health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 9: SYSTEMIC AND HEALTHCARE-ASSOCIATED INFECTIONS
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 Systemic and Healthcare-Associated Infections.

A: NEW STANDARD TREATMENT GUIDELINES

SECTION	CONDITION	MEDICINE MANAGEMENT	MEDICINE ADDED
9.4	**Emerging respiratory pathogens, e.g. Covid-19: coronavirus disease-19; Middle east respiratory syndrome coronavirus infection: MERS COV**	No	n/a
9.8	**Schistosomiasis, acute**	Yes	Prednisone, oral Praziquantel, oral

9.4 EMERGING RESPIRATORY PATHOGENS, e.g. COVID-19: CORONAVIRUS DISEASE-19; MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS INFECTION: MERS COV

Due to concerns of the ongoing threat from Middle East and Asia, the following STG was included in the chapter, aligned with NICD Guidelines[1]:

Note: Consult most recent guidelines from National Department of Health/ NICD.

Description

Middle East Respiratory Syndrome (MERS) is a viral respiratory illness caused by Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Individuals with MERS-CoV present with a wide spectrum of clinical presentation ranging from asymptomatic infection to acute upper respiratory illness, and rapidly progressing lower respiratory illness; respiratory failure, septic shock and multi-organ failure resulting in death.

A typical presentation of MERS includes:

» fever (>38°C), chills or rigors, cough, shortness of breath

Presentation may include:

» hemoptysis, sore throat, myalgias, diarrhoea, vomiting, abdominal pain

Complications:

» severe pneumonia
» ARDS
» acute renal failure
» refractory hypoxaemia

General measures

All suspected, probable cases and contacts must be discussed and managed in consultation with the regional virologist or infectious diseases specialist at the referral centre.

In addition cases should be discussed with the Centre for Respiratory Diseases of the National Institute for Communicable Diseases (NICD).

Tel: 011 386 6392/ 011 3866390 , Outbreak hotline: 082 883 9920

COVID-19 HOTLINE NUMBERS
Clinicians: 080011131
Public: 080002999
http://www.nicd.ac.za/ ; https://sacoronavirus.co.za/

Transfer of patients will only occur once all relevant arrangements have been made to limit further exposure to a potential contagious and life threatening agent.

Droplet precautions should be added to the standard precautions. Airborne precautions should be applied when performing aerosol-generating procedures.

Isolate suspected symptomatic cases at all times.

If MERS coronavirus is suspected, isolate patient to limit further exposure.

[1] NICD: Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Guidelines, June 2016.

Management
Treatment
Treatment is supportive.
No antiviral agents or vaccines are currently available.
Management of contact: consult with NICD and isolate contact.
Record and follow-up all patient contacts.

Prevention
Handwashing and the careful disposal of materials infected with nasal secretions. Antiseptic/disinfectant solutions:choroxylenol, benzalkonium chloride, and cetrimide. Chlorhexidine has been shown to be ineffective.

Referral
All cases after consultation with infectious diseases and NICD.

9.8 SCHISTOSOMIASIS

The following STG was developed to provide guidance for differential diagnosis and management of acute and chronic schistosomiasis, up-referred from PHC level of care. RCT data is limited, and recommendations were informed by observations from case series. A cross-referral was included to the PHC STGs and EML fro management of chronic schistosoma.

Description
A parasitic infestation with:
» *Schistosoma haematobium*: primarily involves the bladder and renal tract, or
» *Schistosoma mansoni*: primarily involves the intestinal tract.

Diagnosis
Acute schistosomiasis syndrome
» Typically occurs in travellers to endemic areas with freshwater exposure 3-7 weeks before onset.
» Clinical features include fever, rigors/chills, urticaria,angioedema, myalgias, arthralgias, dry cough, diarrhea, abdominal pain, and headache. Symptoms are usually relatively mild and resolve spontaneously over a period of a few days to a few weeks.
» The eosinophil count is almost invariably markedly elevated.
» Diagnosis is confirmed serologically – eggs are seldom seen in stool or urine.
» Differential diagnosis includess urinary tract infection, glomerulonephritis, HIV, gastroenteritis (Salmonella), hepatitis A, B and C, malaria.

Chronic schistosomiasis
» Most individuals with schistosomiasis infection are asymptomatic.
» *S. haematobium* may present with macroscopic haematuria and urinary symptoms. Chronic bladder involvement and urinary tract involvement may cause urinary incontinence and obstructive uropathy.
» *S. mansoni* may present with chronic or intermittent dysentery. Periportal fibrosis and portal hypertension may occur.
» Pulmonary hypertension and central nervous system involvement (particularly myelopathy) are uncommon complications.
» Definitive diagnosis is by finding eggs in urine (*S. haematobium*), stool (*S. mansoni*), or on biopsy. Serology is usually positive.

Medicine treatment
Acute schistosomiasis syndrome
- Prednisone, oral, 40 mg daily for 5 days.

<u>4-6 weeks later, after symptoms have resolved:</u>
- Praziquantel, oral, 40 mg/kg as a single dose.

AND
- Prednisone, oral, 40 mg daily for 5 days.

Optimum time for administration of praziquantel is uncertain but sufficient time is required for the worms to mature.

