Guidance included on when it would not be appropriate to reduce the dose of proton pump inhibitors (PPIs) as tabulated below:

AMENDED FROM:

Proton pump inhibitors (PPIs)

A trial with a PPI confirms acid-related disease. Only if no alarm symptoms:

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily for 4 weeks.
  - Ensure adherence to promote healing.

[2] Katz PO et al. ACG Clinical Guideline for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 2022;117:27–56. https://doi.org/10.14309/ajg.0000000000001538; published online November 22, 2021.

[3] Moayyedi PM, Lacy BE, Andrews CN, et al. ACG and CAG clinical guideline: Management of dyspepsia. Am J Gastroenterol. 2017 Jul;112(7):988-1013. http://doi.org/10.1038/ajg.2017.154

[4] Cheddie S et al. Age is a predictor of significant endoscopic findings in dyspepsia patients in South Africa. Southern African Journal of Surgery 2020; 58(1):14-17 http://dx.doi.org/10.17159/2078-5151/2020/v58n1a2814.

Recurrence of symptoms
After endoscopic confirmation of disease:
- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.
  - Decrease dose of PPI after 4 weeks, e.g: omeprazole, oral, 10 mg daily.

Barrett's oesophagus K22.7
Restart PPI:
- PPI, e.g.:

Lansoprazole, oral, 30 mg daily

AMENDED TO:
New onset symptoms
Empiric therapy with a proton pump inhibitor (PPI) may be initiated **in the absence of alarm symptoms** (see referral section). Improvement of symptoms confirms acid-related disease.
- PPI, e.g.:
- Pantoprazole, oral, 40 mg daily for 4 weeks.
  - Ensure adherence to promote healing.

Recurrence of symptoms
After endoscopic confirmation of disease:
- PPI, e.g.:
- Pantoprazole, oral, 40 mg daily.
  - Decrease dose of PPI after 4 weeks, e.g: pantoprazole, oral, 20 mg daily except for severe endoscopic GORD (Grade C or D LA classification) and Barret's oesophagus or specific advice from the endoscopist.

Barrett's oesophagus K22.7
Restart PPI:
- PPI, e.g.:
- Pantoprazole, oral, 40 mg daily.

Referral: *editorial amendments*
The following editorial amendments were made to the referral criteria:

REFERRAL
Discuss with a specialist:
» young patients who are PPI dependent and will require life-long therapy;
» patients unable to take PPIs;
» patients requiring high doses of PPIs;
» patients with large hiatus hernias and "volume reflux";
» a rolling hiatus hernia with obstructive symptoms requires surgery;
» All patients with alarm symptoms. ~~Alarm features that may be suggestive of gastrointestinal malignancy:~~
  ~~— New onset dyspepsia in patient > 60 years~~
  — Evidence of gastrointestinal bleeding,
  — Evidence of gastrointestinal bleeding,
  — Iron deficiency anaemia,
  — Anorexia,
  — Unexplained weight loss,
  — Dysphagia,
  — Odynophagia (painful swallowing),
  — Persistent vomiting, and haematemesis and malaena,
  — Gastrointestinal cancer in a first-degree relative.

1.1.6 PANCREATITIS, ACUTE

General measures: *Editorial amendment*
The following statement was removed from the STG as no longer appropriate: *'Nasogastric suction when persistent vomiting or ileus occurs,'* in line with the European Society for Clinical Nutrition and metabolism (ESPEN) guideline[5]

Antimicrobial therapy: *Editorial amendment*
The following editorial amendment was made to reflect more appropriate medical terminology: amended from 'abscess of the pancreas' to 'infected necrosis of the pancreas'.

[5] Arvanitakis, Met al (2020). ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. Clinical Nutrition, 39(3), 612-631. https://doi.org/10.1016/j.clnu.2020.01.004

Infected necrosis of the pancreas – empirical treatment: *Co-amoxiclav retained*
External comment was received that co-amoxiclav may not be the best choice of antibiotic for infected necrosis of the pancreas. The Committee agreed that co-amoxiclav be retained as empirical treatment until there is clear evidence to support an alternative. Patients with infective pancreatitis should be referred for specialist care.

1.1.7 PANCREATITIS, CHRONIC

General measures: *Editorial amendment*
The following statement was deleted: '*Elemental diets (i.e. parenteral or enteral nutrition) in chronically debilitated patients',* as elemental diets are no longer recommended.

Medicine treatment: *Editorial amendments*
The following editorial amendments were made and aligned with European Society for Clinical Nutrition and metabolism (ESPEN)[6] guideline.

MEDICINE TREATMENT
Treatment is aimed at:
- » pain,
- » exocrine dysfunction (malabsorption, and diarrhoea)
- » endocrine function. See section 8.5.2: Type 1 Diabetes mellitus.

Malabsorption
~~Start treatment when >7 g (or 21 mmol) fat in faeces/24 hours while on a 100 g fat/day diet.~~
~~Reduce dietary fat to <25 g/meal.~~
Supplementation of fat-soluble vitamins may be indicated.

- Pancreatic enzyme replacement e.g. Lipase, oral, equivalent to lipase 30 000 units per day, in divided doses with meals.
- Pancreatic enzyme replacement therapy is titrated until there is symptom control and is taken during meals and with snacks.

~~**Aim for symptom control and/or 5% of normal faecal fat output**~~

1.1.8 PEPTIC ULCER

H.pylori positive - proton pump inhibitors (PPIs): *Duration of therapy amended*
H.pylori negative – proton pump inhibitors (PPIs): *Dose and duration amended*
H.pylori eradication – azithromycin*: Treatment duration retained*

The duration of twice daily PPI therapy has been amended to align to the NEMLC approved NDoH evidence summary for H.pylori eradication[7] (final NEMLC decision as tabulated below). The maximum duration of therapy with the ongoing once daily dosing is aligned to the recommended registered duration of therapy for gastric and duodenal ulcers respectively.

[6] Arvanitakis, Met al (2020). ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. Clinical Nutrition, 39(3), 612-631. https://doi.org/10.1016/j.clnu.2020.01.004
[7] NDoH Evidence Review. H.pylori eradication. 4 June 2020

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	X	☐	☐	☐	☐

Recommendation:

Based on this evidence review, the Adult Hospital Level Committee reccomends that azithromycin be retained as part of the recommended triple therapy for eradicationof *Helicobacter pylori*. However, clarithromycin could be considered as a therapeutic alternative where there are supply constraints with azithromycin.

Duration of therapy for clarithromycin (as part of triple therapy) should be extended for 14 days, whilst azithromycin could be extended to 10 days (as the elimination half-life is 68 to 72 hours).

Of note is that an increase in resistance of metronidazole would limit the therapeutic efficacy of triple therapy in penicillin-allergic pateients – more local antibiotic susceptibility data is required.

Empiric therapy should not be instituted without diagnostics and treatment failure should be guided by sensitivity and culture.

Rationale: Available evidence suggests that azithromycin is comparable to clarithromycin in terms of efficacy; though evidence is of low to moderate quality. Increasing duration of therapy to 14 days has been shown to improve eradication rates of proton pump inhibitor + amoxicillin + clarithromycin (PAC) and proton pump inhibitor + amoxicillin + metronidazole (PAM) regimens. However, local sensitivity patterns is required to guide combination triple therapy for *Helicobacter pylori* eradication.

Level of Evidence: II Moderate quality meta-analyses, Antibiotic susceptibility studies, Expert opinion

NB: PLEASE SEE BELOW FOR FINAL NEMLC RECOMMENDATION.

Review indicator: Price and antimicrobial susceptibility data

Evidence of efficacy	Evidence of harm	Price reduction
X		X

VEN status: n/a

Vital	Essential	Necessary

Monitoring and evaluation considerations: Resistance patterns

Research priorities: Resistance patterns

NEMLC MEETING OF 11 JUNE 2020:

NEMLC DISCUSSION:

Azithromycin: Despite the biological elimination half-life of 68 to 72 hours, tissue concentrations were reported to be as long as 14 days. Thus, the NEMLC recommended that the duration of therapy of azithromycin be retained at 3 days, and not be extended to 10 days.

