health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 1: ALIMENTARY TRACT CONDITIONS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the chapter for alimentary conditions.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
1.1.3 Gastro-oesophageal reflux disease (GORD)	PPIs	Added as a therapeutic class
	Lansoprazole, oral (30 mg)	Amended as an example of therapeutic class – standard dose PPI
	Omeprazole, oral (10 mg)	Amended as an example of therapeutic class – low dose PPI
	Empirical PPI therapy	Duration of PPI therapy where there is no alarm symptoms was retained as "4 weeks"
- Recurrence of symptoms	PPIs	Directions of use not amended
- Pre-endoscopy	Erythromycin	Not added as prokinetic, pre-endoscopy
	Metoclopramide	Not added as prokinetic, pre-endoscopy
1.1.8 Peptic ulcer	PPIs	Added as a therapeutic class
	Lansoprazole, oral (30 mg)	Amended as an example of therapeutic class – standard dose PPI
	Omeprazole, oral (10 mg)	Amended as an example of therapeutic class – low dose PPI
	Amoxicillin, oral	Retained and duration of therapy amended from 7 to 14 days
	Metronidazole, oral	Retained and duration of therapy amended from 7 to 14 days
	Clarithromycin, oral	Not added to the STG, but as an alternative to azithromycin, oral on the therapeutic interchange database (penicillin allergy)
	Azithromycin, oral	Retained and duration of therapy retained as 3 days (penicillin allergy)
1.2.3 Portal hypertension and cirrhosis *- Oesophageal varices*	Beta-blockers, oral	Added as a therapeutic group
	Propranolol, oral	Added as an example of the therapeutic group (listed in the STG)
	Carvedilol, oral	Added as an alternative option in the therapeutic group (listed in therapeutic database)
- Tense ascites	Albumin, IV	Directions for use amended
1.2.4.2 Hepatitis B, chronic (Non-HIV coinfection)	Tenofovir, oral	Directions for discontinuation not amended
	Tenofovir, oral	Monitoring updated
1.3.1 Cholera	Ciprofloxacin, oral	Dosing amended
1.3.4 *Clostridum Difficle* diarrhoea		
- Diagnosis and investigations	Diagnosis and investigations	Amended
- General measures	Infection control recommendations	Added
- Antibiotic therapy	Fidaxomicin, oral	Not added
	Empirical antibiotic treatment	Deleted
	Directed antibiotic treatment	Added
	Metronidazole, oral	Retained
	Metronidazole, IV	Retained
	Vancomycin, oral	Retained
- Fulminant infection: If ileus or toxic megacolon or hypotension/shock	Metronidazole, IV	Added
	Metronidazole, oral	Added (de-escalation)

1.1.3 GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)

PPI's: *added as a therapeutic class*
Lansoprazole, oral (30 mg): *amended as an example of therapeutic class – standard dose PPI*
Omeprazole, oral (10 mg): *amended as an example of therapeutic class – low dose PPI*

Refer to the medicine review: Proton pump inhibitors therapeutic class review, May 2018.

PPIs_TherapeuticClassReview_AdultsRev

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review the Adult ERC recommends PPIs as a therapeutic class with preference to using the dose-equivalent cheapest option.
Uncertainty exits around the safety of long-term use of PPIs (i.e. *C difficle* infection; ESBL carriage; decrease in BMD; pneumonia).
Rationale: Evidence of comparable effectiveness of various dose-equivalent PPIs.
Level of Evidence: II Systematic review of moderate to low evidence[1], Guidelines[2]

Comparative PPI doses (in series) [1 2]*:*

Medicine	High dose	Low dose
Lansoprazole	30 mg	15 mg
Omeprazole	20 mg	10 mg
Pantoprazole	40 mg	20 mg
Rabeprazole	20 mg	10 mg

Empirical PPI therapy: *duration of PPI therapy where there is no alarm symptoms was retained to "4 weeks".*