<u>If in 4-6 weeks, eosinoplilia present and high antibody titres, repeat praziquantel treatment:</u>
- Praziquantel, oral, 40 mg/kg as a single dose.

Chronic schistosomiasis
Manage as recommended in PHC STGs and EML, section 10.12: Schistosomiasis (bilharzia).

Level of Evidence: III Case series[2]

[2] Grandière-Pérez L, Ansart S, Paris L, Faussart A, Jaureguiberry S, Grivois JP,Klement E, Bricaire F, Danis M, Caumes E. Efficacy of praziquantel during the incubation and invasive phase of Schistosoma haematobium schistosomiasis in 18 travelers. Am J Trop Med Hyg. 2006 May;74(5):814-8. https://www.ncbi.nlm.nih.gov/pubmed/16687686

B: AMENDMENTS TO MEDICINE TREATMENT

SECTION	MEDICINE	ADDED/DELETED/AMENDED
9.1.1 Intravascular catheter infections		
- Erythema in patients that are systemically well	Clindamycin, oral	Retained and dose not amended
	Vancomycin, IV	Not added
- S aureus	Vancomycin, IV	Retained for directed therapy
	Linezolid, IV	Not added
- Candidaemia	Candidaemia empiric therapy	Duration of therapy not amended
	Amphotericin B, IV	Retained and dose not amended
	Amphotericin B, lipsomal, IV	Not added
	Fluconazole, oral	Indications amended
	Echinocandins, IV	Added (specialist motivation)
- Peripheral line infections	Ertapenem, IV	Not added to cover Gram negatives
9.1.2 Surgical wound infections	Cloxacillin, IV	Deleted
	Cefazolin, IV	Added
	Flucloxacillin, oral	Dose not amended
-If Gram negative organisms present:	Piperacillin/tazobactam, IV	Added
- Severe penicillin allergy: If Gram negative organisms present	Ertapenem, IV	Added
- If surgery was on female uro-genital tract or open GIT surgery:	Piperacillin/tazobactam, IV	Not added
	Ceftriaxone, IV	Retained
	Metronidazole, IV	Retained
9.1.3 Hospital-acquired pneumonia (HAP) - HAP risk factors for MDR infection	Piperacillin/tazobactam, IV	Retained
	Ertapenem, IV	Not added
	Cefipime, IV	Retained, dose increased and directions for use expanded to include dose adjustment in renal impairment (Appendix II)
	Imipenem, IV	Retained
	Meropenem, IV	Retained
9.1.4 Urinary tract infections, catheter associated	Ertapenem, IV	Not added
	Amikacin, IV	Retained
9.2 Adult vaccination	Influenza vaccine	Indications & contraindications amended
	Human papillovirus vaccine	Not added
9.2.1 Rabies vaccination	Rabies vaccine	Deleted (Cross referenced to PHC STG)
	Human rabies immunoglobulin	Deleted (Cross referenced to PHC STG)
9.3 Brucellosis	Streptomycin, IV	Not added
9.7.1 Malaria, uncomplicated	Artemether/lumefantrine 20/120 mg, oral	Deleted (Cross referenced to PHC STG)
9.7.2 Malaria severe	Artesunate, IV	Directions for use not amended
9.9 Tetanus	Benzyl penicillin, IV	Deleted
	Metronidazole, IV	Retained
	Ampicillin, IV	Not added
- Fever	Paracetamol, oral	Retained
9.10 Tick bite fever	Doxycycline, oral	Directions for use amended
9.12 Varicella (chickenpox), complicated	Corticosteroids	Not added
9.13 Zoster (shingles)	Aciclovir, IV	Dosing not amended
	Aciclovir, ophthalmic ointment	Deleted
	Antiviral (active against herpes zoster)	Added as therapeutic class
	Aciclovir, oral	Retained as the example of antiviral therapeutic class (listed in STG)
	Valaciclovir, oral	Added as a therapeutic alternative
	Famciclovir, oral	Added as a therapeutic alternative
- Post-herpetic neuralgia	Amitryptyline, oral	Retained
	Carbamazepine, oral	Not added

Acknowledgement: NICD collaboration informed antibiotic recommendations.

9.1.1 INTRAVASCULAR CATHETER INFECTIONS

LARGE AREAS OF ERYTHEMA AND SYSTEMICALLY WELL PATIENTS

Clindamycin, oral: *retained and dose not amended*

Vancomycin, IV: *not added*

An external commentator reported that empiric therapy should be as for MRSA due to 90% resistance of S aureus in hospital settings. However, NICD reported clindamycin susceptibility of 72% for viable *S aureus* isolates for 2016 (n=746).[3] Dose of oral clindamycin was retained as "450 mg" 8 hourly and not amended to "600 mg" 8 hourly.

Recommendation: Vancomycin not be recommended for *S aureus* hospital infections; and clindamycin be retained as the empiric antibiotic of choice. Dose of oral clindamycin aligned to South African Antibiotic Stewardship Programme Guidelines, 2015 and SAMF, 2016.

