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Department:
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SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 17: EAR, NOSE AND THROAT CONDITIONS
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 ENT chapter.

SECTION	MEDICINE	ADDED/DELETED/AMENDED
17.2 Rhinitis, allergic, persistent		
-Intranasal corticosteroids (general population)	Corticosteroids, nasal spray	Retained as a therapeutic class
	Fluticasone aqueous nasal spray	Added as example of class (listed in the STG)
	Beclomethasone aqueous nasal spray	Deleted as example of class in the STG (added to therapeutic interchange database)
	Budesonide aqueous nasal spray	Added as therapeutic alternative
	Mometasone aqueous nasal spray	Added as therapeutic alternative
	Triamcinolone aqueous nasal spray	Added as therapeutic alternative
- Patients on protease inhibitors (> 6 years of age)	Beclomethasone, topical nasal solution	Added
- Persistent symptoms	Non-sedating anti-histamines	Recommended as a therapeutic class
	Cetirizine, oral	Amended as an example of therapeutic class (listed in STG)
	Fexofenadine, oral	Added as a therapeutic alternative
- Nasal blockage	Topical nasal decongestants	Caution added
17.3 Sinusitis, bacterial, complicated	Paracetamol, oral	Added
17.4 Otitis media, acute (AOM)		
- In previously untreated patients	Amoxicillin, oral	Dosing amended
- For patients with upper respiratory tract congestion (for 10 days)	Non-sedating anti-histamines	Recommended as a therapeutic class
	Cetirizine, oral	Amended as an example of therapeutic class (listed in STG)
	Fexofenadine, oral	Added as a therapeutic alternative
- Pain	NSAIDs, oral	Deleted
	Paracetamol, oral	Added
- For patients with upper respiratory tract congestion (for 10 days)	Non-sedating anti-histamines	Recommended as a therapeutic class
	Cetirizine, oral	Amended as an example of therapeutic class (listed in STG)
	Fexofenadine, oral	Added as a therapeutic alternative
17.5 Otitis media, chronic, suppurative	Acetic acid 2% in alcohol	Retained
	Ciprofloxacin, topical	Added
	Ciprofloxacin, oral	Deleted
	Paracetamol, oral	Added
17.7.1 Otitis externa, necrotising	Ciprofloxacin, topical	Not added
	Betamethasone/clioquinol/tolnaftate/gentamicin, topical	Not added
	Ciprofloxacin, oral (750 mg 12 hourly)	Retained
17.8 Abscess, Peritonsillar	Benzylpenicillin, IV	Deleted
	Metronidazole, IV	Deleted
	Amoxicillin/clavulanate, IV	Added
- De-escalation	Amoxicillin/clavulanate, oral	Retained
17.9 Vertigo, acute	Cinnarizine, oral	Not added
	Promethazine, oral	Retained

17.2 RHINITIS, ALLERGIC, PERSISTENT

Intranasal corticosteroids:

Corticosteroids, nasal spray: *retained as a therapeutic class*
Fluticasone aqueous nasal spray: *added as example of class (listed in the STG)*
Beclomethasone aqueous nasal spray: *deleted as example of class in the STG (added to therapeutic interchange database)*
Budesonide aqueous nasal spray: *added as therapeutic alternative*
Mometasone aqueous nasal spray: *added as therapeutic alternative*
Triamcinolone aqueous nasal spray: *added as therapeutic alternative*

Cochrane[1] reviewers concluded that there is currently "*no evidence that one type of intranasal steroid is more effective than another in patients with chronic rhinosinusitis, nor that higher doses are better than lower, nor that the effectiveness of a spray differs from an aerosol";* and there were "*no studies that compared nasal drops with spray*". There is "*moderate quality evidence of an increased risk of epistaxis (nosebleed) as an adverse effect of treatment when higher doses were used*".
The following table lists comparative doses for the various agents (derived from SAMF, 2016 and MCC registered package inserts):

Corticosteroid	Dose	Contract circular price (daily dose)*
Beclomethasone diproprionate (50mcg/spray)	100mcg into each nostril twice daily	R 0.57
Budesonide (100mcg/spray)	200mcg into each nostril daily	n/a
Fluticasone propionate (50mcg/spray)	100mcg into each nostril daily	R 0.34
Mometasone furoate (50mcg/spray)	100mcg into each nostril daily	n/a
Triamcinolone acetonide (55mcg/spray)	110mcg into each nostril daily	n/a

