**SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST**

**CHAPTER 9: SYSTEMIC AND HEALTHCARE-ASSOCIATED INFECTIONS**

**NEMLC RECOMMENDATIONS FROM THE MEETING OF 25 AUGUST AND 20 OCTOBER 2022**

**Medicine amendment recommendations, with supporting evidence and rationale are listed below.**

**Kindly review the medicine amendments in the context of the respective standard treatment guidelines (STGs).**

**A: PREVIOUS MEDICINE AMENDMENTS:**

At the NEMLC meeting of the 3 December 2020, the following was accepted:

**NEW STG:**

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| **SECTION** | **CONDITION** | **MEDICINE MANAGEMENT** | **MEDICINE ADDED** |
| **9.4.2** | **Coronavirus disease-19 (COVID-19)** | Yes | Oxygen |
| - *thromboprophylaxis* | Yes | LMWH therapeutic class |
| Enoxaparin, parenteral as an example of LMWH therapeutic class |
| Unfractionated heparin |
| -*therapeutic treatment with heparin* | Yes | LMWH therapeutic class |
| Enoxaparin, parenteral as an example of LMWH therapeutic class |
| Unfractionated heparin |
| -*non-pregnant, requiring supplemental oxygen* | Yes | Corticosteroid therapeutic class |
| Dexamethasone, parenteral as an example of corticosteroid class |
| *-pregnant, requiring supplemental oxygen* |
| * + *fetal lung maturity* ***also*** *required*
 | Yes | Cross referred to section 6.12: Preterm labour (PTL) and preterm prelabour rupture of membranes (PPROM) (Betamethasone, parenteral) |
| Cross referred to section 6.12: Preterm labour (PTL) and preterm prelabour rupture of membranes (PPROM) (Dexamethasone, parenteral) |
| * + *fetal lung maturity* ***not*** *required*
 | Yes | Corticosteroid therapeutic class |
| Dexamethasone, parenteral as an example of corticosteroid class |
| * + *concern of in-utero steroid exposure*
 | Yes | Prednisone, oral |
| Hydrocortisone, parenteral |
| - *management of covid-19 in uncontrolled diabetics* | No | No, but hyperglycaemia in COVID-19 to be treated as in other critically ill patients (target blood glucose of ≤10 mmol/L) |

Refer to the NEMLC report and review that were tabled at the meeting of 3 December 2020; as well as the NEMLC minutes of the respective meeting (Infections chapter extract) embedded below:

Additional amendments were made to the ***rest of the chapter***, following receipt of ***initial comments*** from external stakeholders and following additional recommendations made at the NEMLC meetings of 25 August 2022 and 20 October 2022

**B: ADDITIONAL MEDICINE AMENDMENTS**

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| **SECTION** | **MEDICINE** | **ADDED/DELETED/AMENDED** |
| **9.1.1 Intravascular catheter infections – empiric antibiotic therapy** |
| **-** *S aureus* | Vancomycin, IV | Dosing amended |
| *- Candidaemia – intolerant to amphotericin B (renal impairment)* | Fluconazole, oral | Deleted |
| Echinocandins | Retained as specialist motivation |
| **9.1.2 Surgical wound infections** | Vancomycin, IV | Dosing amended |
| **9.1.3 Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)** | Empiric antibiotic therapy | Duration amended |
| Ceftriaxone, IV | Deleted |
| Severe penicillin allergy | Guidance added |
| Antibiotic treatment protocol for HAP/VAP | Amended |
| Carbapenems (imipenem/cilastin AND meropenem) | Note added (avoid imipenem/cilastan in patients with CNS disorders or history of seizures – use meropenem) |
| **9.2 Adult vaccination** | COVID-19 vaccination | Guidance added |
| **9.10** **Tick bite fever***- Pregnancy* | Doxycycline | Added as initial therapy |
| Azithromycin  | Retained |
| **9.12 Varicella (chickenpox), complicated** | Varicella-zoster immunoglobulin (VZIG), IM | Indication amended |

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| **9.1.1 INTRAVASCULAR CATHETER INFECTIONS** |

Guidance for peripheral and central catheter infections was separated out for clarity purposes.