Level of Evidence: III Antibiotic susceptibility data, Guidelines

***S. AUREUS* INFECTION**

Vancomycin, IV: *retained*

Linezolid, IV: *not added*

Linezolid, IV: External comment received to include linezolid in the STG, as vancomycin was not readily accessible. However, vancomycin is on the current contract[4] and is included in the Tertiary and Quaternary EML.

Level of Evidence: III Expert opinion

CANDIDAEMIA

Duration of candidaemia empiric therapy: *not amended*

The appropriate duration of therapy for candidaemia has not been studied. For patients without metastatic complications, a minimum of two weeks of therapy after blood cultures become negative has been used in most clinical trials and is the recommended duration in the 2016 Infectious Diseases Society of America (IDSA) guidelines.[5]

Recommendation: Duration of empiric therapy for candidaemia associated with intravascular catheter-related infections be retained as a minimum of 14 days.

Rationale: Aligned with guidelines.

Level of Evidence: III Guidelines[6] [7]

National surveillance data

GERMS national surveillance data was shared and analysed with NICD, to further inform recommendations. The cross-sectional study for candidaemia for the period 2016-2016 for public/private sector using laboratory-based blood culture-confirmed cases for the following species of candidaemia.

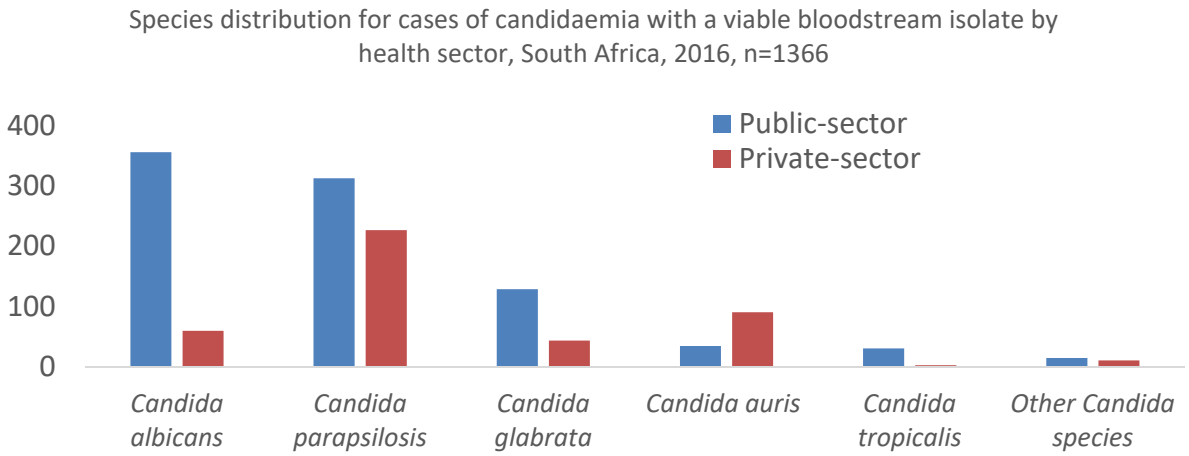
[3] GERMS-SA laboratory-based surveillance for antimicrobial-resistant bacterial and fungal bloodstream infections, 2016. NICD Public Health Surveillance Bulletin. Volume 15. Issue 3 – November 2017. www.nicd.ac.za

[4] Contract circular HP02-2019AI

[5] Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15;62(4):e1-50. https://www.ncbi.nlm.nih.gov/pubmed/26679628

[6] Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15;62(4):e1-50. https://www.ncbi.nlm.nih.gov/pubmed/26679628

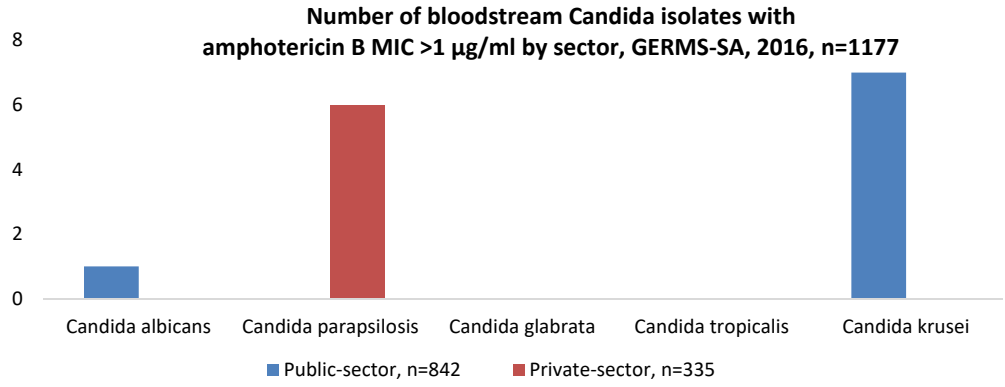
[7] Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJ, Sherertz RJ, Warren DK. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009 Jul 1;49(1):1-45. . Erratum in: Clin Infect Dis. 2010 Apr 1;50(7):1079. Dosage error in article text. Clin Infect Dis. 2010 Feb 1;50(3):457. https://www.ncbi.nlm.nih.gov/pubmed/19489710



(*Candida* species distribution varies by province, facility and unit within facility).

