health
Department:
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2030 NDP

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 4: DERMATOLOGY
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 dermatology conditions chapter.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/RETAINED
4.1 Acne	Benzoyl peroxide 5%, gel	Deleted (cross referral to PHC STG)
	Tretinoin, topical	Deleted (cross referral to PHC STG)
	Doxycycline, oral	Deleted (cross referral to PHC STG)
	Cyproterone acetate 2 mg plus ethinyl estradiol 35 mcg, oral	Retained
4.2 Cellulitis and erysipelas	Intravenous antibiotics (cefazolin, clindamycin)	Directions for use amended
	Cloxacillin, IV	Deleted
	Cefazolin, IV	Added
4.4 Furuncles and abscesses	Cloxacillin, IV	Deleted
	Cefazolin, IV	Added
4.5 Atopic eczema/ dermatitis: Moderate and severe eczema	Betamethasone 0.1%, topical	Application amended from twice daily to once daily
4.7 Leg ulcers, uncomplicated	Dressings	Not amended
4.11.1 Viral warts/ anogenital warts	Podophyllotoxin 0.5% solution	Added
	Podophyllin 20% in Tinct. Benz. Co., topical	Retained
	Trichloroacetic acid, topical	Not added
	Imiquimod, topical	Not added

GENERAL

An external comment was received, recommending that albinism should be added to the list of high risk initials that should probably not be initiated on hydrochlorothiazide.
Recommendation: The Adult Hospital Level Committee recommended that section 5.18.1: Albinism in the PHC STGs and EML be updated in the upcoming review cycle, with a caution box recommending that individuals at high risk of basal cell and squamous cell carcinomas should probably not be initiated on hydrochlorothiazide.

4.1 ACNE

Benzoyl peroxide 5%, gel: *deleted with cross referral to PHC STGs and EML*
Tretinoin, topical: *deleted with cross referral to PHC STGs and EML*
Doxycycline, oral: *deleted with cross referral to PHC STGs and EML*
Cyproterone acetate 2 mg plus ethinyl estradiol 35 mcg, oral: *retained*
Primary management of acne deleted from the Adult Hospital level STG, with cross referral to PHC STGs and EML, section 5.3: Acne vulgaris.

4.2 CELLULITIS AND ERYSIPELAS

Intravenous antibiotics (cefazolin, clindamycin): *directions for use amended*

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America recommends that "*Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible S. aureus (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients as defined in question 13 (severe nonpurulent), broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections".*[1]

Recommendation: Option of intravenous antibiotics when there is rapid progression of erythema included in the STG.

Rationale: Aligned with guideline recommendations.

Level of Evidence: III Guidelines

Cloxacillin, IV: *deleted*

Cefazolin, IV: *added*

Staph aureus resistance to oxacillin has recently been reported in two Provinces, with 9% MRSA detected in community acquired pneumonia.[2]

NEMLC approved circular: Due to continuous supply challenges with Cloxacillin, IV, NEMLC[3] had approved a circular recommending cefazolin, IV in place of cloxacillin, IV for a number of indications based on the systematic review of cohort studies by Loubet et al[4].

Recommendation: Cloxacillin, IV be replaced with cefazolin, IV (that has cover against MSSA and streptococci).

Rationale: Aligned with Guidelines[5] and retrospective cohort study showed that cloxacillin is comparable to cefazolin with regards to mortality at 90 days in ICU (HR 0.58; 95% CI 0.31 to 1.08)[6].

Level of Evidence: II Retrospective cohort study, Susceptibility study, Guidelines

4.4 FURUNCLES AND ABSCESSES

Cloxacillin, IV: *deleted*

Cefazolin, IV: *added*

(Aligned with section 4.2 Cellulitis and erysipelas for consistency – see above).

4.5 ATOPIC ECZEMA/ DERMATITIS

Moderate and severe eczema

Betamethasone 0.1%, topical: *application amended from twice daily to once daily*

[1] Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. https://www.ncbi.nlm.nih.gov/pubmed/24973422

[2] 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

[3] Minutes of the NEMLC meeting of 2 November 2017.

[4] Loubet P, Burdet C, Vindrios W, Grall N, Wolff M, Yazdanpanah Y, AndremontA, Duval X, Lescure FX. Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible Staphylococcus aureus bacteraemia: a narrative review. ClinMicrobiol Infect. 2017 Jul 8.pii: S1198-743X(17)30358-0.https://www.ncbi.nlm.nih.gov/pubmed/28698037

[5] Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. https://www.ncbi.nlm.nih.gov/pubmed/24973422

[6] Bai AD, Showler A, Burry L, Steinberg M, Ricciuto DR, Fernandes T, Chiu A, Raybardhan S, Science M, Fernando E, Tomlinson G, Bell CM, Morris AM. Comparative effectiveness of cefazolin versus cloxacillin as definitive antibiotic therapy for MSSA bacteraemia: results from a large multicentre cohort study. J Antimicrob Chemother. 2015 May;70(5):1539-46. https://www.ncbi.nlm.nih.gov/pubmed/25614044