- *Sampson et al.*[1] evaluated whole blood and intracellular concentrations (peripheral blood mononuclear cells and polymorphonuclear cells) for 21 days after a single dose of azithromycin (250 mg to 1000 mg). Concentrations in cells were measured as two orders of magnitude higher intracellularly than in blood and declines very slowly over 21 days.

Medicine treatment – lansoprazole: Delete

Medicine treatment – pantoprazole: Added

Lansoprazole has been replaced with pantoprazole as the PPI of choice in line with the latest tender (Contract circular HP09-2023SD). Pantoprazole 40mg and 20mg is listed on the therapeutic interchange database as an alternative to lansoprazole 30mg and 15mg respectively.

For H.pylori negative patients, the dose of PPI has been amended to align to the registered once daily dose with the duration of therapy for gastric and duodenal ulcers amended accordingly. Amendments to the STG are as tabulated below:

AMENDED FROM:	AMENDED TO:
1.1.8 PEPTIC ULCER	**1.1.8 PEPTIC ULCER**
DESCRIPTION Ulcer in the stomach mucosa (gastric ulcer: GU) or first few centimetres of the duodenum (duodenal ulcer: DU), which penetrates into or through the muscularis mucosa. Diagnosis is made after endoscopy, as all GUs require biopsy to exclude malignancy. Patients with GUs and complicated DUs, those that have bled, perforated or are recurrent, must be rescoped at appropriate intervals until the ulcer has healed. *H. pylori* can be assessed at scope by rapid urease testing (RUT) or biopsy.	**DESCRIPTION** Ulcer in the stomach mucosa (gastric ulcer: GU) or first few centimetres of the duodenum (duodenal ulcer: DU), which penetrates into, or through the muscularis mucosa. Diagnosis is made after endoscopy as all GUs require biopsy to exclude malignancy.
GENERAL MEASURES Advise patient to avoid ulcerogenic medications, e.g. NSAIDs. Advise patient to stop smoking and drinking alcohol. Dietary advice by dietician.	**GENERAL MEASURES** » Advise patient to avoid ulcerogenic medications, e.g. NSAIDs. » Advise patient to stop smoking and drinking alcohol. » Dietary advice by dietician. » Patients with GUs and complicated DUs, those that have bled, perforated or are recurrent, must be rescoped at appropriate intervals until the ulcer has healed. *H. pylori* can be assessed at scope by rapid urease testing (RUT) or biopsy.

MEDICINE TREATMENT
***H. pylori* +ve**
The vast majority of GUs and DUs are associated with *H. pylori* infection and eradication therapy is indicated if infection is present. This will greatly reduce the rate of recurrent ulceration. Empiric eradication of *H. pylori* is not recommended.
 	
Proton pump inhibitors (PPIs)
▪ PPI, e.g.:
• Lansoprazole, oral, 30 mg 12 hourly.
  ○ Duodenal ulcer: for 7 days.
  ○ Gastric ulcer: for 28 days.
 	
AND
<u>*H. PYLORI* ERADICATION:</u> K25.0-7/K25.9/K26.0-7/K26.9/K27.0-7/K27.9 + (B96.8)
• Amoxicillin, oral, 1 g 12 hourly for 7 days.
OR
<u>For severe penicillin allergy:</u> (Z88.0)
• Azithromycin, oral, 500 mg daily for 3 days.
 	
AND
• Metronidazole, oral, 400 mg 12 hourly for 7 days.
 	
Failure of *H. pylori* eradication: Discuss with specialist.
 	
***H. pylori* –ve**
These are usually a consequence of NSAID use.
Stop NSAID until ulcer has healed.
If patient is unable to stop NSAID, refer to specialist.
 	
▪ PPI, e.g.:
• Lansoprazole, oral, 60 mg daily.
  ○ Duodenal ulcer: for 14 days.
  ○ Gastric ulcer: for 28 days.
 	
Resistant disease
Ulcer not healing.
High-risk patients, i.e. poor surgical risk and the elderly or concomitant disease.
Maintenance therapy:
▪ PPIs, e.g.:
• Lansoprazole, oral, 30 mg daily. Specialist initiated.
	MEDICINE TREATMENT
	***H. pylori* positive:**
	The vast majority of GUs and DUs are associated with *H. pylori* infection and eradication therapy is indicated if infection is present. This will greatly reduce the rate of recurrent ulceration. Empiric eradication of *H. pylori* **is not recommended**.
	
	<u>*H. pylori* eradication:</u> K25.0-7/K25.9/K26.0-7/K26.9/K27.0-7/K27.9 + (B98.0)
	• Amoxicillin, oral, 1 g 12 hourly for 14 days.
	OR
	<u>For severe penicillin allergy:</u> (Z88.0)
	• Azithromycin, oral, 500 mg daily for 3 days.
	
	AND
	• Metronidazole, oral, 400 mg 12 hourly for 14 days.
	
	<u>Proton pump inhibitors (PPIs):</u>
	▪ PPI, e.g.:
	• Pantoprazole, oral, 40 mg 12 hourly for 14 days.
	
	Continue with PPI therapy as follows:
	▪ PPI, e.g.:
	• Pantoprazole, oral, 40 mg daily.
	  ○ Duodenal ulcer: for up to 2 weeks
	  ○ Gastric ulcer: for up to 6 weeks
	
	***H. pylori* negative:**
	» These are usually a consequence of NSAID use.
	» Stop NSAID until ulcer has healed.
	» If patient is unable to stop NSAID, refer to specialist for guidance.
	
	▪ PPI, e.g.:
	• Pantoprazole, oral, 40 mg daily.
	  ○ Duodenal ulcer: for up to 4 weeks
	  ○ Gastric ulcer: for up to 8 weeks.
	
	Resistant disease
	» Ulcer not healing.
	» High-risk patients, i.e. poor surgical risk and the elderly or concomitant disease.
	
	<u>Maintenance therapy:</u>
	▪ PPIs, e.g.:
	• Pantoprazole, oral, 40 mg daily. Specialist initiated.
	
	REFERRAL
	» Failure of *H. pylori* eradication: Discuss with specialist.

Treatment duration of azithromycin: External comment received on whether the treatment duration of azithromycin should be extended for longer than three days for H.pylori eradication. The treatment duration of 3 days was retained, based on the previously updated NEMLC recommendation (June 2020)[8] during which it was noted that despite the biological elimination half-life of 68 to 72 hours, tissue concentrations were reported to be as long as 14 days. A summary of the NEMLC recommendation is tabulated below:

NEMLC RECOMMENDATIONS: NEMLC recommended that the duration of therapy for azithromycin be retained as 3 days. For other antibiotics, amoxicillin and metronidazole, duration of therapy to be extended for 14 days for the eradication of *H.pylori.* Clarithromycin was cost-prohibitive and could be considered as a therapeutic alternative where there are supply constraints with azithromycin. And, more substantial local antimicrobial susceptibility studies were required to confirm metronidazole resistance in our local setting. *Rationale:* Despite an elimination half-life of 68 to 72 hours, azithromycin tissue concentrations have been shown to be adequate (>1 mg/L) 21 days after administration of a single dose of 1.5 g or 3 day course of 500 mg per day. For other antibiotics (amoxicillin and metronidazole), 14-day duration of therapy is recommended as a Cochrane review showed that *H. pylori* eradication rates for 14-days PPI triple therapy was significantly higher than for 7 days (*H. pylori* persistence, regardless of regimen and dose: RR 0.66 (95% CI 0.6 to 0.74), NNT 11 (95% CI 9 to 14). **Level of Evidence: I Metaanalysis and systematic review, Pharmacokinetic studies**	

1.2 HEPATIC DISORDERS

Description: *Editorial amendment*
An editorial amendment was made to include 'non-alcoholic fatty liver disease' as a cause of hepatitis.

1.2.1 HEPATITIS, NON-VIRAL

General measures: *Editorial amendment*
An editorial amendment was made in respect of managing patients with hepatic encephalopathy and the intake of protein was corrected as grams of protein per day, as tabulated below:

With clinical monitoring of hepatic encephalopathy, maintain 1 to 1.5 g~~mg~~/kg daily protein intake.