For peripheral blood line infections, microbiological specimens are not usually indicated unless patient systemically unwell for peripheral blood line infections, and the following additional STG text was added:

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| * If peripheral blood culture negative but central catheter culture positive, monitor closely for signs of infection, and repeat peripheral blood cultures accordingly. If central line has grown *S. aureus*, 5-7 days of treatment is recommended (assuming peripheral blood cultures remain negative).
* If peripheral blood culture is positive, remove catheter, and treat with systemic antibiotics, guided by the culture results.
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**Empiric antibiotic therapy**

* ***S. aureus* infection**

Vancomycin, IV: *dosing amended*

Amended as follows to align with the SAMF, 2022 edition:

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| * Vancomycin, IV, 25–30 mg/kg, empirically as a loading dose.
* Follow with 15­–20 mg/kg/dose 12 hourly. (See Appendix II for guidance on prescribing and therapeutic drug monitoring).
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**Level of Evidence: Very low certainty evidence, conditional recommendation**

Dosing of vancomycin in Appendix II: Prescribing information for specific medicines will likewise be updated.

* **Candidaemia – intolerant to amphotericin B (renal impairment)**

Fluconazole, oral: *deleted*

Echinocandins: *retained as specialist motivation*

As echinocandins are included on the Tertiary & Quaternary EML (June 2022), it was considered more rational to consider echinocandins on specialist motivation, than dose-adjusted oral fluconazole in the renally impaired patient who cannot use amphotericin B. Furthermore, in the previous review cycle, the Adult Hospital Level Committee collaborated with NICD and the following was discussed:

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| ***ADULT HOSPITAL LEVEL COMMITTEE MINUTES OF THE MEETING OF 23 NOVEMBER 2017:******Echinocandins:*** *Surveillance data suggests that this is the most ideal first-line agent, but it is very expensive.****Amphotericin B:*** *Still a reliable first-line antifungal agent, but has serious adverse effects.****Candida auris:*** *Cases of drug-resistant candida auris bloodstream infections recorded by NICD. However, based on CDC cut-off values; despite 85% resistance to fluconazole; only 13% of isolates reported to be resistant to amphotericin B and <1% resistant to echinocandin.**Thus, the text of the STG was amended to recommend treatment with fluconazole, oral, only once susceptibility has been confirmed.* |

**Level of Evidence: Low certainty evidence, conditional recommendation**

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| **9.1.2 SURGICAL WOUND INFECTIONS** |

Vancomycin, IV: *dosing amended*

Aligned with section 9.1.1: Intravascular catheter infections (see above).

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| **9.1.3 HOSPITAL-ACQUIRED PNEUMONIA (HAP) AND VENTILATOR-ASSOCIATED PNEUMONIA (VAP)** |

Title of this STG was amended from “*Hospital-acquired pneumonia (HAP)”* to align with international best practice.

Empiric antibiotic therapy: *duration amended*

Duration of empiric antibiotic therapy amended from *“10”* to *“7”* days, aligned with the 2016 Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) Guidelines[[1]](#footnote-1) that cite the following systematic reviews:

* ***Ventilator-associated pneumonia:***
* *Pugh et al (2015)[[2]](#footnote-2):* Systematic review of 6 RCTs (n=508) compared short courses of antibiotics (7-8 days) to long courses (10-15 days). Majority of patients had VAP.
	+ 28-day antibiotic-free days: Increased with short courses of antibiotics - mean difference, 4.02 days; 95% CI 2.26 to 5.78 days.
	+ Recurrent VAP due to MDR pathogens:42.1% vs 62.3%; OR, 0.44; 95% CI 0.21 to 0.95
	+ Mortality, recurrent pneumonia, treatment failure, hospital length of stay, or duration of mechanical ventilation: no difference.
	+ In the sub-group of patients with VAP due to a non-glucose-fermenting gram-negative bacillus including *Pseudomonas* and *Acinetobacter* (33% of patients), short courses of antibiotics were associated with recurrent infection (OR 2.18; 95% CI, 1.14 to 4.16), but no other differences were observed for pneumonia recurrence or mortality.
* *Dimopoulos et al (2013)[[3]](#footnote-3):* Systematic review of 4 RCTs (n=883) comparing short courses of antibiotics (7-8 days) to long courses (10-15 days) amongst patients with VAP.
	+ 28-day antibiotic-free days: Increased with short courses of antibiotics - mean difference3.40 days: 95% CI 1.43 to 5.37 days.
	+ Mortality, recurrent pneumonia, ventilator-free days, duration of mechanical ventilation, or length of ICU stay: no difference.
* IDSA/ATS Guideline panel’s confidence in the results was moderate as many of the RCTs in the systematic reviews had moderate risk of bias - most RCTs were not blinded, recurrence was measured at 30 days (recurrence more likely to occur in short-course antibiotics RCTs) and there was indirectness as the largest trial excluded patients with early VAP.