Recommendation was amended to align with the NEMLC approved PHC recommendation[7], as indicated below:

PHC NEMLC report for the skin chapter, 12 April 2018:

<u>Betamethasone 0.1%, topical:</u> application amended from twice daily to once daily

Evidence:

- *Authors of a Health Technology Assessment[8] concluded that the available literature suggests that clinical effectiveness of once-daily and more frequent application of potent topical corticosteroids is similar. It was noted that the RCTS reviewed referred mostly to moderate to severe atopic eczema (10 RCTs), whilst patients generally have mild disease. Some statistically significant differences favouring twice-daily treatment were identified; however, these were inconsistent between outcome assessors (physicians versus patients) and outcomes selected for analysis.*
- *Effect sizes:*
    - *Proportion with at least a good response (at least 50% improvement) comparing once daily versus more frequent application:*
        - *i. Potent corticosteroids:*
            - *a. RR 1.03 (95% CI 0.83 to 1.28)*
            - *b. ARR 0.06 (events: 654/802vs 678/785); NNT 18*
        - *ii. Very potent corticosteroids:*
            - *a. RR 0.99 (95% CI 0.89 to 1.10)*
            - *b. ARR 0.01 (events: 99/116 vs 100/116); NNT 100*

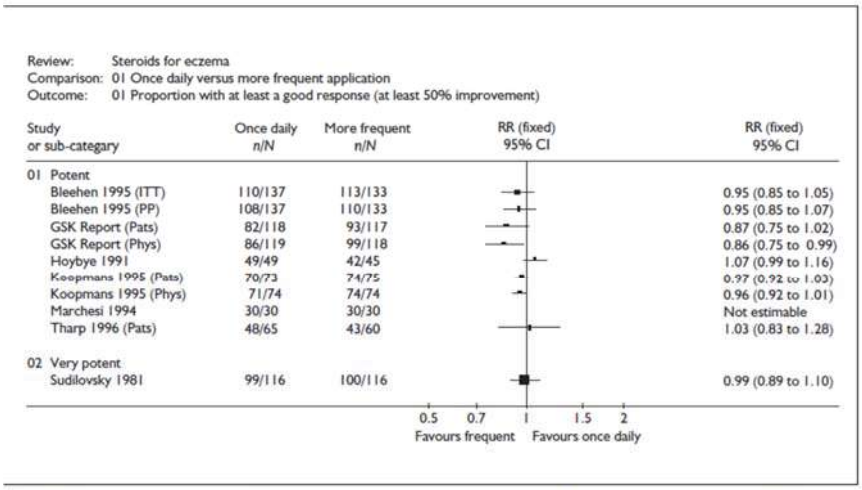

FIGURE 4 Patients with at least a good response at end of treatment: risk ratios. Note: the patients in the studies by Bleehen and colleagues[43], GSK Report[46] and Koopmans and colleagues[44] are included twice in the figure for illustration of different assessments. ITT, intention-to-treat analysis; Pats, patients' assessment; Phys, physicians' assessment; PP, per-protocol analysis.

- *Proportion cleared comparing once daily versus more frequent application:*
    - *i. Potent corticosteroids:*
        - *a. RR 0.88 (95% CI 0.72 to 1.09)*
        - *b. ARR 0.11 (events: 337/723 vs 365/700); NNT 10*

[7] Minutes of the NEMLC meeting of the 12 April 2018.

[8] Green C, Colquitt JL, Kirby J, Davidson P, Payne E. Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation. Health Technol Assess. 2004 Nov;8(47):iii,iv, 1-120. https://www.ncbi.nlm.nih.gov/pubmed/15527669

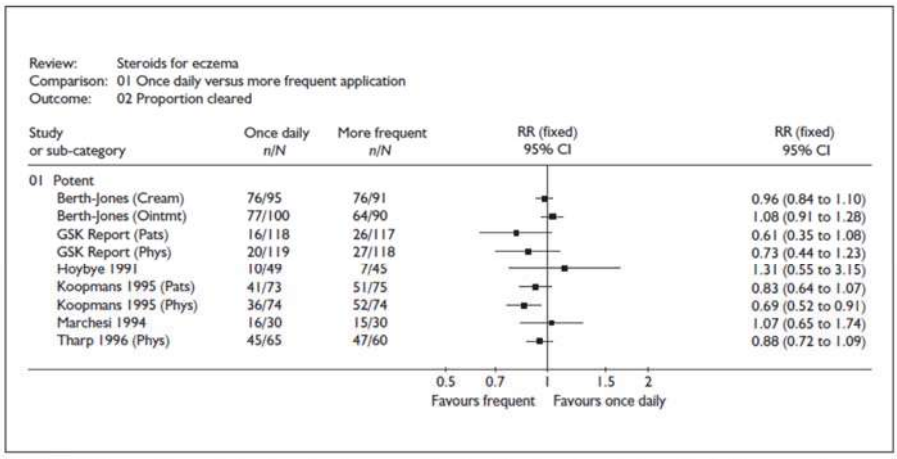

FIGURE 5 *Patients with controlled or cleared atopic eczema: risk ratios. Note: the patients in the studies by Koopmans and colleagues[44] and GSK Report[46] are included twice in the figure for illustration of the different assessments. Pats, patients' assessment; Phys, physicians' assessment.*