Medicine treatment - Lyophilised plasma: *Guidance added*
Medicine treatment – Fresh frozen plasma: *Guidance added*
Medicine treatment – Vitamin K, IV: *Guidance added*
Dosing and administration guidance on the use of vitamin K, lyophilised plasma and Fresh Frozen Plasma has been included in consultation with a hepatic specialist. The use of platelets for the management of bleeding to be considered for prioritisation in the next review cycle.

Updates to the chapter as tabulated below:

AMENDED FROM:	AMENDED TO:
1.2.1 HEPATITIS, NON-VIRAL **MEDICINE TREATMENT** If the patient is bleeding, check INR and correct coagulopathy with: • Lyophilised plasma **or** FFP Parenteral Vitamin K should be provided and the INR reassessed.	**1.2.1 HEPATITIS, NON-VIRAL** **MEDICINE TREATMENT** **If the patient is jaundiced with a prolonged INR (INR>2)** • Vitamin K1, IV, 10 mg ○ Administer as a slow IV injection. ○ Do not dilute or mix with other injectables. **If the patient is bleeding, give** • Lyophilised plasma, IV, 15mL/kg over 20-30 minutes. **OR** • Fresh Frozen Plasma, IV, 15mL/kg over 20-30 minutes. **AND** Discuss further management with a specialist.

[8] NDoH Evidence Review. H.pylori eradication. 4 June 2020

1.2.2 LIVER FAILURE, ACUTE

General measures: *Editorial amendment*

Editorial amendments were made to the STG as tabulated below. The use of parenteral vitamin K1 to be considered for prioritisation for review in the next review cycle.

- Protein restriction is indicated for encephalopathy, however, severe protein restriction may accentuate catabolism. Use increments of 20 g protein per day aiming for 1g/kg/day as tolerated.
- Exclude GI bleed and infection. ~~as a precipitant.~~
- If the patient is bleeding, check INR and correct coagulopathy with FFP or lyophilised plasma. ~~Routine administration of parenteral vitamin K_1 is of unproven value.~~

Acute liver failure – antiviral therapy: *Not added*

The use of antiviral therapy for the management of acute liver failure or progressive synthetic dysfunction was not supported as no compelling evidence was identified to support the use of antivirals for these indications.

1.2.3 PORTAL HYPERTENSION AND CIRRHOSIS

General measures: *Editorial amendment*

An editorial amendment was made in respect of managing patients with hepatic encephalopathy with the intake of protein being corrected as grams of protein per day, as tabulated below.

Hepatocellular carcinoma was added to the list of potential diagnoses to be excluded.

Encephalopathy: with acute HE, protein restrict (ideally under advice of dietician), otherwise 1–1.5 g~~mg~~/kg protein per day. Exclude infection, high protein load, occult bleed, sedatives and electrolyte disturbances and hepatocellular carcinoma

Variceal bleeding: *octreotide not added*

The use of octreotide for the management of variceal bleeds has not been added to the EML as it is yet to be reviewed by the Tertiary Expert Review Committee for potential consideration for inclusion on the Tertiary EML.

Medicine treatment - ascites: *editorial amendments*

The following editorial amendments were made to the STG:

Ascites R18

- Diagnostic paracentesis if indicated
- Single morning dose of oral spironolactone, oral 100 mg and furosemide, oral, 40 mg.
  - Increase the dose by 100 mg and 40 mg, respectively, every 3–5 days, to a maximum dose of 400 mg spironolactone and 160 mg of furosemide depending on serum Na^+, K^+, urea and creatinine.
  - Spironolactone may cause hyperkalaemia.
  - Rapid fluid shifts may precipitate acute liver and/or renal failure.

Medicine treatment – Tense ascites: *editorial amendments*

The following editorial amendments were made to the STG:

Albumin replacement ~~should be considered~~ must be given if ≥5 L of fluid is drained by paracentesis, or if there is pre-existing renal dysfunction:

Medicine treatment – Refractory ascites: *editorial amendments*

The following editorial amendments were made to the STG:

Albumin replacement ~~should be considered~~ must be given if ≥5 L of fluid is removed removed by paracentesis:

Oesophageal varices: *carvedilol not added*

Propranolol included on the therapeutic interchange database as example of class the therapeutic class of beta blockers for the management of oesophageal varices.

Referral: *editorial amendment*

Endoscopic variceal ligation has been added an option for referral to a specialist unit for further management.

1.2.4 HEPATITIS, VIRAL

Description: *editorial amendment*
The description has been amended to include hepatitis D i.e. *'Hepatitis caused by one of the hepatotropic viruses, hepatitis A, B, C, D and E.'*

1.2.4.1 HEPATITIS B, ACUTE

General measures: *editorial amendment*
The STG has been clarified to indicate that patients who are non-immune (negative for surface hepatitis B antibodies), should receive hepatitis B immunisation.
A cross reference to the AH Chp 9 : Infections chapter Section 9.2 Adult vaccination chapter has been added.

Medicine treatment – hepatitis B virus prophylaxis following exposure: *Amended*
Home-based or family caregivers have been included as individuals at high risk for exposure to hepatitis B – they should therefore be screened and vaccinated against hepatitis B.

AMENDED FROM:
Hepatitis B virus: prophylaxis following exposure e.g. needle stick injury
S61.0 + (W46.22+Z20.5+Z29.8)
Persons at risk can be protected by passive immunisation with hyper immune serum globulin prepared from blood containing anti-HBs.
It is essential that all categories of healthcare workers (HCW) who are at risk of exposure, including cleaning staff, be fully vaccinated against hepatitis B.

AMENDED TO:
Hepatitis B virus: prophylaxis following exposure e.g. needle stick injury
S61.0 + (W46.22+Z20.5+Z29.8)
Persons at risk can be protected by passive immunisation with hyper immune serum globulin prepared from blood containing anti-HBs.
It is essential that all categories of healthcare workers (HCW) at risk of contact with bodily fluids, including cleaning staff, home-based or family caregivers are screened and fully vaccinated against hepatitis B if non-immune.

1.2.4.2 HEPATITIS B, CHRONIC (NON-HIV COINFECTION)

Hepatitis B screening and immunization for close family contacts and caregivers: *Amended*
The STG has been amended to include guidance for screening and vaccination against hepatitis B for at risk individuals including home-based or family caregivers. The following statement has been added to the STG:

Screen all categories of healthcare workers (HCW) at risk of contact with bodily fluids, including cleaning staff, home-based or family caregivers and vaccinate against hepatitis B if not immune (see Section 24.1.5 management of close contacts of patients with hepatocellular carcinoma).

Tenofovir disoproxil furmarate (TDF) – eGFR > 50mL/min: *Retained*
TDF 300mg daily has been retained on the EML for the management of chronic hepatitis B (non-HIV coinfection) in patients woithout renal impairment.

Tenofovir alafenamide (TAF) – eGFR > 50mL/min: *Added to TI database*
TDF & TAF - Therapeutic Interchange: *Added*
The NEMLC supported the inclusion of TDF 300mg daily and TAF 25mg daily on the TI database for the management of chronic hepatitis B (non-HIV confection) in patients without renal impairment i.e. eGFR > 50mL/min.

Section (Description)	Indication	Therapeutic Class	INN	Strength	Unit	Formulation
Chronic hepatitis B (non-HIV confection)	Treatment – eGFR > 50mL/min	Antivirals – nucleoside reverse transcriptase inhibitors	Tenofovir disoproxil fumarate (TDF)	300	mg	Oral
Chronic hepatitis B (non-HIV confection)	Treatment – eGFR > 50mL/min	Antivirals – nucleoside reverse transcriptase inhibitors	Tenofovir alafenamide (TAF)	25	mg	Oral

Tenofovir alafenamide (TAF) - eGFR 15-50mL/min (or on haemodialysis): *Added*

Following the NEMLC decision to include TAF in the EML for PLHIV and hepatitis B coinfection with renal impairment (*refer to NEMLC report for AH Chp 10 HIV*) in accordance with the evidence review undertaken in PLHIV[9], the NEMLC recommended a uniform approach to managing patients with chronic hepatitis B and renal impairment (eGFR <50mLs/min), irrespective of HIV status – refer to Addendum 1 of the evidence review on the Knowledge Hub[10] or as included below. It is anticipated that the cohort of patients with chronic hepatitis B and eGFR <50mLs/min, without HIV coinfection, will be a relatively small number of patients.[11] The use of tenofovir disoproxil furmarate (TDF) 300mg daily will be retained in the EML for managing chronic hepatitis B in HIV negative patients, who present with a eGFR>/= 50ml/min. To note, TAF monotherapy can be safely administered from eGFR 15mLs/min, however for PLHIV who are likely to receive TAF in a fixed dose combination with FTC (emtricitabine) or 3TC (lamivudine), an eGFR < 30 mLs/min would be a contraindication to use. The STG has been amended as tabulated below:

AMENDED FROM:

MEDICINE TREATMENT

- Tenofovir, oral, 300 mg daily, if estimated CrCl >50 mL/minute.