**Recommendation:** The IDSA/ATS panel concluded that the evidence indicates that short courses of antibiotics reduce antibiotic exposure and recurrent pneumonia due to MDR organisms and IDSA recommends a 7-day antibiotic course for VAP (strong recommendation).

**Level of Evidence: Moderate certainty evidence, strong recommendation**

* ***Hospital-acquired pneumonia*** *(non-VAP):* The IDSA/ATS guideline panel found no studies that provided useful data for comparing short-term to long-term antibiotic therapy in HAP; however, the duration of therapy has been studied in VAP – see above. Thus, guidance was extrapolated from evidence from VAP; noting that shorter antibiotic course results in reduced antibiotic-related side effects, *C. difficile* colitis, the potential for antibiotic resistance, and costs (strong recommendation). The importance of avoiding therapies that are potentially harmful and costly if there is no evidence of benefit was highlighted.

**Level of Evidence: Low certainty evidence, strong recommendation**

Ceftriaxone, IV: *deleted*

Common hospital-acquired pneumonia pathogens include *Klebsiella* and *Pseudomonas*. As per latest GERMS-SA surveillance, data, in public sector, 71% of invasive isolates are resistant to ceftriaxone (note, this figure includes community-acquired infections too; the resistance rate for hospital-acquired pneumonia is likely even higher than this figure). Pseudomonas is intrinsically resistant to ceftriaxone (i.e., 100% resistance).



*Source:* NICD antimicrobial surveillance reporting dashboard.

**Level of Evidence: Low certainty evidence, conditional recommendation**

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| **NEMLC MEETING OF 25 AUGUST 2022:****Recommendations:**More granular data should be sourced from NICD to allow for a detailed interrogation of the resistance to cephalosporins. Inclusion of the link to the NICD dashboard, to encourage end-users to engage with the dashboard to prompt clinicians to seek local facility level data as an aid to improved prescribing and antibiotic stewardship |

Following NEMLC’s request at the meeting of 25 August 2022, the following was accessed from NICD AMR surveillance dashboard.

AST results stratified by province for 2021, for the public sector shows very high levels of ceftriaxone resistance across provinces.



Across districts (excluding districts with < 20 Klebsiella pneumoniae blood cultures in the year (2021), the median resistance percentage across 39 districts was 69%, with an IQR of 66-81%.

The reported cases are likely an underestimate of ceftriaxone resistance in HAP as:

1. They include a minority of community-acquired infections, which generally have less resistance than hospital-acquired infections.

2. For other, less common, microbiological causes of HAP, the ceftriaxone resistance profile will be much worse - e.g. Pseudomonas (intrinsically resistant) or Acinetobacter spp. (near universal resistance).

Severe penicillin allergy: *guidance added*

For severe penicillin allergy, guidance was added to consult an infectious diseases specialist or microbiologist.

**Level of Evidence: Very low certainty evidence, conditional recommendation**

Antibiotic treatment protocol for HAP/VAP: *amended*

Carbapenems (imipenem/cilastin AND meropenem): *note added (to avoid imipenem/cilastin in patients with CNS disorders or history of seizures – use meropenem)*

The STG was editorially amended so that the antibiotic treatment protocol for HAP/VAP provided guidance towards a carbapenem-sparing approach, and the note for use of carbapenems (imipenem/cilastin and meropenem) was added (aligned with SAMF, 2022):

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| **~~Empiric antibiotic therapy~~** ~~Duration: 7 days.~~~~Antibiotic choice will depend on local susceptibility patterns. One or more of the following antibiotics/classes must be available, dependant on local susceptibility patterns:~~* ~~Piperacillin/tazobactam, IV, 4.5 g 8 hourly.~~