Note: The patients in the studies by Koopmans et al[9] and GSK Report[10] were included twice in the above figures for illustration of the different assessments (i.e. ITT, per protocol analysis. Patient and physician assessments).

Evidence quality: Systematic review was of good methodological quality (clear research question, various data sources used and appropriate assessment of quality of systematic review RCTs). Steps were taken to minimise risk of bias for study selection, data extraction and quality assessment with disagreements between reviewers resolved through discussion. Publication bias was likewise minimised as unpublished data was included in the review. Although, meta-analysis was considered inappropriate as the studies were very heterogeneous, the above forest plots with risk ratios were presented to describe the most commonly reported outcomes.

PHC Committee recommendation: *Potent topical corticosteroids to be recommended for daily rather than twice daily application.*

Rationale: Available RCT evidence suggests that clinical effectiveness of once-daily and more frequent application of potent topical corticosteroids is similar for the management of moderate to severe eczema.

Level of Evidence: I Health technology assessment

4.7 LEG ULCERS, COMPLICATED

Dressings: *not amended*

An external comment was received from the South African Medical Association advising that the Wound Healing Association of Southern Africa (WHASA) Guidelines, 2016 does not recommend gauze dressings, due to pain on removal.

Limited evidence is available for dressings for management of leg ulcers[11] and the Adult Hospital Level Committee recommends that a health technology assessment of dressings for the management of venous ulcers be done going forward to further inform decision-making.

Pending a HTA, management, as stated in the Adult Hospital Level STGs and EML was considered sufficient for secondary level of care; guidance provided for clean uninfected leg ulcer wounds describes frequent dressing with dressings moistened with sodium chloride 0.9%.

Level of Evidence: III Expert opinion

[9] Koopmans B, Lasthein AB, Mork NJ, Austad J, Suhonen RE. Multicentre randomized double-blind study of Locoid Lipocream fatty cream twice daily versus Locoid Lipocream once daily and Locobase once daily. J Dermatol Treat 1995;6:103–6.

[10] GSK. A four week multicentre, double blind study to compare safety and efficacy with an OD and BD administration of fluticasone propionate 0.005% ointment in the treatment of atopic eczema. Report 135L, Protocol No. GL/FLT/002. 1995.

[11] Norman G, Westby MJ, Rithalia AD, Stubbs N, Soares MO, Dumville JC. Dressings and topical agents for treating venous leg ulcers. Cochrane Database Syst Rev. 2018 Jun 15;6:CD012583. https://www.ncbi.nlm.nih.gov/pubmed/29906322

4.11.1 VIRAL WARTS/ANOGENITAL WARTS

Anogenital warts
Podophyllotoxin 0.5% solution: *added*
Podophyllin 20% in Tinct. Benz. Co., topical: *retained*
Trichloroacetic acid, topical: *not added*
Imiquimod, topical: *not added*

Refer to the medicine review: Topical treatment of anogenital warts, May 2018, and supporting costing analysis (appendix II).

Ano-genital warts_Adults_Reviev

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

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends podophyllotoxin 0.5% for clearance of ano-genital warts. However, due to the limited availability of this product, the current recommendation, podophyllin 20% in compound benzoin tincture BP be retained as an alternate intervention.
Rationale: Limited evidence of efficacy suggesting that podophyllotoxin 0.5% is the most effective medicinal intervention for clearing ano-genital warts. However, as supply may be limited, the current recommendation, podophyllin 20% in compound benzoin tincture BP, be retained in the national EML as an extemporaneous preparation.
Level of Evidence: II Health Technology Assesment of low quality evidence, Expert opinion

NEMLC meeting of 26 September 2019:
NEMLC accepted the proposals recommended by the Adult Hospital Level Committee, and further recommended that:

- Health technology assessment (HTA) of dressings for the management of venous ulcers be done going forward to further inform decision-making. Review of evidence to include systematic reviews and network meta-analyses (topic to be added to the HTA prioritisation list).
- A circular be disseminated advising that podophyllotoxin and podophyllum 20-25% in Benzoin compound tincture BP, are superior agents for clearance of ano-genital warts.

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