REFERRAL

Failure of or contraindications to tenofovir.

AMENDED TO:

MEDICINE TREATMENT

If eGFR > 50mL/min/1.75m^2

- Tenofovir disoproxil fumarate (TDF), oral, 300 mg daily

If eGFR 15-50mL/min/1.75m^2 (or on haemodialysis)

- Tenofovir alafenamide (TAF), oral, 25 mg daily

REFERRAL

Failure of, or contraindications to tenofovir. disoproxil fumarate and tenofovir alafenamide.

Monitoring whilst on tenofovir: *Editorial amendments*

Guidance on monitoring requirements while on tenofovir treatment has been aligned to the NDoH viral hepatitis guideline[12] and amended as tabulated below:

AMENDED FROM:

MONITORING WHILST ON TENOFOVIR

Baseline	FBC+diff, ALT, INR, urine protein, serum phosphate and serum creatinine
Week 4 and every 12 weeks	FBC+diff, ALT
Week 4	INR
Week 4, then at 3, 6 and 12 months after initiation and every 12 months thereafter if on TDF	Serum creatinine
Every 6 months	HBeAg-positive patients: HbsAg after anti-HBe seroconversion HBeAg-negative patients: HBsAg with persistently undetectable HBV DNA
Every 12 months	HBeAg-positive patients: HBeAg, anti HBe
HBeAg-positive patients: 12 months after HBeAg seroconversion	HBV DNA levels

AMENDED TO:

Monitoring whilst on tenofovir

Monitoring test	When to perform test
Serum phosphate and urine protein	Baseline
INR	Baseline, Week 4
Serum creatinine	All patients: Baseline

[9] NDoH Evidence Summary: Use of TAF for adults with HIV. V4_14 March 2024.

[10] NDoH Evidence Summary: Use of TAF for adults with HIV. V5_1 July 2024.

[11] The inclusion of TAF 25mg on the EML for the management of hepatitis B in patients with renal impairment and non-HIV coinfected, is subject to review once the price of TAF 25mg is confirmed.

[12] *National Department of Health, National guidelines for the management of viral hepatitis, 2019. Available at www.health.gov.za*

	Patients on TDF: Week 4, then 3 months, 6 months, and 12 months after initiation; then, every 12 months thereafter.
ALT	Baseline, Week 4, and every 12 weeks thereafter
FBC+Diff	Baseline, Week 4, and every 12 weeks thereafter
HBeAg and Anti-HBe	HBeAg-positive patients: Every 12 months
HBsAg	HBeAg-positive patients: HBsAg every 6 months after anti-HBe seroconversion HBeAg-negative patients: HBsAg every 6 months with persistently undetectable HBV DNA
HBV DNA levels	HBeAg-positive patients: 12 months after HBeAg seroconversion

Table 1.3: Monitoring tests whilst on tenofovir

Adapted from: National Department of Health, National guidelines for the management of viral hepatitis, 2019. Available at www.health.gov.za

1.3.1 CHOLERA

Following consultation with the NICD and the NDoH program guideline team, the STG on the management of cholera has been amended as tabulated below.

Ciprofloxacin dose and duration of treatment: *Amended*

Guidance on the dosing and duration of ciprofloxacin treatment for cholera has been amended in line with the GTFCC (Global Task Force on Cholera Control) guideline[13] for adults.

Fluid replacement – ringers lactate: *Added*

A number of international guidelines[14,15,16] recommend ringers lactate as the preferred IV fluid for replacement therapy in patients infected with cholera, due to the inclusion of the electrolytes potassium and bicarbonate. In the absence of good quality evidence demonstrating the superiority of Ringer's lactate over sodium chloride 0.9%, it was agreed that both ringers lactate and sodium chloride be recommended as options for IV fluid replacement in patients infected with cholera, with Ringer's lactate listed as the preferred option particularly when routine monitoring of potassium and other electrolytes is not possible e.g. at the primary healthcare level of care. Retaining sodium chloride 0.9% on the EML will avert delays with initiating IV fluid should Ringer's lactate not be readily available.

AMENDED FROM:

GENERAL MEASURES

Rehydration is the cornerstone of management. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated.

MEDICINE TREATMENT

- Ciprofloxacin, oral, 500 mg 12 hourly for 3 days.
  - Adjust antibiotic choice, according to the sensitivity of the isolate responsible for the local epidemic.

AMENDED TO:

GENERAL MEASURES

Rehydration is the cornerstone of management. Oral rehydration is preferred.

MEDICINE TREATMENT

Oral rehydration solution (ORS) by mouth or nasogastric tube.

[13] Global Task Force on Cholera Control. October 2019

[14] Harris JB et al. Cholera (NIH). Lancet. 2012 June 30; 379(9835): 2466–2476. doi:10.1016/S0140-6736(12)60436-X

[15] Nelson EJ et al. Cholera outbreak training and shigellosis program (COTSPROGRAM). V2 may 2018

[16] Global Task Force on Cholera Control. October 2019

If enteral administration not possible, e.g., patient is vomiting, profoundly dehydrated, or stuporous:
IV treatment:
Ringers lactate, IV (preferred)

OR

Sodium chloride, 0.9%, IV.

AND

- Ciprofloxacin, oral, 1 gram as a single dose
  - Adjust antibiotic choice, according to the sensitivity of the isolate responsible for the local epidemic.

NOTE: Dextrose 5% should not be used for fluid replacement in patients with cholera as it does not contain electrolytes, which are required to ensure adequate fluid resuscitation.

1.3.2 DYSENTRY (ACUTE INFLAMMATORY DIARRHOEA)

Antibiotic therapy: *Editorial amendment*

An editorial amendment with reference to culture and sensitivity results, was made to the STG as tabulated below:

Antibiotic therapy

Consider in patients with signs of sepsis and severe cases or significant underlying disease:

- Ceftriaxone, IV 1g daily.
  - Switch to oral therapy when clinically appropriate i.e. ciprofloxacin, oral, 500 mg 12 hourly, ideally based on culture and sensitivity if available.

1.3.3 DIARRHOEA, ACUTE NON-INFLAMMATORY

Medicine treatment –loperamide: *Dose amended*

The maximum daily dose of loperamide in adults has been amended in accordance with weight based dose banding included in the package insert[17]. Amendments are as tabulated below:

AMENDED FROM:

- Loperamide, oral, 4 mg immediately and 2 mg as required after each loose stool, up to 6 hourly.
  - Maximum daily dose: 12 mg.

AMENDED TO:

- Loperamide, oral, 4 mg immediately and 2 mg as required after each loose stool.
  - Maximum daily dose for adults: refer to dose table below.

Weight band	Maximum daily dose (equivalent maximum number of 2 mg tablets per day)
34-39 kg	10 mg (5 tablets)
40-46 kg	12 mg (6 tablets)
47-53 kg	14 mg (7 tablets)
≥ 54 kg	16 mg (8 tablets)

1.3.4 CLOSTRIDIUM DIFFICILE DIARRHOEA

Description: *Editorial amendment*

An editorial amendment was made to include *Clostridioides difficile* as an alternative description to *Clostridium difficile*, following its reclassification in 2016[18]. As labortatory reporting still refers to *Clostridium difficile*, this has been retained as the more commonly used description in the EML.

[17] Loperamide (max dose). Package Insert. Imodium. Johnson & Johnson (Pty) Ltd.. Renewal of authorisation 04 March 2005.

[18] The Lancet Infectious Diseases. C difficile-a rose by any other name…. Lancet Infect Dis. 2019 May;19(5):449. doi: 10.1016/S1473-3099(19)30177-X. Erratum in: Lancet Infect Dis. 2019 Jun;19(6):e187. PMID: 31034382.