Amphotericin B, IV: *retained and dose not amended*
Amphotericin B, liposomal: *not added*
Amphotericin B is a concentration-dependant antifungal agent, and the highest safe dose is best to be used. The standard dose of 0.7 mg/kg daily is used in most RCTs. Lipsomal amphotericin B is expensive[8] but may be of benefit in mucormycosis, where nephrotoxicity requires to be considered, a condition managed at tertiary and quaternary levels of care.
Recommendation: Amphotericin dose retained as 0.7 mg/kg daily.
Rationale: Standard dose used in practice and most RCTs.
Level of Evidence: I RCTs[9] [10]

Amphotericin B: This is still a reliable first-line antifungal agent, but has serious adverse effects.

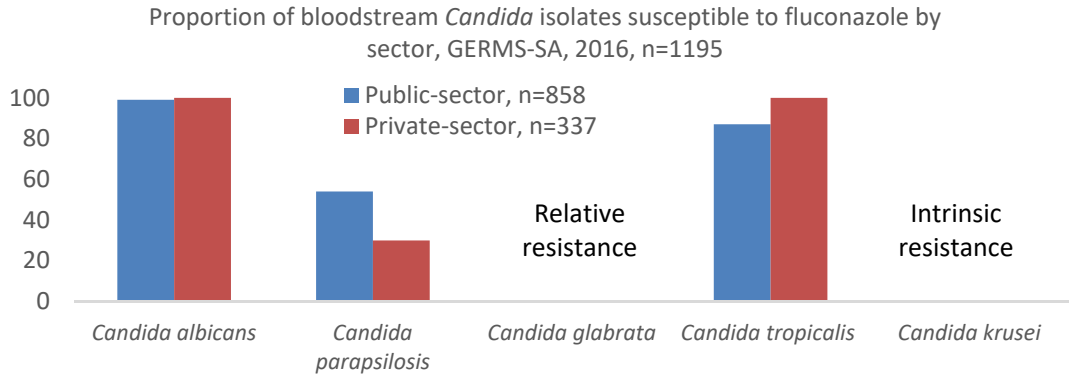


(For suspected non *C albicans* infections, amphotericin B is initiated until confirmed susceptibility).

Fluconazole, oral: *indications amended*
Fluconazole, oral was recommended as step down therapy or as an alternative to amphotericin B, when the latter is poorly tolerated to only occur when sensitivity has been confirmed.

Surveillance data suggests that fluconazole is not a reliable first-line or oral step-down agent in many setting, due to resistance of a number of *Candida* species:

[8] SEP database 27 May 2017: Liposomal amphotericin B, 50 mg: R2480.48 per unit.
[9] Anaissie EJ, Darouiche RO, Abi-Said D, Uzun O, Mera J, Gentry LO, Williams T, Kontoyiannis DP, Karl CL, Bodey GP. Management of invasive candidal infections: results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of the literature. Clin Infect Dis. 1996 Nov;23(5):964-72. https://www.ncbi.nlm.nih.gov/pubmed/8922787
[10] Rex JH, Bennett JE, Sugar AM, Pappas PG, van der Horst CM, Edwards JE, Washburn RG, Scheld WM, Karchmer AW, Dine AP, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute. N Engl J Med. 1994 Nov 17;331(20):1325-30. https://www.ncbi.nlm.nih.gov/pubmed/7935701



Thus, the text of the STG was amended to recommend treatment with fluconazole, oral, only once susceptibility has been confirmed.

Echinocandins, IV: *added (specialist motivation)*
The following was added, aligned with the Tertiary and Quaternary EML[11]:

Invasive candidiasis (resistant to fluconazole/amphotericin B and renal impairment is present and amphotericin B cannot be used):
▪ Echinocandins. (Specialist motivation).

Level of Evidence: III Guidelines

GRAM NEGATIVE INFECTIONS
Ertapenem, IV: *not added to cover Gram negatives*
The Adult Hospital Level Committee was of the opinion that Extended-spectrum beta-lactamases (ESBL) - producing organisms are more prevalent in intensive care unit (ICU), and thus ertapenem was not added to cover Gram negatives for peripheral line infections.

9.1.2 SURGICAL WOUND INFECTIONS

Cloxacillin, IV: *deleted*
Cefazolin, IV: *added*
Flucloxacillin, oral: *dose not amended*

Cloxacillin amended to cefazolin, IV: NEMLC had approved a circular to substitute cloxacillin with cefazolin due to continuous global supply challenges of cloxacillin for last 2-3 years (active pharmaceutical ingredient sources problematic). In a retrospective cohort study, mortality was reported to be lower for cefazolin vs vancomycin for methicillin susceptible *Staph. aureus* (HR 0.65, 95% CI 0.52 to 0.80).
Staph aureus resistance to oxacillin has recently been reported in two Provinces, with 9% MRSA detected in community acquired pneumonia.[12]
Level of Evidence: II Retrospective cohort study, Susceptibility study

Flucloxacillin, oral dose: An external comment was received to amend the dose of oral flucloxacillin from "500 mg 6 hourly" to "2 g 6 hourly". However, the dose was not amended; the current dose is aligned with SAMF, 2016.

