PAEDIATRIC HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 8: INFECTIVE/INFECTIOUS DISEASES
NEMLC 8 DECEMBER 2022 – REPORT

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
General	Ceftriaxone	Dose aligned to 100mg/kg once daily
8.4 Hydatid Disease	Albendazole	Duration amended
	Albendazole plus praziquantel	Dual therapy not added
8.9.2 P. Falciparum Malaria, severe, complicated (or if repeated vomiting)	Artesunate	Dose amended for < 20 kg
	Ceftriaxone	Dose retained
8.9.4 Malaria Prophylaxis	Doxycycline	Retained as only prophylactic option for malaria
8.11 Meningitis, acute bacterial	Ceftriaxone	Dose aligned
8.23 Typhoid	Ceftriaxone	Dose retained
8.24 Non-typhoid salmonella	Cefotaxime	Gestational age dosing added
	Ceftriaxone	Dose and frequency aligned
8.27 Sepsis *Confirmed meningococcal septicaemia* *Suspected staphylococcal infection*	Benzylpenicillin	dosing frequency retained
	Cloxacillin plus ceftriaxone	Dual antibiotics retained
	Ceftriaxone	Dose aligned
8.29 Arthritis, Septic	Ceftriaxone	Dose aligned
8.31 Osteitis/osteomyelitis, acute	Ceftriaxone	Dose aligned

General

Ceftriaxone: IV Dose aligned to 100mg/kg once daily
An external comment was received indicated that ceftriaxone 50mg/kg 12 hourly is preferable to 100mg/kg as a single daily dose. The Paediatric Committee proposed that 100mg/kg/day be retained (and aligned throughout the text) as this was pragmatic for a district/regional hospital setting. The 100mg/kg/daily dose was additionally favoured due to less nursing time required, and would allow for patients to be discharged a day earlier.

8.4 Hydatid Disease

Albendazole: Duration amended
Albendazole plus praziquantel: Dual therapy not added

External comment was received indicating:

- For non-ruptured hydatid, 6 months of therapy is recommended.[1] For ruptured hydatids, post removal albendazole therapy is recommended.[2]
    - The Committee agreed that the duration could be indicated as 3 to 6 months.
- Systematic review and meta-analysis indicates better rates of cure or improvement when using combination therapy with albendazole + praziquantel than with albendazole alone.[3]
    - The systematic review and meta-analysis provided to support the consideration of albendazole plus praziqantel was not able to statistically combine data comparing albenazole alone versus albendazole plus praziqantel. It was noted that for this outcome in the review, meta-analysis could not be undertaken. Additionally, the outcomes evaluated were considered non-clinically significant; one paper looked at number of non-viable scoleces, and another was reduction in number of cysts and cases cured/improved. The Paediatric Committee indicated that surgery was the most important intervention. It is recommended that albendazole alone be retained, however consideration can be given to dual therapy if further evidence becomes available.

The Committee agreed that the text be updated in line with the text recommended in the Adult STGs and EML.

The text was amended as follows:

- Albendazole, oral, 15 mg/kg/day up to maximum of 400 mg 12 hourly with a fatty meal (e.g. a glass of full cream milk).
- Duration is 3–6 months according to response on imaging for inoperable cysts or 14–28 days before and 28 days after PAIR or surgery.
- Monitor liver function tests and FBCs monthly.

- ~~Albendazole, oral, 15 mg/kg/dose daily for 3-6 months.~~
- ~~Monitor FBC/LFT monthly~~

8.6 Candidiasis, systemic and other

An external comment was received noting that it would be appropriate to add a comment that if the Candida species isolated (e.g. on blood culture) is susceptible to fluconazole, a switch from amphotericin B to fluconazole may be considered in discussion with an infectious diseases specialist or clinical microbiologist.

The Committee amended the text as follows:

- Amphotericin B deoxycholate, IV infusion in **5% dextrose water only**, 1 mg/kg/dose once daily over 4 hours for at least 2 weeks after first negative culture, or if no repeat culture available at least 3 weeks after clinical improvement. Discuss options for de-escalation of anti-fungal treatment when sensitivity available with specialist.

[1] Rawat S, Kumar R, Raja J, Singh RS, Thingnam SKS. Pulmonary hydatid cyst: Review of literature. Journal of Family Medicine and Primary Care. 2019, 8(9): 2774-2778.