Systematic review by McDonagh et al, 2009:
- *Esomeprazole compared with lansoprazole.* Two studies comparing esomeprazole 40 mg vs lansoprazole 30 mg reported healing rates in patients with moderate to severe esophagitis at baseline. The pooled risk difference at 4 weeks was 8% (95%, CI 4 to12) and at 8 weeks was 9% (95% CI 5 to 12). These correspond to a number needed to treat of 13 at 4 weeks and 11 at 8 weeks.
- *Lansoprazole compared with omeprazole.* Three studies comparing lansoprazole with omeprazole reported healing rate in patients with moderate to severe (Grades 3 and 4) esophagitis. Two of these compared lansoprazole 30mg with omeprazole 20 mg. There was no difference in healing rate at 4 weeks (pooled risk difference 1%; 95% CI–13 to 16) or 8 weeks (pooled risk difference 3%; 95% CI –4 to 10). The third study compared lansoprazole30 mg with omeprazole 40 mg. There was no significant difference between groups at 4 or 8 weeks. The distribution of the severity of esophagitis among patients in this study is not reported.
Recommendation: Duration of PPI therapy retained to 4 weeks, as no difference In healing rate was seen between a 4 week vs 8 week course. In addition, daily adherence of PPI treatment to be recommended to promote healing.
Level of Evidence: I Systematic review of RCTs of moderate quality

Recurrence of symptoms
PPIs: *directions of use not amended*
Query received querying the need for an endoscopy to continue long-term PPI therapy, as gastroscopy is a scarce resource and should be reserved only for those with alarm symptoms on PPI therapy.

[1] McDonagh MS, Carson S, Thakurta S. Drug Class Review: Proton Pump Inhibitors: Final Report Update 5 [Internet]. Portland (OR): Oregon Health & Science University; 2009 May. Available from http://www.ncbi.nlm.nih.gov/books/NBK47260/
[2] National Institute for Health and Care Excellence: Clinical Guidelines: Gastro-oesophageal reflflux disease and dyspepsia in adults: investigation and management. https://www.nice.org.uk/guidance/cg184

Waiting periods for endoscopy varies in the different Provinces, and thus the pragmatic implication of recommending a 4 week course of empiric PPI treatment course, prior to endoscopy for diagnostic consideration.

Diagnosis needs to be confirmed to guide decision-making on clinical management – e.g. *H. pylori,* erosive GORD and malignancy. Medico-legal implications of continuous PPI therapy without a confirmed diagnosis also requires consideration.

Adverse effects associated with long-term PPI therapy such as *Clostridium difficle* infection and osteonecrosis associated with long-term PPI therapy requires noting.

Recommendation: Continuous empiric PPI therapy without endoscopic confirmation of diagnosis not recommended in patients with recurring symptoms of GORD.
Rationale: Risk-benefit assessment of continuous empiric PPI therapy with or without endoscopic confirmation favours diagnostic confirmation as misdiagnosis and associated *Clostridium difficle* infection and osteonecrosis needs consideration (as well as the medico-legal implications).
Level of Evidence: III Expert opinion

Erythromycin: *not added as prokinetic, pre-endoscopy*
Metoclopramide: *not added as prokinetic, pre-endoscopy*
External comment received from the Council of Medical Schemes querying the use of prokinetics pre-endoscopy; no evidence was submitted. Scoping of the literature determined that evidence is limited and RCTs are small. Meta-analysis[3] of low to moderate quality RCTs, suggests that prokinetics has no effect on length of stay, units of blood transfused, or need for surgery compared to placebo or no treatment. However, prokinetics showed a significant reduction for the need for repeated endoscopy (OR 0.55, 95% CI 0.32 to 0.94; I2 = 32%), which may be more relevant for tertiary and quaternary level of care. The Adult Hospital Level Committee concurs with the Clinical Guidelines by Barkun et al (2010)[4] recommending that "*Promotility agents should not be used routinely before endoscopy to increase the diagnostic yield".*
Level of Evidence: II Meta-analysis of low to moderate quality RCTs, Guidelines

1.1.8 PEPTIC ULCER

PPI's: *added as a therapeutic class*
Lansoprazole, oral (30 mg): *amended as an example of therapeutic class – standard dose PPI*
Omeprazole, oral (10 mg): *amended as an example of therapeutic class – low dose PPI*
Refer to discussion above – section 1.1.3: Gastro-oesophageal reflux disease.