**~~and~~*** ~~Amikacin, IV, 15 mg/kg daily. (See Appendix II, for individual dosing and monitoring for response and toxicity).~~

**~~OR~~*** ~~Cefepime, IV, 2 g 12 hourly. (See Appendix II for guidance on dosing in renal impairment).~~

**~~OR~~**~~Instead of piperacillin/tazobactam + amikacin~~ **~~OR~~** ~~cefepime:~~~~Carbapenem with activity against Pseudomonas:~~* ~~Imipenem/cilastan, IV, 1000/1000 mg 8 hourly (except CNS infections or known epileptics).~~

**~~OR~~**~~Instead of piperacillin/tazobactam + amikacin~~ **~~OR~~** ~~cefepime~~ **~~OR~~** ~~imipenem:~~* ~~Meropenem, IV, 2 g 8 hourly (CNS infections or known epileptics).~~

**~~Note:~~** ~~De-escalate as soon as the culture is available.~~~~For severe pencillin allergy, consult an infectious diseases specialist or microbiologist.~~ |

To:

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| **Empiric antibiotic therapy** Duration: 7 days.Antibiotic choice will depend on local susceptibility patterns: [NICD AMR surveillance dashboard](https://mstrweb.nicd.ac.za/MicroStrategy/asp/Main.aspx?Server=NICDSANDMSTRI01&Project=Surveillance&Port=0&evt=2048001&src=Main.aspx.2048001&documentID=E654D30643F2E930CCF5A192C0E4512C&currentViewMedia=1&visMode=0)* Piperacillin/tazobactam, IV, 4.5 g 8 hourly.

**and*** Amikacin, IV, 15 mg/kg daily. (See Appendix II, for individual dosing and monitoring for response and toxicity).

**OR ALTERNATIVE*** Cefepime, IV, 2 g 12 hourly. (See Appendix II for guidance on dosing in renal impairment).

**IF HIGH LOCAL RESISTANCE RATES TO THE ABOVE REGIMENS, THEN CONSIDER CARBAPENEM**Instead of piperacillin/tazobactam + amikacin **OR** cefepime:Carbapenem with activity against Pseudomonas:* Imipenem/cilastin, IV, 1000/1000 mg 8 hourly.

**Note**: Do not use imipenem/cilastin in patients with central nervous system disorders or history of seizures. for patients with known epilepsy – use meropenem.**OR** Instead of piperacillin/tazobactam + amikacin **OR** cefepime **OR** imipenem:* Meropenem, IV, 2 g 8 hourly

**Note:** 1. De-escalate as soon as the culture is available.
2. For severe pencillin allergy, consult an infectious diseases specialist or microbiologist.
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**Level of Evidence: Guidelines[[4]](#footnote-4)**

And the following STG text was added, providing a cross-reference to section 2.2 for the management of febrile neutropenia:

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| **Note:** If patient is neutropaenic - See section 2.2: Febrile neutropenia. |

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| **9.2 ADULT VACCINATION** |

COVID-19 vaccination: *guidance added*

As COVID vaccination recommendations are being updated regularly as new evidence emerges, guidance was provided to consult the latest National Department of Health vaccine policy recommendations.

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| **9.10 TICK BITE FEVER** |

**In pregnancy**

Doxycycline:*Added as initial therapy*

Azithromycin: *Retained*

Aligned with NEMLC-approved PHC STG (Section 10.14: Tick bite fever)[[5]](#footnote-5):

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| ***NEMLC MEETING OF 23 JUNE 2022 - NEMLC REPORT OF THE PHC INFECTIONS CHAPTER******In pregnancy****Doxycycline:**Added as initial therapy**Azithromycin: Retained**Doxycycline is antibiotic of choice for the treatment of tick bite fever.[[6]](#footnote-6) However, doxycycline is generally avoided for use in pregnancy, as other tetracyclines have been associated with adverse effects on fetal teeth and bones.[[7]](#footnote-7) A systematic review[[8]](#footnote-8) demonstrated that doxycycline use by these patient groups had a safety profile that differed from that of tetracycline, with no correlation between doxycycline and teratogenic effects during pregnancy or dental staining in children. In addition, a retrospective cohort study suggests that doxycycline (and other antibiotics – azithromycin, ciprofloxacin and amoxicllin) used by pregnant women should not result in a greater incidence of overall major congenital malformations in their infants.[[9]](#footnote-9)**As there is a high fetal risk associated with rickettsial illnesses in pregnancy (higher than in malaria),[[10]](#footnote-10) treatment with doxycycline outweighs the risks and consequences of the side effects associated with doxycycline. Early initiation of empirical doxycycline, to bypass any diagnostic challenges associated with rickettsial infections may likely save lives and prevent severe disease.**The PHC STGs and EML recommends initial treatment with doxycycline for 2 days, followed by azithromycin for tick bite fever in pregnancy.**STG text was updated as follows:*