Mild to moderate infection – vanomycin: *Not added*

Metronidazole is retained as the treatment option for the managaement of mild to moderate C.difficile infection in line with the previous NEMLC report published in 2018[19]. A summary of the NEMLC recommendation is tabulated below.

Recommendation:

Based on this review, the Adult Hospital Level Committee recommends that severe and recurrent CDI be treated as follow:

- *For severe cases:* Vancomycin parenteral administered orally and metronidazole, IV if unable to take oral treatment.
- *For recurring cases*: Pulse and tapered vancomycin therapy.

Rationale:

- Systematic review evidence showed no significant difference in the risk of mortality between treatment groups among patients with mild to moderate CDI, but vancomycin significantly reduced the risk of all-cause 30-day mortality among patients with **severe** CDI.
- Recommendations aligned with clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), taking into consideration the costs of the medicines.

Level of Evidence: I Systematic review, Guidelines

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X		

VEN status:

Vital	Essential	Necessary
	X	

NEMLC MINUTES OF THE MEETING OF 27 SEPTEMBER 2018:

NEMLC accepted the evidence review and proposed recommendation at the NEMLC meeting of 27 September 2018

Fulminant infection – rectal vancomycin: *Not added*

The use of rectal vancomycin was not supported as not deemed appropriate for the Adult Hospital level of care.

B. EDITORIAL AMENDMENTS

The associated EML chapter has been subject to clinical editorial review following NEMLC ratification of the chapter. These amendments have been incorporated below.

1.1.1 BOWEL PREPARATIONS

AMENDED FROM:

Bowel preparation is essential for colonoscopy.

Split-dose (half the dose the night before and half the dose on the day of colonoscopy) bowel cleanser and a low residue diet should be commenced the day before.

GENERAL MEASURES

Health care professionals should provide both oral and written patient education instructions and emphasise the importance of adherence to the bowel preparation.

MEDICINE TREATMENT

Preparations containing ingredients such as polyethylene glycol (PEG), and sodium sulphate are adequate for bowel cleansing.

- PEG/sodium sulfate, oral, solution.
  - 2 litres the night before the procedure and 2 litres the following morning within two hours of the procedure.

Routine use of adjunctive agents (e.g. bisacodyl, senna, prokinetics) for

[19] NDoH evidence review: Antibacterials for enterocolitis due to Clostridium difficile. 5 April 2018

bowel cleansing before colonoscopy is not recommended

AMENDED TO:

DESCRIPTION

Bowel preparation is essential for colonoscopy.

GENERAL MEASURES

Health care professionals should provide both oral and written patient education instructions and emphasise the importance of adherence to the bowel preparation.

MEDICINE TREATMENT

Start bowel preparation as a split-dose regimen the day before the scheduled procedure: half the dose the night before and half the dose on the day of colonoscopy.
Commence a low residue diet the day before.

Preparations containing ingredients such as polyethylene glycol (PEG) and
sodium sulphate are adequate for bowel cleansing.

- PEG/sodium sulphate oral, solution:
  - Prescribe 2 litres the night before the procedure and 2 litres the following morning, two hours prior to the procedure.

Note:
Routine use of adjunctive agents (e.g. bisacodyl, senna, prokinetics) for bowel cleansing before colonoscopy is not recommended

1.1.2 DIVERTICULOSIS

AMENDED FROM:

<u>If unable to tolerate oral therapy:</u>

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly.

AMENDED TO:

<u>If unable to tolerate oral therapy:</u>

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly.
  - Switch to oral therapy once able to tolerate.

1.1.8 PEPTIC ULCER

AMENDED FROM:

DESCRIPTION

Ulcer in the stomach mucosa (gastric ulcer: GU) or first few centimetres of the duodenum (duodenal ulcer: DU), which penetrates into or through the muscularis mucosa.
Diagnosis is made after endoscopy, as all GUs require biopsy to exclude malignancy.
Patients with GUs and complicated DUs, those that have bled, perforated or are recurrent, must be rescoped at appropriate intervals until the ulcer has healed. *H. pylori* can be assessed at scope by rapid urease testing (RUT) or biopsy.

GENERAL MEASURES

Advise patient to avoid ulcerogenic medications, e.g. NSAIDs.
Advise patient to stop smoking and drinking alcohol.
Dietary advice by dietician

AMENDED TO:

DESCRIPTION

Ulcer in the stomach mucosa (gastric ulcer: GU) or first few centimetres of the duodenum (duodenal ulcer: DU), which penetrates into, or through the muscularis mucosa. Diagnosis is made after endoscopy as all GUs require biopsy to exclude malignancy.

GENERAL MEASURES

» Advise patient to avoid ulcerogenic medications, e.g. NSAIDs.
» Advise patient to stop smoking and drinking alcohol.
» Dietary advice by dietician.

» Patients with GUs and complicated DUs, those that have bled, perforated or are recurrent, must be rescoped at appropriate intervals until the ulcer has healed. *H. pylori* can be assessed at scope by rapid urease testing (RUT) or biopsy.

1.2.3 PORTAL HYPERTENSION AND CIRRHOSIS

AMENDED FROM:

GENERAL MEASURES

Ascites: sodium restriction, i.e. ≤ 2 g/day or ≤ 88 mmol/day.
Monitor weight regularly.
Encephalopathy: with acute HE, protein restrict otherwise 1–1.5 g/kg protein per day.
Exclude infection, high protein load, occult bleed, sedatives and electrolyte disturbances and hepatocellular carcinoma.
Variceal bleeding: endoscopic variceal ligation and/or immediate referral for advanced management.

MEDICINE TREATMENT

Ascites R18

- Diagnostic paracentesis if indicated
- Single morning dose of spironolactone, oral 100 mg and furosemide, oral, 40 mg.
  - Increase the dose by 100 mg and 40 mg, respectively, every 3–5 days, to a maximum dose of 400 mg spironolactone and 160 mg of furosemide depending on serum Na+, K+, urea and creatinine.
  - Spironolactone may cause hyperkalaemia.
  - Rapid fluid shifts may precipitate acute liver and/or renal failure.

Monitoring of sodium, potassium and renal function is essential in patients taking spironolactone. Avoid spironolactone if eGFR <30 mL/minute.

Measure response to diuretics by weighing patient daily. Aim for maximal weight loss of:

500 g/day	patients without oedema
1 000 g/day	patients with oedema

AMENDED TO:

GENERAL MEASURES

» Ascites: Perform diagnostic paracentesis if indicated. Restrict sodium intake, i.e. ≤ 2 g/day or ≤ 88 mmol/day.
» Monitor weight regularly.
» Encephalopathy: with acute HE, protein restrict (ideally under advice of dietician), otherwise 1–1.5 g/kg protein per day.
» Exclude infection, high protein load, occult bleed, sedatives, electrolyte disturbances and hepatocellular carcinoma.
» Variceal bleeding: endoscopic variceal ligation and/or immediate referral for advanced management.

MEDICINE TREATMENT

Ascites R18

- Spironolactone, oral, 100 mg daily.
  AND
- Furosemide, oral, 40 mg daily.

For spironolactone and furosemide:

- Increase spironolactone and furosemide dose by 100 mg and 40 mg, respectively, every 3–5 days, to a maximum dose of 400 mg spironolactone and 160 mg of furosemide depending on serum Na^+, K^+, urea and creatinine.
- Spironolactone may cause hyperkalaemia.
- Rapid fluid shifts may precipitate acute liver and/or renal failure.

Monitoring of sodium, potassium and renal function is essential in patients taking spironolactone. Avoid spironolactone if eGFR <30 mL/minute.

Measure response to diuretics by weighing patient daily. Aim for maximal weight loss of:
» Patients without oedema: 500 g/day
» Patients with oedema: 1 000 g/day

AMENDED FROM:

Oesophageal varices

To reduce the risk of bleeding:

- Beta-blocker, e.g.:
- Propranolol, oral, 20–40 mg 12 hourly. Titrate to resting pulse rate of 55-60 beats per minute (bpm). Monitor pulse and BP.