Antibiotic therapy for Helicobacter pylori eradication
Amoxicillin, oral: *retained and duration of therapy amended from 7 to 14 days*
Metronidazole, oral: *retained and duration of therapy amended from 7 to 14 days*
Clarithromycin, oral: *not added to the STG, but as an alternative to azithromycin, oral on the therapeutic interchange database (penicillin allergy)*
Azithromycin, oral: *retained and duration of therapy retained as 3 days (penicillin allergy)*

Background: The South African Gastroenterology Society (SAGES) submitted a recommendation for the review of the treatment of *H. pylori* infection. Numerous trials utilising azithromycin-based

[3] Barkun AN, Bardou M, Martel M, Gralnek IM, Sung JJ. Prokinetics in acute upper GI bleeding: a meta-analysis. Gastrointest Endosc. 2010 Dec;72(6):1138-45. https://www.ncbi.nlm.nih.gov/pubmed/20970794
[4] Barkun AN, Bardou M, Kuipers EJ, Sung J, Hunt RH, Martel M, Sinclair P; International Consensus Upper Gastrointestinal Bleeding Conference Group. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med. 2010 Jan 19;152(2):101-13. https://www.ncbi.nlm.nih.gov/pubmed/20083829

regimens with different methods, drug combinations and treatment durations have demonstrated conflicting results. As an infectious disease, SAGES further recommended that the ultimate aim of *H.pylori* eradication should be 100%, given the association with adverse gastrointestinal and non-gastrointestinal pathology. It was requested to review the current standard of care against international standard of care regimens.

Evidence review: The medicine review for the previous review cycle informed the decision to recommend azithromycin for H pylori eradication in penicillin allergic patients:

azithromycin_h
pylori eradication_a

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

External comment: The South African Medical Association (SAMA) questioned the evidence which informed the duration of treatment with azithromycin and ask that this be reviewed. SAMA noted that the level of evidence for meta-analysis of RCTs of low quality was incorrectly stated as level one. The meta-analysis by Dong et al[5] demonstrated "azithromycin-containing triple therapy has equal efficacy to standard triple eradication therapy", but only 2 of the 14 RCTs[6] [7] included in the meta-analysis had examined the impact of 3-day azithromycin. The RCTs yielded conflicting results, and reported a wide range of eradication rates. Furthermore, only one of these RCT (Ivashkin et al) compared an azithromycin-containing triple regimen to one with no macrolide at all (eradication rate 82% (33/41 vs 40/41); ARR 17%; NNT = 6). Thus, the level of evidence for this was amended to level 2: systematic review of low to moderate quality RCTs.

The Adult Hospital Level Committee undertook an evidence review and also appraised the previous evidence that informed the previous NEMLC recommendation of an azithromycin-containing triple therapy regimen for the eradication for *H.pylori* – see the medicine review, below:

Helicobacter Pylori
Eradication-Adult R

Will be made available at http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee reccomended that azithromycin be retained as part of the recommended triple therapy for eradication of *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 possibly be extended to 10 days (as the elimination half-life is 68 to 72 hours)[8].
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.

