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Department:
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SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 11: SURGICAL ANTIBIOTIC PROPHYLAXIS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2020)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the surgical antibiotic prophylaxis chapter.

SECTION	MEDICINE	ADDED/DELETED/AMENDED
Antibiotic prophylaxis		
• *Orthopaedic surgery: Lower limb amputation*	Metronidazole, IV	Deleted
	Cefazolin, IV	Retained
• *Gastrointestinal surgery: Gastrointestinal bleeds*	Ceftriaxone, IM	Prolonged course not added
• *Obstetrics/ gynaecology*	Cefazolin, IV	Retained
- Caesarean section:	Azithromycin, IV	Added
Dosage recommendations		
• *Routine dosing*	Cefazolin, IV	Dosing amended & treatment protocol not amended in obese women, undergoing C-section
• *Pregnancy*	Cefazolin, IV	Dosing amended
• *Obese women undergoing C-section*	Cefazolin, IV	Prolonged antibiotic course not recommended
Special considerations: Elective splenectomy	Pneumococcal vaccine	Dosing schedule amended; amended to specify 23 valent polysaccharide (PPS23); dose of PCV13 added to regimen

GENERAL PRINCIPLES

Preoperative hair removal not routinely recommended, and if required to remove hair for surgery procedure clipping is preferred.

Evidence: Cochrane review[1] showed that routine removal of hair preoperatively does not reduce surgical site infections. However, where hair removal is necessary to facilitate surgery, evidence suggests that clipping is associated with fewer surgical site infections than shaving. (Three RCTs;n=1343; RR 2.09, 95% CI 1.15 to 3.80 for shaving vs clipping).

The following was accepted for inclusion in the STG:

» Do not remove hair preoperatively unless the hair at or around the incision site will interfere with the operation. If hair removal is necessary, remove immediately before the operation, with clippers.

Level of Evidence: I Systematic review

The following additional recommendations were added to the STG, aligned with guidelines for surgical prophylaxis[2].

» Implement perioperative glycaemic control and use blood glucose target levels less than 11.1mmol/L in patients with and without diabetes.
» Maintain perioperative normothermia.
» Advise patient to shower or bathe with soap or antiseptic agent on at least the night before the procedure.

L**evel of Evidence: III Guidelines**

ANTIBIOTIC PROPHYLAXIS

ORTHOPAEDIC SURGERY:

Metronidazole, IV: *deleted*
Cefazolin, IV: *retained*
Rationale: A definitive amputation only cuts healthy tissue - a definitive procedure.
Level of Evidence: III Expert opinion

[1] Tanner J, Norrie P, Melen K. Preoperative hair removal to reduce surgical site infection. Cochrane Database Syst Rev. 2011 Nov 9;(11):CD004122.
[2] Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, Reinke CE, Morgan S, Solomkin JS, Mazuski JE, Dellinger EP, Itani KMF, Berbari EF, Segreti J, Parvizi J, Blanchard J, Allen G, Kluytmans JAJW, Donlan R, Schecter WP; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017 Aug 1;152(8):784-791.

GASTROINTESTINAL SURGERY

Ceftriaxone, IV: *prolonged course not added*

The use of a prolonged course of ceftriaxone as surgical prophylaxis for upper gastrointestinal bleeds was not considered appropriate for secondary level of care. Evidence[3] for ceftriaxone used this indication was of poor quality and heterogeneous (duration of antibiotics, type of antibiotics, etc). The Adult Hospital Level Committee was of the opinion that this is more appropriate for management by gastroenterologists at tertiary level of care.

OBSTETRICS/ GYNAECOLOGY: CAESAREAN SECTION:

Background: Previously NEMLC had reviewed the surgical prophylaxis chapter, but made additional recommendations[4] [5] [6] [7], including the following:

- NEJM article comparing cefazolin+azithromycin vs cefazolin be reviewed by the Adult Committee[8].
- The NCCEMD be engaged to consider the use of adjunctive azithromycin as opposed to a prolonged course of coamoxyclav as prophylaxis in women undergoing Caeserean section.