AMENDED TO:

Oesophageal varices I85.0/I85.9

To reduce the risk of bleeding:

- Beta-blocker, e.g.:
- Propranolol, oral, 20–40 mg 12 hourly. Titrate to resting pulse rate of 50–60 beats per minute. Monitor pulse and BP

1.2.4.1 HEPATITIS B, ACUTE

AMENDED FROM:

Hepatitis B virus: prophylaxis following exposure e.g. needle stick injury

S61.0 + (W46.22+Z20.5+Z29.8)

Persons at risk can be protected by passive immunisation with hyper immune serum globulin prepared from blood containing anti-HBs.

It is essential that all categories of healthcare workers (HCW) at risk of contact with bodily fluids , including cleaning staff, home-based or family caregivers are screened and fully vaccinated against hepatitis B if non-immune.

All exposure incidents must be adequately documented for possible subsequent compensation.

Recommended post-exposure management for HCW exposed to infectious material from patients with infectious hepatitis B (either surface antigen or e antigen positive).

Vaccination status and antibody response status of HCW	**Source patient status & treatment**		
	HBsAg positive	**HBsAg negative**	**HBsAg unknown**
Unvaccinated **OR** vaccination incomplete	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)	• Initiate Hep B vaccination (month 0, 1 and 6)	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)
Vaccinated AND HBsAb >10 units/mL#	No treatment	No treatment	No treatment
Vaccinated **AND** HBsAb <10 units/mL	• HBIG, IM, 500 units * • Repeat Hep B vaccine (3 doses at monthly intervals)	• Initiate Hep B vaccination (month 0, 1 and 6)	• HBIG, IM, 500 units* • Repeat Hep B vaccine (3 doses at monthly intervals)

* HBIG and first dose of vaccine to be given simultaneously, but at different sites.

If the delay in obtaining HBsAb results is more than 24 hours initiate treatment as for vaccinated AND HBsAb <10 units/mL.

AMENDED TO:

Hepatitis B virus: prophylaxis following exposure e.g. needle stick injury

S61.0 + (W46.22+Z20.5+Z29.8)

» Persons at risk can be protected by passive immunisation with hyper immune serum globulin prepared from blood containing anti-HBs.

» It is essential that all categories of healthcare workers (HCW) at risk of contact with bodily fluids, including cleaning staff and home-based or family caregivers, are screened and fully vaccinated against hepatitis B if nonimmune.

» All occupational exposure incidents must be adequately documented for possible subsequent compensation.

» Recommended post-exposure management for HCW exposed to infectious material from patients with infectious hepatitis B (either surface antigen or e antigen positive).

Check vaccination status and antibody response of HCW (See table below for management depending on immunity

Vaccination status and antibody response status of HCW	**Source patient status & treatment**		
	HBsAg positive	**HBsAg negative**	**HBsAg unknown**
Unvaccinated **OR** vaccination incomplete	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)	• Initiate Hep B vaccination (month 0, 1 and 6)	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)
Vaccinated **AND** HBsAb ≥10 units/mL#	No treatment	No treatment	No treatment
Vaccinated **AND** HBsAb <10 units/mL	• HBIG, IM, 500 units * • Repeat Hep B vaccine (3 doses at monthly intervals)	• Initiate Hep B vaccination (month 0, 1 and 6)	• HBIG, IM, 500 units* • Repeat Hep B vaccine (3 doses at monthly intervals)

* HBIG and first dose of vaccine to be given simultaneously, but at different sites.

If the delay in obtaining HBsAb results is more than 24 hours initiate treatment as for vaccinated AND HBsAb <10 units/mL.

Table 1.1: Prophylaxis following Hepatitis B exposure

AMENDED FROM:

Treat all patients with cirrhosis regardless of ALT level, HBeAg status and DNA level, to prevent hepatitis B flares that will lead to decompensation

AMENDED TO:

Treat all patients with cirrhosis regardless of ALT level, HBeAg status and HBV viral load, to prevent hepatitis B flares that will lead to decompensation.

1.2.4.4 HEPATITIS C, CHRONIC

Acute liver failure

Consult a specialist.

1.3.2 DYSENTRY (ACUTE INFLAMMATORY DIARRHOEA)

AMENDED FROM:

GENERAL MEASURES

Rehydration is the cornerstone of management. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated.

Stool culture is advised.

AMENDED TO:

GENERAL MEASURES

» Rehydration is the cornerstone of management. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated.

» Perform a stool culture.

AMENDED FROM:

Antibiotic therapy

Consider in patients with signs of sepsis and severe cases or significant underlying disease:

- Ceftriaxone, IV 1g daily.
  - Switch to oral therapy when clinically appropriate i.e. ciprofloxacin, oral, 500 mg 12 hourly, ideally based on culture and sensitivity if available.

For uncomplicated dysentery in patients with no co-morbidity:

- Ciprofloxacin, oral, 500 mg 12 hourly for 3 days.

For uncomplicated dysentery in patients with significant co-morbidity e.g. immunocompromised patients:

- Ciprofloxacin, oral, 500 mg 12 hourly for 7 days.

AMENDED TO:

Antibiotic therapy

Consider in patients with signs of sepsis, severe cases, or significant underlying disease:

- Ceftriaxone, IV 1 g daily.

Switch antibiotic when clinically appropriate:

- Ciprofloxacin, oral, 500 mg 12 hourly, ideally based on culture and sensitivity if available.

For uncomplicated dysentery in patients with no co-morbidity:

- Ciprofloxacin, oral, 500 mg 12 hourly for 3 days.
  - Extend treatment duration to 7 days in patients with significant co-morbidity, e.g. immunocompromised patients.

South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Alimentary (Hepatic Disorders)
Addendum to the NDoH review: Tenofovir alafenamide for PLHIV (Adults)

Date: 27 June 2024
Reviewers: [1.] Dr Nel, [2.] Ms Z Adam
Affiliation and declarations:
[1.] Helen Joseph Hospital, Faculty of Health Sciences, University of the Witwatersrand,
[2.] Consultant to NDoH EML program (Clinton Health Access Initiative).
Both reviewers have no applicable conflicts of interest to declare.

Use of Tenofovir alafenamide (TAF) for the treatment of chronic hepatitis B (non-HIV co-infection) in patients with renal impairment.

Introduction
Hepatitis B virus (HBV) infection is deemed to be endemic in South Africa, and is predominantly seen in adult PLHIV. The predominant strain of HBV circulating in SA is subgenotype A1, is regarded as having unique molecular characteristics with a high hepato-carcinogenic potential (Maepa MB et al, 2022).

The main goal of chronic hepatitis B (CHB) therapy is to improve survival and quality of life by preventing disease progression to cirrhosis and liver failure and to avert disease-related complications such as hepatocellular carcinoma. Two classes of antiviral drugs are generally recommended for the treatment of chronic hepatitis B, namely interferon alpha and nucleoside analogues. The nucleoside analogues are preferentially considered as they are available as oral treatments which are usually cheaper than interferon alpha, are generally regarded to be well tolerated, and are options for a wider range of patients than interferon (Spearman CWN et al, 2013).

Several nucleoside analogues are used for the management of hepatitis B, including lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) (Scherer de Fraga R et al, 2020), although not all are registered by SAHPRA for local use. ETV, TDF and TAF are generally preferred as they have demonstrated a higher barrier to resistance (Scherer de Fraga R et al, 2020).

Locally, the South African Adult Hospital EML includes the use of TDF tenofovir disoproxil fumarate (TDF) for the treatment of chronic hepatitis B in the non-HIV cohort with eGFR > 50mL/min. There is currently **no** recommended treatment in the Adult Hospital level EML for patients whose eGFR <50 mL/min, because TDF is contraindicated in with renal dysfunction. Until recently, TAF was not SAHPRA registered.

Background
In March 2024, a decision was taken by the NEMLC to include a TAF-containing fixed dose combination (either emtricitabine 200mg or lamivudine 300mg together with tenofovir alafenamide 25mg and dolutegravir 50mg) to the EML for PLHIV with hepatitis B coinfection and renal impairment (eGFR 30-50 ml/min/1.73m2).[1] As part of the deliberations on equity of care, the NEMLC supported the inclusion

[1] NDoH Evidence review. Tenofovir alafenamide (TAF) for HIV_Adult review_14 March 2024_v4.0

of TAF 25mg once daily for the management of hepatitis B for the non-HIV cohort with renal impairment[2], specifically for patients with a eGFR 15-50mL/min or requiring haemodialysis. A summary of the evidence in support this decision is included below, which will be added as an Addendum to the original evidence review in PLHIV. Note that tenofovir disoproxil fumarate (TDF) is retained on the EML for the treatment of chronic hepatitis B in the non-HIV cohort with eGFR > 50mL/min.