[2] Hamouri S, Odat H, Syaj S, Hecker E, Alrabadi N. Rupture of hydatid cyst in pediatrics: A cross-sectional study. Annals of Medicine and Surgery. 2021, 62: 31-36.

[3] Velasco-Tirado V, Alonso-Sardon M, Lopez-Bernus A, Romero-Alegria A, Burguillo FJ, Muro A, et.al. Medical treatment of cystic echinococcosis systematic review and meta-analysis. BMC infectious disease. 2018, 18: 306

8.7 Cytomegalovirus infection

CNS Disease

- An external comment was received outlining that discontinuing secondary prophylaxis may be considered for children who are receiving ART and have a sustained (such as >6 months) increase in CD4 cell count (defined as an increase in CD4 percentage to >15% for children aged <6 years, or an increase in CD4 cell count to >100 cells/mm3 for children aged ≥6 years).[4]

The text was amended as follows:

CNS disease **(Specialist initiated)**

- Initial therapy:
  - Ganciclovir, IV: 5 mg/kg administered over 1 hour, 12 hourly for 7 days.
  - Follow with: Valganciclovir, oral, 16 mg/kg, 12 hourly for 5 weeks.
- Maintenance therapy: Indicated for patients with good clinical response
  - Valganciclovir, oral, 16 mg/kg, daily until CD4 count rises for >6months to >15% (<6years) or > 100 cell/mm3 (>6years) on ART. ~~if available~~

8.9.2 Falciparum Malaria, Severe, Complicated (or if repeated vomiting)

Urgent Treatment

Artesunate: Dose amended for children < 20 kg

The artesunate dose was amended in line with the PHC STGs and EML recommendation. This is supported by the 2022 WHO Malaria Guidelines[5] and SAMF[6], based on a pharmacokinetic modelling study[7] that showed that smaller children need higher dosing of intramuscular artesunate.

The text was updated as follows:

Urgent:

Children ≥ 20 kg:

- Artesunate, IVI, 2.4mg/kg at hours 0, 12 and 24, then daily until patient is able to tolerate oral treatment.

Children < 20 kg:

- Artesunate IM, 3 mg/kg at hours 0, 12 and 24, then daily until patient is able to tolerate oral treatment.

Bacterial sepsis

Ceftriaxone: Dose and frequency retained

8.9.4 Malaria Prophylaxis

Doxycycline: retain as only prophylactic option for malaria.

[4] https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-pediatric-opportunistic-infections/cytomegalovirus?view=full

[5] WHO Guidelines for malaria, 25 November 2022. Geneva: World Health Organization; 2022 (WHO/UCN/GMP/2022.01 Rev.3).

[6] SAMF, 2022

[7] Hendriksen IC, Mtove G, Kent A, Gesase S, Reyburn H, Lemnge MM, et al. Population pharmacokinetics of intramuscular artesunate in African children with severe malaria: implications for a practical dosing regimen. Clin Pharmacol Ther. 2013 May;93(5):443-50. https://pubmed.ncbi.nlm.nih.gov/23511715/

An external comment was received querying why only doxycycline is listed for prophylaxis in children > 8 years of age. The Committee outlined that this was previously discussed, and doxycycline was currently the only option that could be included.

8.11 Meningitis, acute bacterial

Ceftriaxone: IV dose aligned

Referral
An external comment was received proposing that a referral to occupational therapy be added. The Committee noted the comment, however proposed that a referral to occupational therapy specifically in this section was not necessary. It was however proposed that mention of allied health services be added to the preamble of the book.

8.23 Typhoid

Ceftriaxone: dose and frequency retained

8.24 Non-typhoid Salmonella

Cefotaxime: gestational age dosing added
Ceftriaxone: dose and frequency aligned.

Cefotaxime
An external comment was received outlining that it was not appropriate for 8 hourly dosing of cefotaxime. It was proposed that Cefotaxime dosing be added according to changing postnatal age. The Committee proposed that this should be in the neonatal section and aligned to this section. The neonatal Chapter was updated with Cefotaxime gestational dosing, and incorporated in this chapter.