Subsequent collaboration between National Committee for the Confidential Enquiries into Maternal Deaths (NCCEMD) and the National Ministerial Advisory Committee for Antimicrobial Resistance (MAC-AMR) and the following additional medicine recommendations are proposed:

Cefazolin, IV: *retained*

Azithromycin, IV: *added*

Evidence review:

The Caesarean Section Optimal Antibiotic Prophylaxis (C/SOAP) trial published in the New England Journal of Medicine[9] showed that adjunctive azithromycin, IV prophylaxis was more efficacious than placebo[10] in reducing wound infection in pregnant women undergoing Caesarean section (ARR: 4.2%; p<0.001).

Outcome	Relative risk (95% CI), p value	ARR	NNT (95% CI)
Primary composite outcome (endometritis, wound infection, or other infections)	0.51 (0.38 to 0.68), p <0.001	5.9%	17 (12 to 30)
Endometritis	0.62 (0.42 to 0.92), p = 0.02	2.3%	44 (24 to 245)
Wound infection (overall)	0.35 (0.22 to 0.56), p < 0.001	4.2%	24 (17 to 41)

RR: relative risk; CI: confidence interval; NNT: number needed to treat; n: study participants

Budget impact analysis:

Refer to the report for detailed information:

Azithromycin_C-sect
ion Prophylaxis_Cos

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

Assuming that all women undergoing a Caesarean section (elective or emergency) requires antibiotic prophylaxis as a single dose of cefazolin (which is current standard of care) together with and azithromycin 500 mg infusion, the estimated budget impact analysis would be as follows. Noting that there is an estimated 1 million births and the rate of Caesareans is 26.2% (as reported in the District Health Barometer, 2015-6) in South Africa per annum.

[3] Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, Soares-Weiser K, Mendez-Sanchez N, Gluud C, Uribe M. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - an updated Cochrane review. Aliment Pharmacol Ther. 2011 Sep;34(5):509-18.

[4] Minutes of the NEMLC meeting of 2 November 2017

[5] Minutes of the NEMLC meeting of 21 February 2019

[6] Minutes of the NEMLC meeting of 11 April 2019

[7] Minutes of the NEMLC meeting of 11 July 2019

[8] Ragusa A, Svelato A. Adjunctive Azithromycin Prophylaxis for CesareanDelivery. N Engl J Med. 2017 Jan 12;376(2):181-2.https://www.ncbi.nlm.nih.gov/pubmed/28079335

[9] Tita ATN, Boggess K, Saade G. Adjunctive Azithromycin Prophylaxis for Cesarean Delivery. N Engl J Med. 2017 Jan 12;376(2):182. https://www.ncbi.nlm.nih.gov/pubmed/28076707

[10] *Note*: Both treatment arms included current standard of care (cefazolin) as part of the treatment regimens.

	Per annum
Estimated births	1,000,000[11]
Caesarean section rate	262,000[12]
Estimated budget impact	R 16,217,800
Incremental budget	R 14,663,340

Recommendation: Following collaboration with NCCEMD and MAC-AMR, the Adult Hospital Level Committee recommended that adjunctive azithromycin, 500 mg IV be recommended with cefazolin, IV (dose adjusted according to weight) as antibiotic prophylaxis in pregnant women undergoing Caesarean section.

Rationale: Evidence suggests that azithromycin with cefazolin (current standard of care) be administered as surgical antibiotic prophylaxis prior to Caesarean section to reduce endometritis and wound infection. Despite the C/SOAP RCT's exclusion criteria of scheduled Caesareans, 10.2% of study participants had a Caesarean section for failed induction of labour and 9.2% had an elective procedure. Furthermore, it is biologically plausible that the benefit of adjunctive azithromycin would extend to elective Caesareans and the American College of Obstetricians and Gynecologists advises: *'the addition of AZI, infused over one hour, to a standard antibiotic prophylaxis regimen may be considered for women undergoing a non-elective C-section'*[13]. The C/SOAP treatment protocol is cost-effective, but there is an incremental cost of R 14,663,340 per annum. In the light of antimicrobial stewardship concerns and the high maternal mortality and morbidity rates in South Africa, adjunctive azithromycin as prophylaxis for all Caesarean sections is a more feasible option compared to routine administration of a treatment course of coamoxyclav to all HIV-infected women post-delivery.

Level of Evidence: I RCT, Guidelines, Expert opinion

DOSAGE RECOMMENDATIONS:

General adult population

Cefazolin, IV: *dosing amended*

No RCT evidence available to evaluate weight-adjusted dosing and its impact on the risk of developing surgical site infections. However, Clinical Practice Guidelines recommends dosages for various weights.

