

**SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 2: GASTRO-INTESTINAL CONDITIONS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2016-2018)**

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the complete gastro-intestinal chapter.

| SECTION | MEDICINE | ADDED/DELETED/AMENDED |
|---|--------------------------------------|---|
| 2.2 Dyspepsia, heartburn and indigestion, in adults | Antacids (aluminium hydroxide, oral) | Not added |
| | Lansoprazole, oral | Retained |
| 2.6 Appendicitis | Ceftriaxone, IM | Not added as a pre-referral dose |
| 2.9.1 Diarrhoea, acute in children | Ceftriaxone, IM | Indications amended |
| 2.11.2 Helminthic infestation, excluding tapeworm | Mebendazole, oral | Retained as an example of benzimidazole therapeutic class |
| | Albendazole, oral | Added as a therapeutic alternative |

2.2 DYSPEPSIA, HEARTBURN AND INDIGESTION, IN ADULTS

Previously the NEMLC (9 November 2017) recommended that:

- ***Clostridium difficile* infections:** Association of short-course proton pump inhibitor (PPI) therapy on *C. difficile* infection (CDI) to be interrogated; although it was previously mentioned at NEMLC that the risk was minimal.
- ***Use of PPIs vs antacids:*** It was proposed that comparative evidence of efficacy be reviewed as well as price comparisons of PPIs vs antacids. Also, more appropriate criteria for PPI's be included in the STG (e.g. persistently frequent and recurring symptoms).

Antacids (aluminium hydroxide, oral): not added

Lansoprazole, oral: retained

During the previous PHC STGs and EML review cycle, the Cochrane systematic review¹ reviewed showed that PPIs were more effective than H2-receptor antagonists in relieving heartburn in patients with gastro-oesophageal reflux disease (GORD) who are treated empirically and in those with endoscopy negative reflux disease.

Prices: Antacids² are more expensive than PPIs³.

Criteria for management with PPIs: Current indication for management with PPIs was considered appropriate, and the current referral criteria was considered to be adequate:

- | | |
|--|----------------------------|
| » Presence of warning signs: | |
| – weight loss | – anaemia |
| – persistent vomiting | – haematemesis |
| – dysphagia | – palpable abdominal mass |
| » No response within 7 days of starting proton-pump therapy treatment. | |
| » Recurrence of symptoms, especially: | |
| – > 50 years of age | – previous gastric surgery |
| – family history of gastric carcinoma | |

¹ Sigterman KE, van Pinxteren B, Bonis PA, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2013 May 31;5:CD002095.

² SEP database, 6 March 2018: Aluminum hydroxide gel 400 mg/10 ml, 200 ml = R 21.50

³ Contract circular HP09-2016SD : Lansoprazole 30 mg (14 tabs) = R 6.55

***C.difficile* infections:**

- Meta-analysis⁴ shows possible increased risk of *CDI* with long-term use of PPIs often with antibiotics (all observational data): Risk of *CDI* amongst PPI vs non-PPI users: OR = 1.99, 95% CI: 1.73 to 2.30, $I^2 = 85.41\%$.
- Based on reported incidence of *CDI* (at 14 days after hospital admission) of 1.67% in patients who have not used PPI, estimated NNH of 63 (95%CI: 48-78), if these patients will receive PPIs.
- Observational data with high heterogeneity and publication bias (Egger's test of asymmetry proved no significance; $z=0.3699$; $p=0.711$):

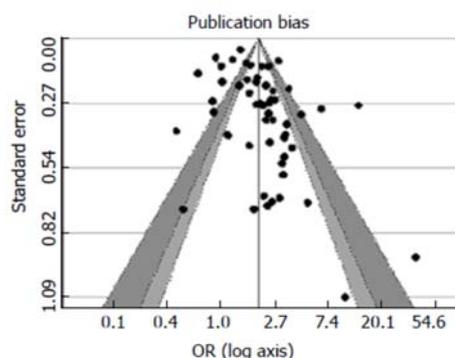


Figure 3 Funnel plot with 95% confidence limits.

- Authors recommend that “further high-quality, prospective studies are needed to assess whether the association is causal”.