*Contract circular HP07-2017DAI, accessed 11 December 2019: Beclomethasone dipropionate 50 mcg, 150 doses = R 21.41; Fluticasone propionate 50mcg, 120 doses = R 20.622 (weighted average price)

Fluticasone aqueous nasal spray is currently cheaper than beclomethasone aqueous nasal spray when approximate therapeutic comparable doses are compared (see table above); and is thus listed as the example of class in the STG.
Level of Evidence: I Systematic review, Expert opinion

Patients on protease inhibitors (> 6 years of age):

Beclomethasone, topical nasal solution: *added*
Beclomethasone aqueous nasal spray is the recommended nasal corticosteroid for patients on protease inhibitors.
Rationale: Case reports of drug-drug interaction of protease inhibitors with inhaled corticosteroids (budesonide, fluticasone, mometasone and ciclosenide), except beclomethasone resulting in iatrogenic Cushing's syndrome and adrenal insufficiency.
Level of Evidence: III Case reports[2] [3] [4] [5]

The evidence for the drug-drug interaction of corticosteroids with protease inhibitors was initially reviewed by the PHC Expert Review Committee (ERC). However, at the NEMLC meeting of the 12 April 2018[6], the NEMLC recommended that patients on protease inhibitors requiring nasal corticosteroids rather be referred to higher level of care for further management.

[1] Chong LY, Head K, Hopkins C, Philpott C, Burton MJ, Schilder AG. Different types of intranasal steroids for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016 Apr 26;4:CD011993. https://www.ncbi.nlm.nih.gov/pubmed/27115215
[2] Foisy MM, Yakiwchuk EM, Chiu I, Singh AE. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Med. 2008 Jul;9(6):389-96. https://www.ncbi.nlm.nih.gov/pubmed/18459946
[3] University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/
[4] Frankel JK, Packer CD. Cushing's syndrome due to antiretroviral-budesonide interaction. Ann Pharmacother. 2011 Jun;45(6):823-4. https://www.ncbi.nlm.nih.gov/pubmed/21558486
[5] Yoganathan K, David L, Williams C, Jones K. Cushing's syndrome with adrenal suppression induced by inhaled budesonide due to a ritonavir drug interaction in a woman with HIV infection. Int J STD AIDS. 2012 Jul;23(7):520-1. https://www.ncbi.nlm.nih.gov/pubmed/22844010
[6] Minutes of the NECML meeting of 12 April 2018

Extract from the minutes of the NEMLC meeting of the 12 April 2018 (PHC referral):

- ***19.1 ALLERGIC RHINITIS:*** *Previously the NEMLC (29 June 2017) recommended that the PHC Committee critically appraise the evidence for a drug-drug interaction between inhaled corticosteroids and protease inhibitors. The PHC Committee recommended that beclomethasone inhaled corticosteroid be recommended in patients on protease inhibitors as case reports of drug-drug interaction of protease inhibitors with most inhaled corticosteroids (budesonide, fluticasone, mometasone and ciclosenide), except beclomethasone were reported in the literature, resulting in iatrogenic Cushing's syndrome and adrenal insufficiency. However, the NEMLC deliberated the need to have both beclomethasone and another corticosteroid metered dose inhaler (MDI) (fluticasone/budesonide, etc.) at every primary level clinic. Stocking beclomethasone inhalers for a small patient cohort was not considered pragmatic.*

NEMLC Recommendation: *The NEMLC recommended that patients on protease inhibitors requiring nasal corticosteroids be referred to higher level of care for management.*

See the consolidated PHC NEMLC report for the PHC ENT chapter (2016-2018 review cycle)

PHC_EarNoseThroat_NEMLC report_2016

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/285-phc

Symptoms persist despite adequate trial of topical corticosteroids administered with correct technique

Non-sedating antihistamines, oral: *recommended as therapeutic class*

Cetirizine, oral: *retained as example of class (listed in STG)*

Fexofenadine, oral: *added as therapeutic alternative*

Refer to the medicine review, non-sedating antihistamines for persistent allergic rhinitis (November 2017):

Non-sedating Antihistamines for A

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

Recommendation: Fexofenadine and cetirizine appear to be statistically and clinically similar in regards to SAR symptom reduction. Fexofenadine has less drowsiness, but this is not statistically significant. Based on the medicine review, recommendations were guided by availability of agents based on price.

Prices

Medicine	Source	Price
Cetirizine 10 mg tablets (28)	Contract circular RT289-2019, accessed 11/12/2019	R 3.08
Fexofenadine 120 mg tablets (30)	SEP database (60% of cheapest generic)[7]	R 71.98

Level of Evidence: I RCT, Expert opinion

For relief of nasal blockage

Topical nasal decongestants: *caution added*

The following caution was added, aligned with SAMF, 2016:

Note: Rebound nasal congestion occurs with prolonged use (>5 days) of topical nasal decongestants.