PICO

The following eligibility criteria was approved for the review.

Population	HIV negative patients with chronic hepatitis B
Intervention	Tenofovir alafenamide (TAF)
Comparator	Tenofovir Disoproxil Fumarate (TDF)
Outcome	Efficacy outcomes: • Virological response Safety outcomes: • Adverse events
Studies	Systematic reviews and/or meta-analysis
Excluded studies	• Studies in PLHIV with Hepatitis B co-infection (subject of original review) • Studies involving mother to child transmission of Hepatitis B (subject of summary included in Addendum 2)

Literature search

A Pubmed search was conducted on 13 June 2024 for systematic reviews (refer to appendix 1 below) which yielded 39 citations. During the title screen and abstract screen, 31 titles were excluded as studies involved co-infected PLHIV or mother to child transmission during pregnancy and a further 3 titles were excluded as, one was a letter to the editor in response to a SR, one an economic evaluation and the third, a network meta-analysis (NMA) of *only cohort studies* (i.e. no RCTs included). A search of the Cochrane database did not yield any citations relevant to our PICO. One title (Chen L et al) was identified from a manual search as a pre-print e-publication which has not been included as not yet subject to peer review.

The existing literature compares TAF to TDF in a scenario where both are available as first line therapies. However, it should be noted that historically there has not been any treatment option in the EML for those with an eGFR <50.

Summary of Evidence

EFFICACY

1. Tenofovir Alafenamide Fumarate (TAF), Tenofovir Disoproxil Fumarate (TDF) and Entecavir (ETV): Which is the Most Effective Drug for Chronic Hepatitis B? A Systematic Review and Meta-analysis (Ma X, Liu S et al., 2021)

This SR included 28 studies that compared 3 antiviral agents in the management of chronic hepatitis B (TDF v ETV [n=17], TAF vs TDF [n=5] and TDF+ETV v TDF [n=6]). This comprised of 13 RCTs, 14 cohort studies and 1 cross sectional study in which patients co-infected with HIV or other hepato-tropic viruses were excluded. For the TAF v TDF comparison, which is the focus of our evidence summary, 5 studies *which were all RCTs* were included and which included a total of 5192 participants. Virological response was reported at 48 weeks in 4 of the studies and at 96 weeks in 2 of the studies. Virological response of TAF was equivalent to that of TDF (OR=0.97, 95% CI: 0.83–1.14, p>0.05) at 48 weeks (see figure 1 below). According to the review authors, results at 96 weeks suggested that there was no obvious differences in the virological response after treatment with TAF and TDF. Limitations of the meta-analysis was that factors associated with virological response such as age, sex, hepatitis B e antigen status, cirrhosis stage, and HBV DNA level before therapy, duration of previous therapy, and baseline HBV DNA level were not accounted and which the review authors acknowledged.

[2] Adult Hospital EML. AH Chp 1 Alimentary Section 1.2.4.2 Hepatitis B, Chronic (Non-HIV con-infection)_2020-4 review

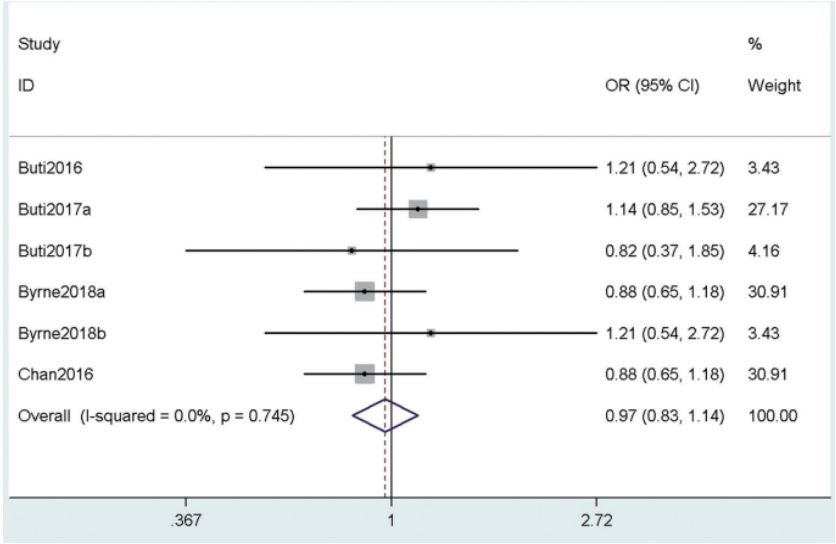

Fig 1: Pooled OR of virological response in TAF-treated vs. TDF-treated CHB patients after 48 weeks of treatment

2. Antiviral treatment for treatment-naïve chronic hepatitis B: systematic review and network meta-analysis of randomized controlled trials (Wong WL et al., 2019))

This review involved a network meta-analysis of RCTs investigating the comparative effectiveness of different treatments for hepatitis B (PEG-IFN, ADV, LAM, ETV, TBV, TDF, TAF as monotherapy or combination therapy) in a treatment-naïve adult population who were either HBeAg-positive or negative, without co-infections, decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation. Efficacy endpoints for the HBeAg-positive population included: virologic response (VR), normalization of alanine aminotransferase level (ALT norm), HBeAg loss, HBeAg seroconversion, and hepatitis B surface antigen (HBsAg) loss; and two efficacy endpoints for the HBeAg-negative population included: VR and ALT norm. RCTs that compared at least two antiviral treatments or one treatment with placebo/no treatment were included in the SR. The review included 12 885 participants across 42 publications of which, 23 studies were in HBeAg-positive patients, 13 in HBeAg-negative patients and 6 included both patient groups. In the case of HBeAg-positive patients, for the comparison of TAF v TDF, the authors reported an OR = 0.88, 95CrI 0.38–1.99. TDF had a probability of 43% being the best treatment for achieving virologic response, followed by the combination strategy ETVTDF (29%) and TAF (26%). In HBeAg-negative patients, TAF and TDF had the highest probabilities of achieving viral suppression (48% and 28% respectively). The authors concluded that *"across all outcomes and in both HBeAg-positive and HBeAg-negative populations, TAF emerged as the treatment with the most consistent performance."*

ADVERSE EFFECTS

3. Renal and bone side effects of long-term use of entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide fumarate in patients with Hepatitis B: a network meta-analysis (Liu Z et al., 2023)

This study was a network meta-analysis of RCTs assessing the safety of longterm use of ETV, TAF and TDF with respect to bone and kidney effects. Quantitative measures of renal function were assessed by a decrease in eGFR and increase in creatinine, and decreased bone mineral density (BMD) and blood phosphorous for assessing bone injury. The analysis included 4278 participants across 16 RCTs, however the sample represents a limited ethnic pool as all studies were conducted in Asia. The authors reported that ETV and TAF were associated were less of an effect on eGFR reduction compared to TDF (SMD = -3.60; 95%CI: -1.94 ~ -5.26 and SMD = -4.27; 95%CI: -2.62 ~ -5.93, respectively) and there was not a statistically significant increase in creatinine with TAF or TDF (SMD=0.06; 95%CI: -0.03~0.15). TAF exhibited the lowest eGFR reduction probability (SUCRA 8.8%) and TDF the highest eGFR reduction probability (SUCRA 100.0%). The authors concluded that overall, TDF was associated with a greater

degree of renal damage compared to TAF or ETV (refer to Figure 2 for more detail). With regard to BMD, TAF was associated with a lower reduction in BMD compared to TDF (SMD = -0.02; 95%CI: -0.01 ~ -0.02). Furthermore, the authors reported no statistically significant differences in the levels of blood phosphorus among the three drugs. TAF exhibited the lowest probability of decreasing BMD (SUCRA 19.6%), and TDF the highest probability TDF (SUCRA 79.7%).