Extended-spectrum beta-lactamases colonisation

Despite a recent cross-sectional hospital survey (2017)⁵ showing association of PPI use with ESBL rectal carriage; the use of PPIs at primary level of care for dyspepsia/heartburn is limited to a 14-day course. Risk factors for extended-spectrum beta lactamases (ESBL) colonisation reported to include long-term use of PPIs, ICU stay, intravascular catheters, haemodialysis, healthcare-associated infections, extended corticosteroid use, percutaneous tubes, prior antibiotic use^{6 7}. However, the clinical significance of the association of these risk factors with ESBL colonisation is unclear.

PHC Expert Review Committee recommendations: 14-day course of PPI be retained for management of dyspepsia, heartburn and indigestion, in adults at primary level of care.

Rationale: Limited data shows that the risk of *CDI* and ESBL colonisation associated with short-term course of PPIs remains small. Available data are observational and the risk of bias cannot be ruled out. Further high-quality, prospective studies are needed to assess whether the epidemiological association is causal. There is insufficient evidence for discontinuation of PPIs as a means of preventing *CDI* and ESBL infection, though unnecessary use of PPIs should be discontinued.

Level of Evidence: III Meta-analysis of observational studies

2.6 APPENDICITIS

Ceftriaxone, IM: pre-referral dose not added

⁴ Trifan et al. Proton pump inhibitors therapy and risk of *Clostridium difficile* infection: Systematic review and meta-analysis. *World J Gastroenterol* 2017 September 21; 23(35): 6500-6515

⁵ Huizinga P, van den Bergh MK, van Rijen M, Willemsen I, van 't Veer N, Kluytmans J. Proton Pump Inhibitor Use Is Associated With Extended-Spectrum β -Lactamase-Producing Enterobacteriaceae Rectal Carriage at Hospital Admission: A Cross-Sectional Study. *Clin Infect Dis*. 2017 Feb 1;64(3):361-363. <https://www.ncbi.nlm.nih.gov/pubmed/27965302>

⁶ Sidler JA, Battagay M, Tschudin-Sutter S, Widmer AF, Weisser M. Enterococci, *Clostridium difficile* and ESBL-producing bacteria: epidemiology, clinical impact and prevention in ICU patients. *Swiss Med Wkly*. 2014 Sep 24;144:w14009. <https://www.ncbi.nlm.nih.gov/pubmed/25250957>

⁷ Lee JA, Kang CI, Joo EJ, Ha YE, Kang SJ, Park SY, Chung DR, Peck KR, Ko KS, Lee NY, Song JH. Epidemiology and clinical features of community-onset bacteremia caused by extended-spectrum β -lactamase-producing *Klebsiella pneumoniae*. *Microb Drug Resist*. 2011 Jun;17(2):267-73. <https://www.ncbi.nlm.nih.gov/pubmed/21388296>

There is a paucity of evidence in the published literature for a single pre-referral dose of ceftriaxone for suspected appendicitis at primary level of care. Ceftriaxone is recommended for prevention of postoperative complications in appendectomised patients⁸, one hour prior to surgery.⁹ Although perforated appendicitis warrants antibiotics, diagnosis of this clinical condition is mostly not possible at primary level of care.

Recommendation: Pre-referral ceftriaxone, IM for patients with suspected appendicitis not be administered at primary level of care.

Rationale: Paucity of evidence for pre-referral antibiotics for suspected appendicitis at primary level of care. Furthermore, diagnosis of perforated appendicitis in this clinical setting would be a challenge and antimicrobial stewardship requires consideration.

Level of Evidence: I Systematic review

2.9.1 DIARRHOEA, ACUTE IN CHILDREN

Ceftriaxone, IM: *indications amended*

Previously the NEMLC (9 November 2017) recommended that guidance be reworded, limiting use of ceftriaxone for diarrhoea in specific paediatric patients.

The text was updated to align with the Paediatric Hospital Level STGs and EML, 2017.

Text amended from:

Special risk situations

Diarrhoea in:

- » ~~Neonates with dehydration and/or shock.~~
- » ~~Severe acute malnutrition (See Section: xxx)~~
- » ~~Associated conditions should be assessed. These include: :~~
 - ~~convulsions~~
 - ~~altered level of consciousness~~
 - ~~persistent vomiting/vomiting everything~~
 - ~~respiratory distress~~
 - ~~persistent diarrhoea~~
 - ~~hypothermia~~
 - ~~surgical abdomen~~
 - ~~blood in stool in babies <1 year of age~~

Note: ~~Refer these babies urgently for treatment.~~

~~Before referral, begin management for dehydration (see below), and administer:~~

- ~~Ceftriaxone, IM, 80 mg/kg/dose immediately as a **single dose**. See dosing table, pg 22.2.~~
 - Do not inject more than 1 g at one injection site.