Level of Evidence: III Guidelines

[7] SEP database, accessed 11 December 2019. Available at: https://mpr.code4sa.org/

17.3 SINUSITIS, BACTERIAL, COMPLICATED

Paracetamol, oral: *added*
Paracetamol, oral was added for pain management in this clinical setting.
Level of Evidence: III Expert opinion

17.4 OTITIS MEDIA, ACUTE (AOM)

In previously untreated patients:
Amoxicillin, oral: *dosing amended*
There is limited available RCT data for amoxicillin to treat AOM in adults. However, based on the most recent local guideline recommendations[8], the dosing of amoxicillin was amended from "*500 mg 8 hourly*" to "*1 g 8 hourly*".
Level of Evidence: III Guidelines

Patients with upper respiratory tract congestion, secondary to allergy:
Non-sedating antihistamines, oral: *recommended as therapeutic class*
Cetirizine, oral: *retained as example of class (listed in STG)*
Fexofenadine, oral: *added as therapeutic alternative*

Refer to the evidence summary, above in section 17.2: Rhinitis, allergic, persistent.
There is no clear RCT evidence[9] that antihistamines have any benefit in AOM, especially in children; and the side effect profiles supersedes any clinical benefit. No available published RCTs could be sourced for adults. The indication for antihistamines was strengthened for use only when there is upper respiratory tract congestion.
Recommendation: The indication for antihistamine use in AOM was amended from, "For *patients with upper respiratory tract congestion*", to "*For patients with upper respiratory tract congestion, secondary to allergy*".
Rationale: Cochrane review indicated that antihistamines do not have clinical benefit and that the side effect profiles supersede any clinical benefit in management of acute otitis media.
Level of Evidence: II Systematic review extrapolated from children

NEMLC recommended a further evidence search for oral antihistamine versus nasal corticosteroid in this clinical setting i.e.: patients with acute otitis media *and upper respiratory tract congestion, secondary to allergy*. However, no available RCT evidence could be sourced in the published literature for nasal corticosteroids in this clinical setting. There is no clear RCT evidence that antihistamines have any benefit in AOM, especially in children; and the side effect profiles supersedes any clinical benefit. No available published RCTs could be sourced for adults. The indication for antihistamines was strengthened for use *only* when there is upper respiratory tract congestion, as shown in the Cochrane review[10].

Pain
NSAIDs, oral: *deleted*
Paracetamol, oral: *added*
NEMLC recommended that the Adult ERC review the evidence for changing pain management treatment from NSAIDs to paracetamol, despite this being a PHC STG and EML recommendation. However, the PHC ERC had recommended that paracetamol be retained and ibuprofen not be added, which was accepted by the NEMLC; and the Adult Hospital Level recommendation was aligned, accordingly (although the systematic review reviewed the evidence for pain relief in acute otitis media in children).

[8] Brink AJ, Cotton M, Feldman C, Finlayson H, Friedman R, Green R, Hendson W, Hockman M, Maartens G, Madhi S, Reubenson G, Silverbauer E, Zietsman I. Updated recommendations for the management of upper respiratory tract infections in South Africa. S Afr Med J. 2015 Apr 6;105(5):344-52. https://www.ncbi.nlm.nih.gov/pubmed/26242659
[9] Griffin G, Flynn CA. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. Cochrane Database Syst Rev. 2011 Sep 7;(9):CD003423. https://www.ncbi.nlm.nih.gov/pubmed/21901683
[10] Griffin G, Flynn CA. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. Cochrane Database Syst Rev. 2011 Sep 7;(9):CD003423. https://www.ncbi.nlm.nih.gov/pubmed/21901683

Authors of a Cochrane review[11] concluded that there is limited evidence for paracetamol or ibuprofen, alone or combined, in relieving pain in children with acute otitis media and that both paracetamol or ibuprofen are more effective than placebo in relieving short-term pain. However, NSAIDs should essentially not be used in viral infections.
The Adult Hospital Level Guidelines were aligned with the PHC and Paediatric Hospital level STGs, for consistency with a cross reference to the pain chapter, if additional pain control is required.
Level of Evidence: III Guidelines

17.5 OTITIS MEDIA, CHRONIC, SUPPURATIVE

Acetic acid 2% in alcohol: *retained*
Ciprofloxacin, oral: *deleted*
Ciprofloxacin, topical: *added*