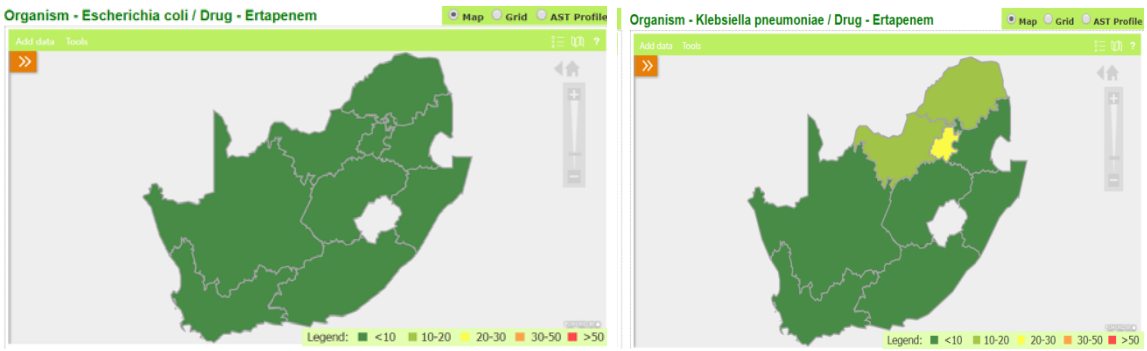
If Gram negative organisms present:
Piperacillin/tazobactam, IV: *added*
Level of Evidence: III Standard of care

[11] Tertiary and Quaternary EML, July 2019
[12] Perovic O, Singh-Moodley A, Govender NP, Kularatne R, Whitelaw A, Chibabhai V, Naicker P, Mbelle N, Lekalakala R, Quan V, Samuel C, Van Schalkwyk E; for GERMS-SA. A small proportion of community-associated methicillin-resistant Staphylococcus aureus bacteraemia, compared to healthcare-associated cases, in two South African provinces. Eur J Clin Microbiol Infect Dis. 2017 Dec;36(12):2519-2532. https://www.ncbi.nlm.nih.gov/pubmed/28849285

Severe penicillin allergy: If Gram negative organisms present:
Ertapenem, IV: *added*

Evidence of efficacy:
Meta-analysis showed comparable microbiological treatment success of ertapenem vs piperacillin/tazobactam for complicated infections treatment at test-of-cure visit. The results of the analysis, based on microbiologically evaluable population (n=1699) was OR 1.11 (95% CI 0.84 to 1.4, I^2=0%).

Local antimicrobial susceptibility patterns:
NICD surveillance data for ertapenem; source - NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.



Price:
At a daily dose of 1 g daily, ertapenem costs R347.78; whilst for patients that are not allergic to penicillin the daily cost of piperacillin/tazobactam 4.5 g 8 hourly is R119.04(R39.68 x 3 doses).[13]
Recommendation: Ertapenem, IV 1 g daily be added for confirmed Gram negative infections in severe penicillin allergic patients with surgical wound infections.
Rationale: Evidence of comparable microbiological treatment success of ertapenem compared to piperacillin/tazobactam and local surveillance data shows susceptibility of *E coli* and *K pneumoniae* to ertapenem.
Level of Evidence: I Meta-analysis[14], Susceptibility data

If surgery was on female uro-genital tract or open GIT surgery:
Piperacillin/tazobactam: *not added*
Ceftriaxone, IV: *retained*
Metronidazole, IV: *retained*
The Committee was of the opinion that current recommendation: Ceftriaxone, IV 2 g daily + Metronidazole, IV 8 hourly for 7 days was sufficient.
Level of Evidence: III Expert opinion

9.1.3 HOSPITAL-ACQUIRED PNEUMONIA (HAP)

HAP risk factors for MDR infection

- **Criterion for MDR empiric antibiotic therapy:**

Previous criteria - hospitalised >5 days, hospitalised for >2 days in the past 3 months, immunocompromised with poor functional status, developed pneumonia after admission to ICU: *deleted*

Updated criterion - prior intravenous antibiotic use within 90 days: *added*

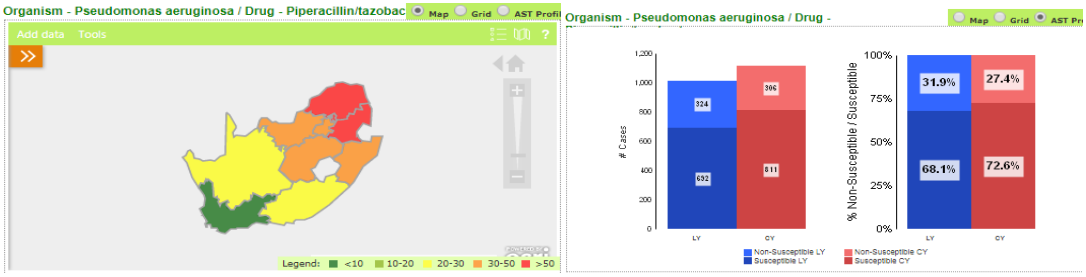
Aligned with Infectious Diseases Society of America and the American Thoracic Society 2016 guideline[15] recommendation that included a meta-analysis that investigated fifteen potential risk factors for MDR-HAP.