[5] Dong J, Yu XF, Zou J. Azithromycin-containing versus standard triple therapy for Helicobacter pylori eradication: a meta-analysis. World J Gastroenterol. 2009 Dec 28;15(48):6102-10. https://www.ncbi.nlm.nih.gov/pubmed/20027685
[6] Zhao Y, Hang YQ. Effect of PPI-triple therapy in eradication treatment of Helicobacter pylori. Zhongguo Shiyong Xiangcun Yisheng Zazhi 2005; 12: 30-31
[7] Ivashkin VT, Lapina TL, Bondarenko OY, Sklanskaya OA, Grigoriev PY, Vasiliev YV, Yakovenko EP, Gulyaev PV, Fedchenko VI. Azithromycin in a triple therapy for H.pylori eradication in active duodenal ulcer. World J Gastroenterol. 2002 Oct;8(5):879-82. https://www.ncbi.nlm.nih.gov/pubmed/12378634
[8] Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for Helicobacter pylori eradication. Cochrane Database Syst Rev. 2013;(12):CD008337. https://pubmed.ncbi.nlm.nih.gov/24338763/

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-aalyses; small antimicrobial susceptibility studies

Review indicator: Price and antimicrobial susceptibility data

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.*[9] 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.
- *Amsden et al.*[10], similarly, showed similar intracellular concentrations over 10 days after administration of an azithromycin dose of 1500 mg as a single dose or over 3 days to healthy volunteers. Mean cellular concentrations at 10 days was 18 and 17 mg/L for granulocytes (PMNs) and 27 and 21 mg/L for monocyte/lymphocyte (M/Ls) for the respective doses. In contrast the corresponding serum concentrations for both dosage regimens was <0.05 mg/L.
- *Minimum inhibitory concentrations (MIC):* MIC for azithromycin for *H.pylori* eradication is lacking (noting that azithromycin is concentrated in cellular tissues). EUCAST only provides MICs for clarithromycin. Expert opinion recommends that MIC of 1 mg/L for azithromycin is adequate. Both studies (Sampson et al and Amsden et al) showed that at 21 days, cellular concentrations was generally higher than 1 mg/L.

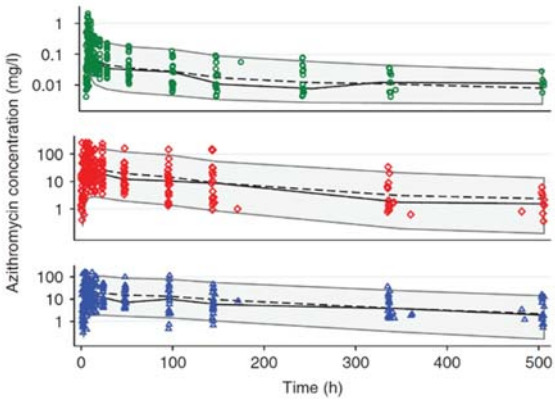

Figure 5 Visual predictive checks. Markers, observed data; shaded area, 90% prediction interval; solid lines, median of observed data; dashed lines, median of simulated data; green circles, whole blood; red diamonds, peripheral blood mononuclear cells; blue triangles, polymorphonuclear cells.

Sourced from Sampson et al (2014)

[9] Sampson MR, Dumitrescu TP, Brouwer KL, Schmith VD. Population pharmacokinetics of azithromycin in whole blood, peripheral blood mononuclear cells, and polymorphonuclear cells in healthy adults. CPT Pharmacometrics Syst Pharmacol. 2014;3(3):e103. https://pubmed.ncbi.nlm.nih.gov/24599342/

[10] Amsden GW, Gray CL. Serum and WBC pharmacokinetics of 1500 mg of azithromycin when given either as a single dose or over a 3 day period in healthy volunteers. J Antimicrob Chemother. 2001;47(1):61-66. https://pubmed.ncbi.nlm.nih.gov/11152432/

Duration of therapy of other antibiotics: Cochrane review by Yuan et al (2013)[11] states that the optimal duration of therapy for PAC and PAM is at least 14 days.

Metronidazole: More substantial antimicrobial susceptibility data is needed to inform whether metronidazole should be included in the regimen to for H.pylori eradication or not.