The following was accepted for inclusion in the STG:

- *Cefazolin, IV.*
  - <60 kg: 1g
  - 60–120 kg and BMI ≤35: 2g
  - I≥ 120 kg or BMI >35: 3g

Rationale: Aligned with Clinical Practice Guidelines

Level of Evidence: III Guidelines[14] [15]

Pregnant women (HIV-infected and HIV-uninfected):

Cefazolin, IV: *dosing amended*

- Swank et al[16] showed that "with 2 g of cefazolin, only 20% of the cohort with a BMI of 30-40 kg/m^2 and none of the cohort with a BMI of >40 kg/m^2 reached an MIC of 8 mg/mL. With 3-g, all women with a BMI of 30-40 kg/m^2 reached target MIC values; 71% of the women with a BMI of >40 kg/m2 attained this cutoff". The Committee it was not pragmatic to use BMI scale, and obesity determined by weight was considered.

[11] StatsSA

[12] Health Systems Trust, District Health Barometer, 2015-6.

[13] Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 199: Use of Prophylactic Antibiotics in Labor and Delivery. Obstet Gynecol. 2018 Sep;132(3):e103-e119. https://www.ncbi.nlm.nih.gov/pubmed/30134425

[14] Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, Reinke CE, Morgan S, Solomkin JS, Mazuski JE, Dellinger EP, Itani KMF, Berbari EF, Segreti J, Parvizi J, Blanchard J, Allen G, Kluytmans JAJW, Donlan R, Schecter WP; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017 Aug 1;152(8):784-791.

[15] Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA; American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013 Feb 1;70(3):195-283.

[16] Swank ML, Wing DA, Nicolau DP, McNulty JA. Increased 3-gram cefazolin dosing for cesarean delivery prophylaxis in obese women. Am J Obstet Gynecol. 2015 Sep;213(3):415.e1-8.

- Elkomy et al[17] showed that "maternal administration of up to 2 g of cefazolin is effective and produces exposure within clinically approved limits in neonates".

The following was included in the text of the STG:

Pregnant women:	
o < 60 kg:	1 g
o 60–100 kg:	2 g
o >100 kg:	3 g

Level of Evidence: III Pharmacokinetic studies

Obese women undergoing C-section

Cefazolin, IV: *prolonged antibiotic course not recommended*

No available evidence could be sourced for longer courses of antibiotic prophylaxis in in the obese pregnant women undergoing C-section, be reviewed.

Generally, the shortest effective duration of antibiotic prophylaxis for preventing any SSI is not known; however, there is evidence suggesting that postoperative administration of antibiotics is not required for most procedures[18].

Recommendation: Cefazolin, IV be administered as a single dose prior to C-section with dose-adjustment for the obese.
Rationale: Paucity of evidence for postoperative administration of antibiotics following C-section to prevent surgical site infections. Limited evidence suggests dose-adjustment of prophylactic cefazolin, IV amongst obese pregnant women.
Level of Evidence: III Pharmacokinetic studies, Expert opinion

SPECIAL CONSIDERATIONS: ELECTIVE SPLENECTOMY

Polyvalent pneumococcal vaccine: *dosing schedule amended; amended to specify 23 valent polysaccharide (PPS23); dose of PCV13 added to regimen*

Dosing schedule: Dose corrected from, "*Revaccinate every 5 years*" to "*Revaccinate after 5 years and then at 65 years*", to align with the Adult Hospital Level, 2015 infections chapter and the CDC: Advisory Committee on Immunization Practices Guidelines[19].
Level of Evidence: III Guidelines

Additional dose of PCV13: The NEMLC had recommended that the Adult Committee review the option of recommending conjugated polyvalent pneumococcal vaccine (PCV) in patients undergoing elective splenectomy[20]. In addition, an external comment was received that the recommendation be amended to specify the specific pneumococcal vaccine, as PCV13 is not sufficient in this clinical setting[21].