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| *In pregnancy:** *Doxycycline, oral, 100 mg 12 hourly for 2 days.*

*Then switch to:** *Azithromycin, oral, 500 mg 12 hourly for 3 days.*
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***Level of Evidence: Very low certainty, conditional recommendation*** |

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| **9.12 VARICELLA (CHICKENPOX), COMPLICATED** |

Varicella-zoster immunoglobulin (VZIG), IM: *indication amended*

The indication for VZIG was amended to align with the Centers for Disease Control and Prevention (CDC) guidelines[[11]](#footnote-11) and corrected from:

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| ~~For patients who are severely immunologically compromised and are not immune:~~ |

To:

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| For close contacts (household contacts or patients in adjacent beds in the same ward) who are severely immunologically compromised and are not immune (i.e. no history of chickenpox/shingles or negative VZV IgG) following a significant exposure (household contacts): |

**Level of Evidence: Low certainty evidence, conditional recommendation**

1. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1;63(5):e61-e111. doi: 10.1093/cid/ciw353. Epub 2016 Jul 14. Erratum in: Clin Infect Dis. 2017 May 1;64(9):1298. Erratum in: Clin Infect Dis. 2017 Oct 15;65(8):1435. Erratum in: Clin Infect Dis. 2017 Nov 29;65(12):2161. [↑](#footnote-ref-1)
2. Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev. 2015 Aug 24;2015(8):CD007577. [↑](#footnote-ref-2)
3. Dimopoulos G, Poulakou G, Pneumatikos IA, Armaganidis A, Kollef MH, Matthaiou DK. Short- vs long-duration antibiotic regimens for ventilator-associated pneumonia: a systematic review and meta-analysis. Chest. 2013 Dec;144(6):1759-1767. [↑](#footnote-ref-3)
4. SAMF, 2022 [↑](#footnote-ref-4)
5. Minutes of the NEMLC meeting of 23 June 2022 [↑](#footnote-ref-5)
6. Frean J, Grayson W. South African Tick Bite Fever: An Overview. Dermatopathology (Basel). 2019 Jun 26;6(2):70-76. https://pubmed.ncbi.nlm.nih.gov/31700846/ [↑](#footnote-ref-6)
7. SAMF, 2022 [↑](#footnote-ref-7)
8. Cross R, Ling C, Day NP, McGready R, Paris DH. Revisiting doxycycline in pregnancy and early childhood--time to rebuild its reputation? Expert Opin Drug Saf. 2016;15(3):367-82. https://pubmed.ncbi.nlm.nih.gov/26680308/ [↑](#footnote-ref-8)
9. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer SM, Gideon PS, et al. Antibiotics potentially used in response to bioterrorism and the risk of major congenital malformations. Paediatr Perinat Epidemiol. 2009 Jan;23(1):18-28. https://pubmed.ncbi.nlm.nih.gov/19228311/ [↑](#footnote-ref-9)
10. McGready R, Prakash JA, Benjamin SJ, Watthanaworawit W, Anantatat T, Tanganuchitcharnchai A, et al. Pregnancy outcome in relation to treatment of murine typhus and scrub typhus infection: a fever cohort and a case series analysis. PLoS Negl Trop Dis. 2014 Nov 20;8(11):e3327. https://pubmed.ncbi.nlm.nih.gov/25412503/ [↑](#footnote-ref-10)
11. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of VariZIG--United States, 2013. MMWR Morb Mortal Wkly Rep. 2013 Jul 19;62(28):574-6. [↑](#footnote-ref-11)