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, but could be considered as a therapeutic alternative where there are supply constraints with azithromycin. 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 evidence 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: II Metaanalysis and systematic review of low to moderate quality RCTs, Pharmacokinetic studies

1.1.4 HIATUS HERNIA *and* 1.1.5 INFLAMMATORY BOWEL DISEASE (IBD)

External comment received that diagnostic criteria for hiatus hernia and IBD is lacking in the STG was noted for consideration during the next review cycle.

1.2.3 PORTAL HYPERTENSION AND CIRRHOSIS

Oesophageal varices
Beta-blockers, oral: *added as a therapeutic group*
Propranolol, oral: *added and listed as an example of the therapeutic group in the STG*
Carvedilol, oral: *added as an alternative option in the therapeutic group (listed in therapeutic database)*

Evidence: There is no clear beneficial or harmful effects of carvedilol versus traditional, non-selective beta-blockers on mortality, upper gastrointestinal bleeding, serious or non-serious adverse events despite the fact that carvedilol was more effective at reducing the hepatic venous pressure gradient. However, the evidence was of low or very low quality, and the findings are uncertain. Additional evidence is required from adequately powered, long-term, double-blind, randomised clinical trials, which evaluate both clinical and haemodynamic outcomes.[12] [13]
Price: Propranolol[14] is cheaper than carvedilol[15], despite the additional requirement of dose titration.

[11] Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for Helicobacter pylori eradication. Cochrane Database Syst Rev. 2013;(12):CD008337. https://pubmed.ncbi.nlm.nih.gov/24338763/
[12] Li T, Ke W, Sun P, Chen X, Belgaumkar A, Huang Y, Xian W, Li J, Zheng Q. Carvedilol for portal hypertension in cirrhosis: systematic review with meta-analysis. BMJ Open. 2016 May 4;6(5):e010902. https://www.ncbi.nlm.nih.gov/pubmed/27147389
[13] Zacharias AP, Jeyaraj R, Hobolth L, Bendtsen F, Gluud LL, Morgan MY. Carvedilol versus traditional, non-selective beta-blockers for adults with cirrhosis and gastroesophageal varices. Cochrane Database Syst Rev. 2018 Oct 29;10:CD011510. https://www.ncbi.nlm.nih.gov/pubmed/30372514
[14] Contract circular RT289-2019: Average weighted price of propranolol 40 mg = R 0.22 (Daily dose price - Propranol 20-40mg 12 hourly = R 0.44 to R0.88)

Recommendation: Beta-blockers be recommended as a therapeutic class for oesophageal varices, with propranolol as the example of class and carvedilol as an alternative option. The therapeutic interchange database to be updated, accordingly.
Level of Evidence: III Guidelines[16] [17], Expert opinion

Tense ascites
Albumin, IV: *directions for use amended*
Guidance for use of albumin IV in this clinical setting was editorially amended as follows:

Albumin replacement should be considered if ≥ 5 L of fluid is removed or pre-exsiting renal dysfucntion:
- Albumin, IV, 40 g (20%) , as an infusion.
  - Refer to specialist unit to consider transjugular intrahepatic portosystemic (TIP) shunt or potential transplant.

Level of Evidence: III Standard of care

1.2.4.2 HEPATITIS B, CHRONIC (NON-HIV COINFECTION)

MANAGEMENT OF CHRONIC HEPATITIS B
External comment received from South African Medical Association requesting that the table for management of hepatitis B be reviewed and referenced accordingly.

The table was updated as follows, aligned with European Association for the Study of the Liver 2017 Guidelines[18]:

Phase	Serology	Viral load (HBV DNA) IU/mL	ALT	Management
1. HBeAg-positive chronic HBV infection (Immune Tolerant)	HBsAg positive HBeAg positive	>20000 (usually >200000)	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	>20000	Elevated	» Treatment required.
3. HBeAg- negative chronic HBV infection (Immune Control)	HBsAg positive HBeAg negative	<2000	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	>2000	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.