Ceftriaxone
The ceftriaxone dose was aligned to 100mg/kg/day in line with other areas of the chapter. A maximum dose was added in line with the South African Medicines Formulary.

Invasive disease
If < 1 month of age:

- Cefotaxime, IV/IM~~, 50–75 mg/kg/dose 8 hourly~~.

Gestational age	Postnatal age	Dose
< 32 weeks	< 14 days	50 mg/kg/dose every 12 hours
	14 to 28 days	50 mg/kg/dose every 8 hours
≥ 32 weeks	≤ 7 days	50 mg/kg/dose every 12 hours
	8 to 28 days	50 mg/kg/dose every 8 hours

OR
If > 1 month of age:

- Ceftriaxone, IV, ~~50–80~~ 100 mg/kg once daily, (maximum 2g/dose)
  Duration:
  - Bacteraemia: 10–14 days.
  - Acute osteomyelitis: 4–6 weeks.
  - Meningitis: 4 weeks.

8.27 Sepsis

Ceftriaxone: dose and frequency aligned.

Confirmed meningococcal septicaemia

Benzylpenicillin: dosing frequency retained

- An external comment was received indicating that benzylpenicillin for confirmed septicimaemia is usually given 6 hourly, and it was proposed that text could be amended to say 4-6 hourly, with a maximum dose of 24 million units per day. The Paediatric Committee proposed that for more severe conditions, a higher frequency dose would be warranted. It was agreed to retain recommendation.

Suspected stapholococcal infection

Cloxacillin plus ceftriaxone: Dual antibiotics retained

- An external comment was received around recommendation for cloxacillin plus ceftriaxone for suspected staphylococcal infection (like osteomyelitis) The commenter indicated that dual therapy was not appropriate as from a microbiological and antibiotic stewardship perspective, as ceftriaxone or cefotaxime provides cover against *S. aureus*, thus additional cloxacillin is not adding benefit. It the *S. aureus* is susceptible to cloxacillin, confirmed on culture then a switch to cloxacillin should be considered. The Paediatric Committee noted that the recommendation is not to continue both agents, this was clarified in the text to indicate that descalation must be done, with aim for monotherapy as soon as cultures become available.

  The text was amended as follows:

  Suspected staphylococcal infection (e.g. osteomyelitis)
  - Cloxacillin, IV, 50 mg/kg/dose 6 hourly.

  PLUS
  - Ceftriaxone, IV, 100 mg/kg once daily.

  Reconsider choice and descalation of antibiotics, aiming for monotherapy where possible, when the results of cultures become available or if the child does not improve.

8.29 Arthritis, Septic

Ceftriaxone: dose and frequency aligned.

8.31 Osteitis/osteomyelitis, acute

Ceftriaxone: dose and frequency aligned.

Previous amendments made

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
8.5 Schistosomiasis (Bilharzia)	Praziquantel – mass dose administration	Not added
8.9.4 Malaria Prophylaxis – Self provide care	Doxycycline	Added
8.12 Meningitis, Cryptococcal	Amphotericin B liposomal	Not added
	Flucytosine	Added
8.15 Mycobacterium Avium Complex (MAC)	Three Drug regimen	Retained
8.21 Tick Bite Fever	Azithromycin	Added for mild to moderate disease
	Doxycycline	Retained for severe disease

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NEMLC 25 AUGUST 2022 – REPORT

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
8.5 Schistosomiasis (Bilharzia)	Praziquantel – mass dose administration	Not added
8.9.4 Malaria Prophylaxis – Self provide care	Doxycycline	Added
8.12 Meningitis, Cryptococcal	Amphotericin B liposomal	Not added
	Flucytosine	Added
8.15 Mycobacterium Avium Complex (MAC)	Three Drug regimen	Retained
8.21 Tick Bite Fever	Azithromycin	Added for mild to moderate disease
	Doxycycline	Retained for severe disease

8.5 Schistosomiasis (Bilharzia)

Praziquantel: mass dose administration: Not added

The Communicable Diseases Programme within the National Department of Health (NDoH) has a working group evaluating the epidemiology of schistosomiasis, and the possibility of mass dose administration of praziquantel. Currently praziquantel is available on the Essential Medicines List (EML) for schistosomiasis treatment. Mass drug administration was not considered in this review.