To

If diarrhoea has been present for more than 7 days, see Persistent Diarrhoea.

Assess and manage dehydration according to the table below.

Children with severe dehydration require referral. Begin management for dehydration immediately whilst awaiting referral (see below).

The following children should receive ceftriaxone prior to referral

- neonates with severe dehydration
- children with Severe Acute Malnutrition AND severe dehydration or shock
- Ceftriaxone, IM, 80 mg/kg/dose immediately as a **single dose**. See dosing table, pg 22.2.
 - o Do not inject more than 1 g at one injection site.

If blood is present in stools, treat as for dysentery.

All children should be assessed and treated for associated conditions e.g. hypothermia, convulsions, altered level of consciousness, respiratory distress, surgical abdomen.

Level of Evidence: III Guidelines

⁸ Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendectomy. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD001439.

⁹ Bratzler DW, Houck PM; Surgical Infection Prevention Guidelines Writers Workgroup. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004 Jun 15;38(12):1706-15.

2.11.2 HELMINTHIC INFESTATION, EXCLUDING TAPEWORM

Mebendazole, oral: Retained as an example of benzimidazole therapeutic class

Albendazole, oral: Added as a therapeutic alternative

Local epidemiology: Current prevalence data suggests that *Ascaris lumbricoides* (roundworm) is the most prevalent pathogen in South Africa.^{10, 11, 12, 13} However, it is noted that World Health Organisation is presently conducting a country-wide prevalence survey which will provide more accurate and detailed information.

Efficacy and safety: Available evidence¹⁴ suggests that albendazole is comparable to mebendazole for the eradication of *Ascaris lumbricoides*.

Dosing in children: Guidelines¹⁵ recommend a reduced dose of albendazole in children > 1 year; whilst mebendazole is indicated in children > 1 year.¹⁶

(Refer to the medicine review - Benzimidazoles for soil-transmitted helminth infestation for detailed information).



Benzimidazoles for
soil-transmitted hel

Recommendation: Benzimidazoles (albendazole and mebendazole) be recommended as a therapeutic class for soil-infected helminth infestations in adults and children > 1 year of age, at primary level of care.

Rationale: Evidence of comparable efficacy of mebendazole and albendazole for eradication of *Ascaris lumbricoides*, currently the most common soil-transmitted helminth in South Africa. In addition, available evidence indicates that albendazole and mebendazole may be used in children aged 12 months and older provided that the case for their use is established. The health benefits of treatment appear to override any risks associated with the correct administration of these antihelminthic agents.

Level of Evidence: II low to moderate quality RCT

¹⁰ Appleton CC, Mosala TI, Levin J, Olsen A. Geohelminth infection and re-infection after chemotherapy among slum-dwelling children in Durban, South Africa. *Ann Trop Med Parasitol*. 2009 Apr;103(3):249-61.

¹¹ Jinabhai CC, Taylor M, Coutsooudis A, Coovadia HM, Tomkins AM, Sullivan KR. Epidemiology of helminth infections: implications for parasite control programmes, a South African perspective. *Public Health Nutr*. 2001Dec;4(6):1211-9.

¹² Adams VJ, Markus MB, Adams JF, Jordaan E, Curtis B, Dhansay MA, Obihara CC, Fincham JE. Paradoxical helminthiasis and giardiasis in Cape Town, South Africa: epidemiology and control. *Afr Health Sci*. 2005 Sep;5(3):276-80.

¹³ Nxasana N, Baba K, Bhat V, Vasaikar S. Prevalence of intestinal parasites in primary school children of mthatha, eastern cape province, South Africa. *Ann Med HealthSci Res*. 2013 Oct;3(4):511-6.

¹⁴ Steinmann P, Utzinger J, Du ZW, Jiang JY, Chen JX, Hattendorf J, Zhou H, Zhou XN. Efficacy of single-dose and triple-dose albendazole and mebendazole against soil-transmitted helminths and *Taenia* spp.: a randomized controlled trial. *PLoSOne*. 2011;6(9):e25003

¹⁵ American Academy of Pediatrics. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2012:241.

¹⁶ SAMF, 2016 edition.