Level of Evidence: III Guidelines

[15] Contract circular RT289-2019: Price of carvedilol 6.25mg = R 0.67 and 12.5mg = R 0.84 (Daily dose price – Carvediolol 6.25 mg 12 hourly = R 1.34; carvedilol 12.5 mg 12 hourly = R 1.68).
[16] Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology. 2017 Jan;65(1):310-335. https://www.ncbi.nlm.nih.gov/pubmed/27786365
[17] Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, Austin A, Ferguson JW, Olliff SP, Hudson M, Christie JM; Clinical Services and Standards Committee of the British Society of Gastroenterology. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut. 2015 Nov;64(11):1680-704. https://www.ncbi.nlm.nih.gov/pubmed/25887380
18 European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug;67(2):370-398. https://www.ncbi.nlm.nih.gov/pubmed/28427875

Tenofovir, oral: *directions for discontinuation not amended*

Similar to the NEMLC approved recommendation for retaining the caution for hepatitis B co-infection with tenofovir (see below); directions for discontinuing tenofovir only when HBV DNA levels are undetectable was retained in the Adult Hospital Level STG.

At the NEMLC meeting of 12 April 2018[19], "Additional data suggesting that there is a risk of flares, in patients stopping TDF, if HbsAG positive was discussed: There is data from the SMART[20] and STACCATO[21] RCTs that indicated that people co-infected with hepatitis B who stopped TDF experienced flares. In a Swiss cohort[22], stopping lamivudine caused flares, three patients presented with fulminant hepatitis and one death was recorded".

MONITORING WHILST ON TENOFOVIR

Tenofovir, oral: *monitoring updated*

The table was updated as follows, aligned with the National guidelines for the management of viral hepatitis, 2018[23].

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

Adapted from: National Department of Health, National guidelines for the management of viral hepatitis, 2018. Available at www.health.gov.za

1.3 DIARRHOEA

External comment received that diagnostic criteria for diarrhoea IBD lacking in the STG noted and for consideration during the next review cycle, as the current cycle is nearing completion.

1.3.1 CHOLERA

Ciprofloxacin, oral: *dosing amended*

National Institute of Communicable Diseases reported decreasing susceptibility of *V. cholera* to ciprofloxacin, with increasing MIC^{50} for ciprofloxacin bordering on the EUCAST cut-off of 0.250 µg/ml[24], with two recent 2020 cases in KwaZulu Natal[25]. Thus, an extended 3-day course of ciprofloxacin (500mg 12 hourly) is recommended.

Level of Evidence: III Antibiotic susceptibility data

[19] Minutes of the NEMLC meeting of 12 April 2018.

[20] Dore GJ, Soriano V, Rockstroh J, Kupfer B, Tedaldi E, Peters L, Neuhaus J, Puoti M, Klein MB, Mocroft A, Clotet B, Lundgren JD; SMART INSIGHT study group. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. AIDS. 2010 Mar 27;24(6):857-65. https://www.ncbi.nlm.nih.gov/pubmed/20216301

[21] Nüesch R, Ananworanich J, Srasuebkul P, Chetchotisakd P, Prasithsirikul W, Klinbuayam W, Mahanontharit A, Jupimai T, Ruxrungtham K, Hirschel B. Interruptions of tenofovir/emtricitabine-based antiretroviral therapy in patients with HIV/hepatitis B virus co-infection. AIDS. 2008 Jan 2;22(1):152-4. https://www.ncbi.nlm.nih.gov/pubmed/18090405

[22] Bellini C, Keiser O, Chave JP, Evison J, Fehr J, Kaiser L, Weber R, Vernazza P, Bernasconi E, Telenti A, Cavassini M; Swiss HIV Cohort Study. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. HIV Med. 2009 Jan;10(1):12-8. https://www.ncbi.nlm.nih.gov/pubmed/18795964

[23] National Department of Health, National guidelines for the management of viral hepatitis, 2018. Available at www.health.gov.za

[24] National Institute for Communicable Diseases. Data on file, 2020.