[13] Contract circular HP02-2019AI
[14] An MM, Zou Z, Shen H, Zhang JD, Chen ML, Liu P, Wang R, Jiang YY. Ertapenem versus piperacillin/tazobactam for the treatment of complicated infections: a meta-analysis of randomized controlled trials. BMC Infect Dis. 2009 Dec 2;9:193. https://www.ncbi.nlm.nih.gov/pubmed/19951447
[15] Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB 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. https://www.ncbi.nlm.nih.gov/pubmed/27418577

The analysis showed that only one risk factor was significantly associated with increased risk of MDR-HAP: previous IV antibiotic use (OR, 5.17; 95% CI, 2.11 to 12.67). The analysis concludes that whilst other risk factors may be relevant, evidence is lacking. Similarly, prior use of IV antibiotics in the past 90 days was identified as a predisposing factor for MDR-VAP (OR, 12.3; 95% CI, 6.48 to 23.35).
Level of Evidence: I Meta-analysis, Guidelines

• **Empiric antibiotic therapy:**
Piperacillin/tazobactam, IV: *retained*
Ertapenem, IV: *not added*
Cefipime, IV: *retained, dose increased and directions for use expanded to include dose adjustment in renal impairment (guidance included in Appendix II)*
Imipenem, IV: *retained*
Meropenem, IV: *retained*

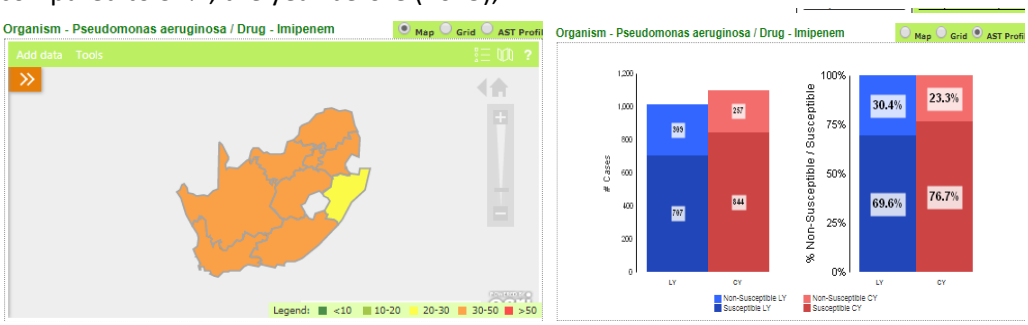
Piperacillin/tazobactam: NICD surveillance data[16] reports approximately 28% resistance of Pseudomonas to piperacillin/tazobactam nationally:



Cefepime: NICD surveillance data[17] reports approximately 30% resistance of Pseudomonas to cefepime; and thus dosing recommended as 2 g 12 hourly.[18]

Ertapenem has no activity against *Pseudomonas*, and thus not recommended in this clinical setting.

Imipenem, IV: NICD surveillance data[19] reports approximately 24% resistance of Pseudomonas to imipenem compared to 31%, the year before (2015);



[16] NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.
[17] NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.
[18] SAMF, 2016.
[19] NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.

Recommendation: Piperacillin/tazobactam and imipenem be retained, ertapenem not be recommended, and cefepime be recommended at a dose of 2 g 12 hourly for treatment of HAP.
Rationale: Guided by local susceptibility data that varies between regions.
Level of Evidence: **III Antimicrobial susceptibility data**

Price of empiric antibiotics (daily doses)

ANTIBIOTIC UNIT PRICE	DAILY DOSE	COST OF DAILY DOSE
Cefipime, IV 2g = R99.00**	2 g 12 hrly	R198.00
Amikacin, IV 500 mg =11.38; 100 mg = R8.58**	70 kg adult: = 1050 mg	R31.34
Ceftriaxone, IV, 1 g = R6.04**	2 g daily	R12.09
Moxifloxacin, oral 400mg= R5.18**	400 mg/day	R5.18
Moxifloxacin, IV 400 mg = R149.32**	400 mg/day	R 149.32
Piperacillin/tazobactam, IV 4.5 g = R39.68**	4.5 g 8 hrly	R119.04
Imipenem/cilastatin , IV 500/500 mg = R59.72**	1 g 8 hrly	R358.32
Meropenem, IV 1 g = R 82.80**	2 g 8 hrly	R496.80

** Weighted average tender price, Contract circular HP02-2019AI

TREATMENT	COST OF DAILY TREATMENT
HAP WITH NO RISK FACTORS	
Ceftriaxone + amikacin	R43.42
Moxifloxacin, IV + amikacin	R180.66
Moxifloxacin, oral + amikacin	R36.52
HAP WITH RISK FACTORS	
Piperacillin/tazobactam + amikacin	R150.38
Cefipime 2 g 12 hourly	R198.00
Imipenem	R358.32
Meropenem	R496.80

9.1.4 URINARY TRACT INFECTIONS, CATHETER ASSOCIATED

Ertapenem, IV: *not added*
Amikacin, IV: *retained*
An external comment to include ertapenem as an option to amikacin as empiric therapy was not accepted, as the former is cost prohibitive[20].