Although biologically plausible and recommended in most international guidelines[22] [23] [24]; the evidence for combined therapy (i.e. initial dose of PCV13 2 weeks prior to surgery, followed later by PPS23 8 weeks later which is repeated at

[17] Elkomy MH, Sultan P, Drover DR, Epshtein E, Galinkin JL, Carvalho B. Pharmacokinetics of prophylactic cefazolin in parturients undergoing cesarean delivery. Antimicrob Agents Chemother. 2014 Jun;58(6):3504-13. 61
[18] McDonald M, Grabsch E, Marshall C, Forbes A. Single- versus multiple-dose antimicrobial prophylaxis for major surgery: a systematic review. Aust N Z J Surg. 1998 Jun;68(6):388-96.
[19] ACIP Practice Guidelines - CDC. Morbidity and Mortality Weekly Report, October 12, 2012, Vol 61, No 40.
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm?s_cid=mm6140a4_w
[20] Minutes of the NEMLC meeting of 2 November 2017: ACIP Practice Guidelines - CDC. Morbidity and Mortality Weekly Report, October 12, 2012, Vol 61, No 40.
https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm
[21] SAMF, 2016
[22] Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014 Jul 1; 59(1):144.
[23] ACIP Practice Guidelines - CDC. Morbidity and Mortality Weekly Report, October 12, 2012, Vol 61, No 40.
https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm
[24] Public Health England. 2011. The Green Book. Immunisation of individuals with underlying medical conditions Chapter 7.
https://www.gov.uk/government/publications/immunisation-of-individuals-with-underlying-medical-conditions-the-green-book-chapter-7

1 year and 65 years of age[25]), is limited to immunogenicity studies[26] [27]. No available RCTs with good quality patient-outcome data could be sourced in the published literature. PPS23 has been the standard of care for a number of years and no randomised controlled trials are likely.
The possible benefits of this approach are based on immunological differences between the two vaccines. PCV13 produces greater immunoglobulin levels and opsonization activity. PCV13 also induces immunological memory and provides mucosal immunity with resultant decrease carriage. All of which may provide greater protection against the included serotypes (including 6A and which is not covered by PPS23) than PPS23. However, PPS23 is still required to extend the serotype spectrum.

Cost: The addition of an extra dose of PCV13 vaccine would cost an additional R 227.04[28] per patient and an additional patient visit would be required.

Despite the additional costs incurred for an extra dose of PCV13, the latter is recommended in most guidelines probably based on biologically plausible benefit for a disease/procedure with high mortality[29]. However, it should be acknowledged that evidence is limited to immunogenicity studies with a paucity of good quality patient outcome data. PPS23 has been the standard of care for a number of years[30].

Recommendation: The NEMLC recommended that an additional dose of PCV13 be added to the PPS23 regimen for patients undergoing elective splenectomy; as this is a small group of patients and the recommendation is aligned with international guidelines.
Level of Evidence: III Guidelines

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

[25] Minutes of the NEMLC meeting of 2 November 2017: NEMLC ratified this recommendation aligned with ACIP Practice Guidelines - CDC. Morbidity and Mortality Weekly Report, October 12, 2012, Vol 61, No 40.
[26] Forstner C, Plefka S, Tobudic S, Winkler HM, Burgmann K, Burgmann H. Effectiveness and immunogenicity of pneumococcal vaccination in splenectomized and functionally asplenic patients. Vaccine 2012 Aug 10; 30(37):5449-52; PMID:22749594; http://dx.doi.org/10.1016/j.vaccine.2012.06.048
[27] Clutterbuck EA, Lazarus R, Yu LM, Bowman J, Bateman EA, Diggle L, Angus B, Peto TE, Beverley PC, Mant D, et al. Pneumococcal conjugate and plain polysaccharide vaccines have divergent effects on antigen-specific B cells. J Infect Dis 2012 May 1; 205(9):1408-16; PMID:22457293; http://dx.doi.org/10.1093/infdis/jis212
[28] Contract circular PPVAC-2013
[29] Waghorn DJ. Overwhelming infection in asplenic patients: current best practice preventive measures are not being followed. J Clin Pathol 2001; 54:214-8; PMID:11253134; http://dx.doi.org/10.1136/ jcp.54.3.214
[30] Bonanni P, Grazzini M, Niccolai G, Paolini D, Varone O, Bartoloni A, Bartalesi F, Santini MG, Baretti S, Bonito C, Zini P, Mechi MT, Niccolini F, Magistri L, Pulci MB, Boccalini S, Bechini A. Recommended vaccinations for asplenic and hyposplenic adult patients. Hum Vaccin Immunother. 2017 Feb;13(2):359-368. http://dx.doi:10.1080/21645515.2017.1264797