Background: During the review of the 2012 Adult Hospital Level Standard Treatment Guidelines a Cochrane Review[12] on the benefits of topical over oral treatment for chronic otitis media was reviewed - three underpowered industry-sponsored trials showed a benefit of topical over oral ciprofloxacin. However, the evidence reviewed was not sufficiently robust to formulate a recommendation to support topical ciprofloxacin.
The current Adult Hospital Level Expert Review Committee upheld the previous recommendation. Only one additional recent RCT[13] (n=100) published in 2018 and not sponsored by industry, showed that topical ciprofloxacin drops was as effective as combined oral and topical ciprofloxacin; and oral ciprofloxacin did not provide any additional benefit, merely added to the cost of treatment.
However, in light of recent concerns with the use of fluoroquinolones the use of topical ciprofloxacin is probably recommended. Safety data is limited.

Recommendation: The Adult Hospital Level Committee recommended ciprofloxacin, topical for CSOM instead of oral formulation.
Rationale: The Cochrane review[14] suggests that topical ciprofloxacin drops were as effective as systemic ciprofloxacin oral treatment for for the management of chronic otitis media in adults (though evidence was from three small industry-sponsored RCTs). However, with the recent safety concerns with systemic fluoroquinolones[15], ciprofloxacin topical is preferred.
Level of Evidence: I Systematic review, RCT, Expert opinion

Pain
Paracetamol, oral: *added*
This was aligned with the PHC and Paediatric Hospital level STGs, for consistency with a cross reference to the pain chapter, if additional pain control is required.
Level of Evidence: III Guidelines

17.7.1 OTITIS EXTERNA, NECROTISING

Ciprofloxacin, topical: *not added*

[11] Sjoukes A, Venekamp RP, van de Pol AC, Hay AD, Little P, Schilder AGM, Damoiseaux RAMJ. Paracetamol (acetaminophen) or nonsteroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitismedia in children. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD011534.
[12] Macfadyen CA, Acuin JM, Gamble C. Systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations. *Cochrane Database Syst Rev.* 2006 Jan 25;(1):CD005608.
[13] Onali MA, Bareeqa SB, Zia S, Ahmed SI, Owais A, Ahmad AN. Efficacy of Empirical Therapy With Combined Ciprofloxacin Versus Topical Drops Alone in Patients With Tubotympanic Chronic Suppurative Otitis Media: A Randomized Double-Blind Controlled Trial. Clin Med Insights Ear Nose Throat. 2018 Jan 11;11:1179550617751907. https://www.ncbi.nlm.nih.gov/pubmed/29348711
[14] Macfadyen CA, Acuin JM, Gamble C. Systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations. *Cochrane Database Syst Rev.* 2006 Jan 25;(1):CD005608.
[15] European Medicines Agency: Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics, 16 Nov 2018. https://www.ema.europa.eu/documents/press-release/disabling-potentially-permanent-side-effects-lead-suspension-restrictions-quinolone-fluoroquinolone_en.pdf

Betamethasone/clioquinol/tolnaftate/gentamicin, topical: *not added*
Ciprofloxacin, oral (750 mg 12 hourly): *retained*

High dose oral ciprofloxacin was considered more appropriate than topical ciprofloxacin for necrotising otitis externa as topical treatment (acetic acid or antibiotic) would probably not influence the outcome.
There is also a paucity of evidence for use of betamethasone/clioquinol/tolnaftate/gentamicin, topical in this clinical setting. Steroids could be considered for cases not responding to antibiotics, but this would probably be managed at tertiary level of care. Guidance is provided in the STG for referral of non-responders.
Level of Evidence: III Expert opinion

17.8 ABSCESS, PERITONSILLAR

Benzylpenicillin, IV: *deleted*
Metronidazole, IV: *deleted*
Amoxicillin/clavulanate, IV: *added*
Empiric parenteral antibiotic therapy updated to provide cover for common pathogen, *Staphylococcus aureus,* and anaerobic bacteria associated with peritonsillar abscess.

De-escalation from parenteral therapy, once patient is apyrexial for 24 hours:
Amoxicillin/clavulanate, IV: *retained*

17.9 VERTIGO, ACUTE

Cinnarizine, oral: *not added*
Promethazine, oral: *retained*
An external comment was received to add cinnarizine, oral to the EML for vertigo. However, no supporting evidence was submitted. The STG currently recommend promethazine, oral and the Committee was of the opinion that this would suffice.
Level of Evidence: III Expert opinion

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.*