9.2 ADULT VACCINATION

Influenza vaccine: *indications and contraindications amended*

- **Indications**

Aligned with the most current National Influenza policy[21], as follows:

» Pregnant women
» Elderly patients >65 years.
» HIV-infected patients.
» Patients with chronic pulmonary, cardiac, and renal conditions.
» Healthcare workers with direct patient contact.**

**Healthcare workers are not routinely offered immunisation during the annual campaign. Although it is recommended that healthcare workers are vaccinated against influenza, they will not be provided with publically funded vaccines unless they fall within any of the designated high risk groups.

Level of Evidence: III Guidelines

However, with consideration of the current COVID-19 pandemic the following note was added to the STG text:

NOTE: Prioritisation strategies may vary in a pandemic.

[20] Contract circular RT301-2017: Ertapenem 1 g = R331.50; Amikacin, 15 mg/kg = R23.29 (cost for daily antibiotic dose)
[21] National Department of Health: National Influenza Policy and Strategic Plan, 2017 to 2021
- Programme advised that updated policies are not routed through NAGI; NAGI to address this matter.

- **Contraindications**

As allergy to eggs is not an absolute contraindication, STG text was amended as follows:

- Contraindication: severe egg allergy, age <6 months
- Dose: IM, 0.5 mL.
- Repeat annually.

Level of Evidence: III Guidelines[22]

Human papillomavirus vaccine: *not added*

This is a limited School Health Programme, and thus not included in the EML.

9.2.1 RABIES VACCINATION

Rabies vaccine: *deleted*

Human rabies immunoglobulin: *deleted*

The Committee recommended the deletion of the following text with a cross reference to the PHC STG: Section 21.3.1.1: Animal bites to minimise duplication and consistency between guidelines on the EML Clinical Guide application.

9.3 BRUCELLOSIS

Streptomycin: *not added*

Not considered, as currently not available on the South African market.

9.7.1 MALARIA, UNCOMPLICATED

Artemether/lumefantrine 20/120 mg, oral: *deleted*

The Committee recommended the deletion of the following text with a cross reference to the PHC STG: Section 10.7.1: Malaria uncomplicated, to minimise duplication and consistency between guidelines on the EML Clinical Guide application.

9.7.2 MALARIA SEVERE

Artesunate, IV: *directions for use not amended*

External comment was received to editorially amend directions for use of artesunate, IV. However, the Adult Hospital Committee considered the current guidance to be adequate. It is noted that this medicine is registered with the MCC/SAHPRA registered; though is currently not on tender, and procured through quotation.

9.9 TETANUS

Antibiotic treatment

Benzyl penicillin, IV: *deleted*

Metronidazole, IV: *retained*

Ampicillin, IV: *not added*

Evidence could not be sourced for ampicillin in this clinical setting. Due to the continuous supply challenges of benzyl penicillin (currently available through section 21), metronidazole has been recommended as the alternative option, aligned with WHO Guidelines[23].

Level of Evidence: III Guidelines

[22] SAMF, 2016

[23] World Health Organisation. Technical note: Current recommendations for treatment of tetanus during humanitarian emergencies, January 2010. https://www.who.int/diseasecontrol_emergencies/who_hse_gar_dce_2010_en.pdf

Fever

Paracetamol, oral: *retained*

An observational study (n=1425) suggested that high fever ≥ 39.5°C was associated with an increased risk of 28-day mortality in septic patients (adjusted OR 8.14, p= 0.01), but not in non-septic patients (adjusted odds ratio 0.47, p =0.11). The findings suggest that fever and antipyretics may have different biological and/or clinical implications for patients with and without sepsis.

Recommendation: Paracetamol be retained for management of pain associated with tetanus in the hospital setting.

Rationale: There is no RCT evidence for paracetamol for management of fever tetanus. The Adult Hospital Level Committee reviewed the observational study that suggested that high fever ≥ 39.5°C was associated with an increased risk of 28-day mortality in septic patients (adjusted OR 8.14, p= 0.01). However, the study was done in the setting of critical care and cannot be extrapolated to management of fever in tetanus. Paracetamol was retained for analgesic as opposed to antipyretic effect.

Level of Evidence: III Observational study[24]

9.10 TICK BITE FEVER

Doxycyline, oral: *directions for use amended*

The following was amended, aligned with CDC Guidelines[25]:

- Doxycycline, oral, 100 mg 12 hourly, for at least 3 days after the fever subsides with clinical improvement.
  - Total duration of treatment is 7 days.

Level of Evidence: III Guidelines.

Referral

The following referral criteria was added, aligned with above-mentioned CDC Guidelines:

Tick bite fever responds rapidly to treatment and fever persisting for > 48 hours after initiation of treatment should prompt consideration of an alternative or additional diagnosis.

9.11 TYPHOID FEVER (ENTERIC FEVER)

Referral

Referral criteria updated to include: *"Drug resistant organism: consult microbiology/infectious diseases services".*

9.12 VARICELLA (CHICKENPOX), COMPLICATED

Corticosteroids: *not added*

An external comment was received motivating for corticosteroids for life-threatening varicella pneumonia based on retrospective study[26]. However, the Adult Hospital Level Committee was of the opinion that the evidence base was not sufficiently robust (small observational studies that showed a trend towards improved mortality, not statistically significant).