8.9.4 Malaria Prophylaxis

Doxycycline: Added

Oral doxycycline added for children over 8 years old – in line with the Primary Health Care (PHC) Standard Treatment Guidelines (STGs) and EML, recently published updated chapter.[8]

For children under 8 years, a referral to the National Malaria Prevention Guidelines, 2017 has been added. [9]

8.12 Meningitis, Cryptococcal

Liposomal amphotericin B: Not added
Flucytosine: Added

Liposomal amphotericin B was not considered for addition due to its current high price.

[8] National Department of Health. Primary Health Care STGs and EML – Infections Chapter ratified at NEMLC on 23 June 2022.
[9] National Malaria Prevention Guidelines, 2019. https://www.knowledgehub.org.za/elibrary/guidelines-prevention-malaria-2017

Flucytosine was added for the management of Cryptococcal Meningitis, in line with recommendations made by the Adult Hospital Level Expert Review Committee. [10, 11]

The text was added as follows:

Treatment

Preferred Initial treatment (2 weeks)

First week

- Amphotericin B deoxycholate, IV, 1 mg/kg/day as a daily infusion in 5% dextrose water over 4 hours.

PLUS

- 5-Flucytosine 100mg/kg/day in 4 divided doses

Second week:

- Fluconazole, IV/PO, 12 mg/kg/day.
  - Maximum dose: 800 mg.

OR

Alternative initial treatment (2 weeks)

- Amphotericin B deoxycholate, IV, 1 mg/kg/day as a daily infusion in 5% dextrose water over 4 hours.

PLUS

- Fluconazole, IV/PO, 12 mg/kg/day.
  - Maximum dose: 800 mg.

Prehydration before administering amphotericin B to prevent renal impairment:

- Sodium chloride 0.9%, IV, 15 mL/kg **plus** potassium chloride, 20 mmol/L infused over 2–4 hours.

OR

Additional alternative: Only if Amphotericin is not available/not tolerated or contraindicated, as this regimen is associated with poorer outcomes. Initial treatment (2 weeks)

First week

- Fluconazole, IV/PO, 12 mg/kg/day.
  - Maximum dose: 800 mg.

PLUS

- 5-Flucytosine 100mg/kg/day in 4 divided doses

Second week:

- Fluconazole, IV/PO, 12 mg/kg/day.
  - Maximum dose: 800 mg.

8.15 Mycobacterium Avium Complex (MAC)

Three drug regimen for MAC: Retained

The three drug regimen for MAC was retained. This is in line with the updated IDSA guideline 2020.[12]
There is an ongoing adult trial comparing a two versus a three drug regimen, however results are only expected in2024. [13]

[10] NEMLC Medication Review. Adult Hospital Level. Flucytosine for cryptococcal meningitis_November 2018.

[11] NEMLC, Adult Hospital Level. Flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV infected adults. Health Economics and Budget Impact Analysis. June 2019.

[12] Daley CL, Iaccarino JM, Lange C, Cambau E, Wallace RJ, Andrejak C. Treatmetn of nontuberculous mycobacterial pulmonary disease: An official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. Clinical Infectious Diseases. 2020:71. https://www.idsociety.org/practice-guideline/nontuberculous-mycobacterial-ntm-diseases/

[13] Comparison of Two- versus Three- antibiotic therapy for pulmonary mycobacterium avium complex disease. Clinical Trials.gov NCT03672630. *https://clinicaltrials.gov/ct2/show/NCT03672630*

8.21 Tick bite fever

Azithromycin: Added for mild to moderate disease

Azithromycin was added for milder to moderate disease, in line with the PHC STG and EML recommendations.[8]

Doxycycline: Retained for severe disease.

The text was amended as follows:

Mild to Moderate disease:

- Azithromycin, PO/IV, 10 mg/kg daily for 3 days

Severe disease:

- Doxycycline, oral.
  - If < 50 kg: 4 mg/kg/24 hours in 2 divided doses on the first day, then 2 mg/kg/24 hours in 2 divided doses for second day.
  - If > 50 kg: 100 mg 12 hourly for 2 days.

Then switch to:

- Azithromycin, PO/IV, 10 mg/kg daily for 3 days

~~If unable to take oral therapy:~~

- ~~Azithromycin, IV, 10 mg/kg/day for 5 days.~~