[25] NICD. Communicable Diseases Communiqué, January 2020, Vol. 19 (1). http://www.nicd.ac.za/

1.3.4 CLOSTRIDUM DIFFICLE DIARRHOEA

Section title amended from "*Diarrhoea, antibiotic-associated*" to, "*Clostridum Difficle diarrhoea*", with a cross reference to the infections chapter.

Diagnosis and investigations: *amended*

Aligned with the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) Guidelines[26], recommendations for diagnosis was amended:

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.

And, clinical criteria for severe infection was added as follows:

Severe infection

Laboratory results confirm *Clostridium difficile* infection, WCC > 15 or serum creatinine >132 umol/L, or other clinical indicators of severe infection (e.g. immunodeficiency, intensive care admission, serious comorbidity, age > 65 years).

General measures

Infection control recommendations: *added*

Recommendations for contact precautions provided, aligned with Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA).Guidelines[27]:

- Patients with known or suspected *Clostridium difficile* infection should be placed on contact precaution according 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.

Antibiotic therapy

Fidaxomicin, oral: *not added*

The Adult Hospital Level Committee was of the opinion that this medicine be reviewed for Tertiary and Quaternary Level of Care for possible consideration on named-patient access. The single exit price for fidaxomicin 200 mg, 20 tablets is R 14 950.00[28].

Empirical antibiotic treatment: *deleted*
Directed antibiotic treatment: *added*
Metronidazole, oral: *retained*
Metronidazole, IV: *retained*
Vancomycin, oral: *retained*

Directed antibiotic therapy rather than empirical treatment is recommended. Refer to the medicine review: Antibiotic therapy for *Clostridium difficile* infection, April 2018.

Antibiotics for Clostridium Difficile

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

[26] McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Kelly C, Loo V, Shaklee Sammons J, Sandora TJ, Wilcox MH. 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). Clin Infect Dis. 2018 Mar 19;66(7):987-994. https://www.ncbi.nlm.nih.gov/pubmed/29562266

[27] McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Kelly C, Loo V, Shaklee Sammons J, Sandora TJ, Wilcox MH. 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). Clin Infect Dis. 2018 Mar 19;66(7):987-994. https://www.ncbi.nlm.nih.gov/pubmed/29562266

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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 are 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

Fulminant infection: If ileus or toxic megacolon or hypotension/shock

Metronidazole, IV: *added*

Metronidazole, oral: *added (de-escalation)*

Text of the updated STG:

Mild to moderate infection

Laboratory results confirm *Clostridium difficile* infection, diarrhoea does not settle on antibiotic withdrawal:

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

Severe infection

Laboratory results confirm *Clostridium difficile* infection, WCC > 15 or serum creatinine >132 umol/L, or other clinical indicators of severe infection (e.g. immunodeficiency, intensive care admission, serious comorbidity, age > 65 years).

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

If ileus or toxic megacolon or hypotension/shock:

Fulminant infection

If ileus or toxic megacolon or hypotension/shock:

- 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 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, consider oral vancomycin as tapered and pulsed regimen:

- Vancomycin, oral, 125 mg 6 hourly (give parenteral formulation orally) for 10 days, then 12 hourly for 7 days, then once per day for 7 days, and then every 2nd or 3rd day for 2 to 8 weeks.

NEMLC meeting of 26 September 2019:

NEMLC accepted the proposals recommended by the Adult Hospital Level Committee and recommended that despite management of hepatitis C taking place at tertiary & quaternary level of care, the Adult Hospital Level STGs and EML guide that for management of hepatitis C, a specialist should be consulted.

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)

- ***Note:*** *Information sourced from NEMLC ratified minutes and NEMLC-approved documents.*