Recommendation: Corticosteroids not be recommended in life-threatening varicella pneumonia.

[24] Lee BH, Inui D, Suh GY, Kim JY, Kwon JY, Park J, et al: Fever and Antipyretic in Critically ill patients Evaluation (FACE) Study Group. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. Crit Care. 2012 Feb 28;16(1):R33. https://www.ncbi.nlm.nih.gov/pubmed/22373120

[25] Chapman AS, Bakken JS, Folk SM, Paddock CD, Bloch KC, Krusell A, Sexton DJ, Buckingham SC, Marshall GS, Storch GA, Dasch GA, McQuiston JH, Swerdlow DL, Dumler SJ, Nicholson WL, Walker DH, Eremeeva ME, Ohl CA; Tickborne Rickettsial Diseases Working Group; CDC. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis--United States: a practical guide for physicians and other health-care and public health professionals. MMWR Recomm Rep. 2006 Mar 31;55(RR-4):1-27. https://www.ncbi.nlm.nih.gov/pubmed/16572105

[26] Mer M, Richards GA. Corticosteroids in life-threatening varicella pneumonia. Chest. 1998 Aug;114(2):426-31. https://www.ncbi.nlm.nih.gov/pubmed/9726725

Rationale: Evidence was found to be currently insufficient for recommending corticosteroids for varicella pneumonia, and further RCT research is required.
Level of Evidence: III Observational study

9.13 ZOSTER (SHINGLES)

Aciclovir, IV: *dosing not amended*
Aciclovir, ophthalmic ointment: *deleted as discontinued from the South African market*
Antiviral (active against herpes zoster): *added as therapeutic class*
Aciclovir, oral: *retained as the example of antiviral therapeutic class (listed in STG)*
Valaciclovir, oral: *added as a therapeutic alternative*
Famciclovir, oral: *added as a therapeutic alternative*

Aciclovir, IV:
An external comment was received suggesting therapy be decreased from 7 to 5 days. However, no evidence was submitted and no evidence could be sourced for a shorter duration of treatment.
Recommendation: Treatment course of aciclovir; IV be retained as 7 days for complicated cases of zoster.
Rationale: Available evidence is limited for a shorter treatment course of IV aciclovir, for complicated cases of zoster.
Level of Evidence: III Expert opinion
(Dose adjustment of aciclovir, IV for decreased renal function will be included in Appendix II: Guidance on prescribing and monitoring).

Aciclovir, ophthalmic ointment:
This product is no longer available on the South African market, and it was considered reasonable to treat zoster with secondary dissemination or neurological/ eye involvement with intravenous acyclovir.
Level of Evidence: III Expert opinion

Aciclovir, oral:
Evidence[27] was reviewed in the previous cycle, but it is noted that aciclovir has the largest evidence base and is the cheapest antiviral agent:

The following therapeutic agents are recommended for use in adults (excluding pregnancy and children[28]), with aciclovir listed as the example of class:

Medicine (INN)	Strength	Unit	ROA	Dosing interval (times per day)	DDD	Unit	Course (days)	ATC	Total price for course of therapy	MSH drug price indicator, 2015[29] (Price for course of therapy)
Aciclovir	800	mg	oral	4	3200	mg	7	J05AB01	R40.32*	R 26.32***
Valaciclovir	1000	mg	oral	3	3000	mg	7	J05AB11	R459.40**	R 357.80****
Famciclovir	250	mg	oral	3	750	mg	7	J05AB09	R662.40**	n/a

* Contract circular HP02-2019AI (Aciclovir 400 mg tabs, 60 = R43.20)
** SEP database, 7 February 2020 - 60% of SEP (cheapest generic), accessed 7 February 2020. https://mpr.code4sa.org/
***SUDANMSF - CIF: Aciclovir 400 mg - $0.0310/tab-cap i.e. R0.470/tab-cap
****OECS/PPS - CIF: Valaciclovir 500 mg - $0.5625/tab-cap i.e. R8.519/tab-cap
ROA=route of administration

Level of Evidence: I Systematic review

[27] McDonald EM, De Kock J, Ram FS. Antivirals for management of herpes zoster including ophthalmicus: a systematic review of high-quality randomized controlled trials. Antiviral Therapy 2012; 17(2): 255-264.https://www.ncbi.nlm.nih.gov/pubmed/22300753
[28] Acyclovir versus Valacyclovir for Herpes Virus in Children and Pregnant Women: A Review of the Clinical Evidence and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014 Sep 5. Available from http://www.ncbi.nlm.nih.gov/books/NBK253720/
[29] MSH International drug price indicator guide, 2015. https://www.msh.org/resources/international-drug-price-indicator-guide

Post-herpetic neuralgia:
Amitryptyline, oral: *retained*
Carbamazepine, oral: *not added*
The Adult Hospital Level Committee was of the opinion that the current recommendation, amitryptyline would suffice; and a cross reference was made to section: 26.1.4 Management of neuropathic pain, in the pain chapter.

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)
- ***Note:*** *Information sourced was from NEMLC ratified minutes and NEMLC-approved documents.*