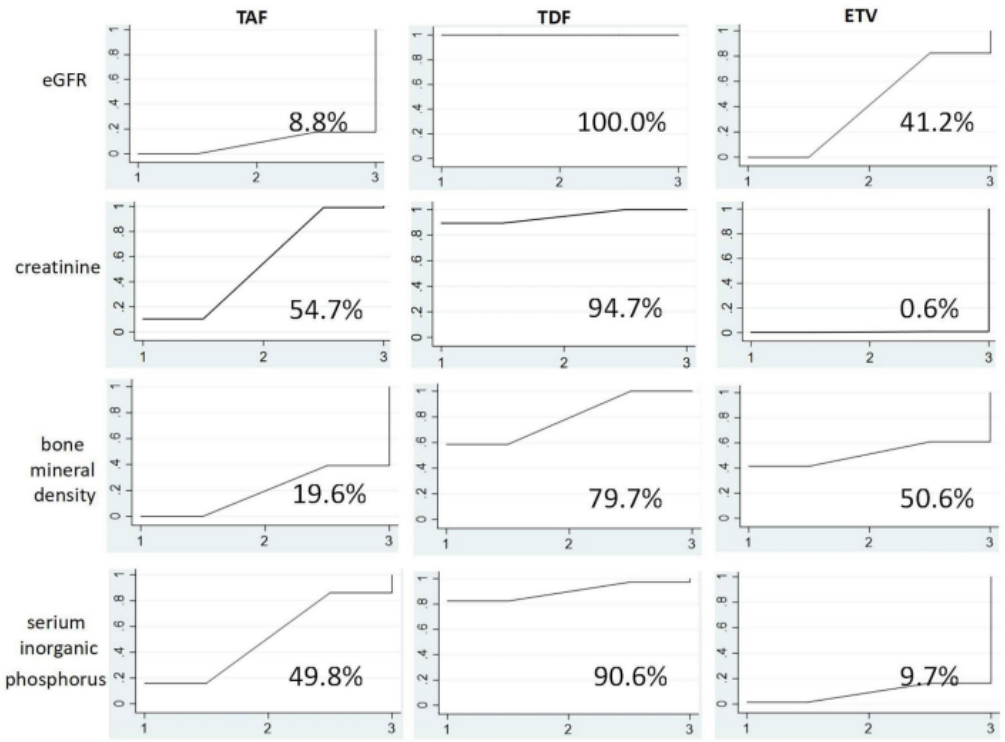

Figure 2: SUCRA diagram of side effects. The figure shows the probability of the effects of three drugs on eGFR, creatinine, bone mineral density, and blood phosphorus before and after medication. According to the level of area under the curve (SUCRA), the larger the area, the greater the index change value.

The authors also undertook a subgroup analysis of the duration of exposure to treatment. As this was a comparison of TDF versus ETV, we have not reported on these findings as ETV is not included in our PICO.

4. Adverse events of nucleos(t)ide analogues for chronic hepatitis B: a systematic review (Scherer de Fraga R et al, 2020)

This aim of this SR, which included both RCTs and observational studies, was to address 3 key research questions, namely:

- What are the most common AEs with the use of NAs in the CHB treatment?
- Is there any difference in the incidence of AEs between the different NAs?
- Do patients receiving TAF have fewer AEs compared to TDF?

The analysis was based on 120 publications, with 6419 participants receiving lamivudine (LAM), 5947 receiving ETV, 3566 receiving TDF, 3096 receiving telbivudine (LdT), 1178 receiving Adefovir dipivoxil (ADV) and 876 receiving TAF. We have limited our reporting on the comparison of TAF vs TDF in line with our PICO.

Data from 2 studies comparing TDF and TAF and *which were both RCTs,* informed the following conclusion by the study authors (refer to Figure 3 and 4 below for details):

- TDF caused greater bone loss in both hip and spine compared to TAF
- There was no clinically significant difference between the two drugs regarding the elevation of serum creatinine, but there was a greater reduction in the glomerular filtration rate in patients who received TDF

The authors however do acknowledge that "t*he number of patients treated with TAF still is too small to consolidate that TAF is really safer than TDF*".

Study	Follow-up		TAF	TDF	p
Buti, 2016 [29]	48 weeks	hip	− 0.29%	− 2.16%	< 0.0001
		spine	− 0.88%	− 2.51%	0.0004
Chan, 2016 [30]	48 weeks	hip	− 0.1%	− 1.72%	< 0.0001
		spine	− 0.42%	− 2.29%	< 0.0001

Figure 3: Mean percentage decrease in hip and spine bone mineral density with TDF and TAF in studies comparing the two drugs

Study	Follow-up		TAF	TDF	*p*
Buti, 2016 [29]	48 weeks	↑Cr (mg/dl)	0.01	0.02	0.32
		↓eGFR (ml/min)	1.8	4.8	0.004
Chan, 2016 [30]	48 weeks	↑Cr (mg/dl)	0.01	0.03	0.02
		↓eGFR (ml/min)	0.6	5.4	< 0.0001

Figure 4: Mean increase in serum creatinine (Cr) from baseline and the median decrease in estimated glomerular filtration rate (eGFR) with TDF and TAF in studies comparing the two drugs

5. Risk of dyslipidemia in chronic hepatitis B patients taking tenofovir alafenamide: a systematic review and meta-analysis. (Hwang EG et al, 2023)

This aim of this SR was to assess changes in the lipid profile of chronic hepatitis B sufferers following treatment with TAF and other drugs used to treat hepatitis B. The review included 12 studies, 5 (2 RCTs and 3 retrospective cohort studies) of which compared TAF vs TDF, 3 cohort studies comparing TAF vs ETC or TDF, 3 cohort studies where TAF was compared to placebo and 1 study with TAF v ETV. Clinical outcomes were reported as a change in lipid profile under 2 scenarios: i) pre and post TAF treatment in the same patient and ii) difference between TAF and non-TAF antiviral groups. In line with our PICO, we have limited reporting to the comparison between TAF v TDF only, which the study authors included as a sub-group analysis: the mean difference in the TAF group versus the TDF group was reported as follows: LDL-cholesterol level 14.52 mg/dL (95% CI 10.95–18.10), total cholesterol 23.72 mg/dL (95% CI 19.12–28.33) and triglycerides 14.25 mg/dL (95% CI 12.64–15.86).

Outcome	No. of studies	Mean difference	95% CI	I^2	*p* for heterogeneity
HDL-cholesterol	4	7.93	7.44 to 8.42	99	< 0.01
LDL-cholesterol	4	14.52	10.95 to 18.10	100	< 0.01
Total cholesterol	5	23.72	19.12 to 28.33	100	< 0.01
Triglyceride	2	14.25	12.64 to 15.86	91	< 0.01

TAF Tenofovir Alafenamide Fumarate; *TDF* Tenofovir Disoproxil Fumarate; *HDL-cholesterol* High-Density Lipoprotein cholesterol; *LDL-cholesterol* Low-Density Lipoprotein cholesterol

Figure 5: Change in lipid profle during TAF treatment (vs. TDF only)

Recommendation*

The Committee supports the inclusion of TAF on the EML for the management of chronic hepatitis B without HIV co-infection as treatment for eligible patients who have renal impairment i.e.

If eGFR 15-50mL/min (or on haemodialysis):

- Tenofovir alafenamide, oral, 25 mg daily.

***Note:** *At the time of publication, TAF 25mg tablets were listed on the SAHPRA website as locally registered products. However as there is no confirmed SEP, this NEMLC recommendation is subject to review following price confirmation.*

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APPENDIX

Pubmed search History

History and Search Details

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Search	Actions	Details	Query	Results	Time
#5	•••	›	Search: **#1 AND #2** Filters: **Meta-Analysis, Systematic Review**	39	05:36:46
#4	•••	›	Search: **#1 AND #2** Filters: **Systematic Review**	27	05:30:05
#3	•••	›	Search: **#1 AND #2**	1,311	05:29:59
#2	•••	›	Search: **Tenofovir Disoproxil Fumarate**	10,196	05:29:33
#1	•••	›	Search: **Tenofovir Alafenamide**	1,311	04:44:36
#0	•••	›	Search: **Clipboard**	5	06:53:30