South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level Medication Review Process
Component: Skin Conditions/Dermatology

EVIDENCE SUMMARY

Title: Evidence summary of the use of cephalexin for *S Aureus* skin infections

Date: 8 September 2022

Reviewers: Milli Reddy, Halima Dawood, Zahiera Adam

Affiliation and declaration of interests: MR (Right to Care), HD (Grey's Hospital, Caprisa, University of KwaZulu-Natal, Combined Primary Healthcare/Adult Hospital Level Committee, 2021-2023 & National Essential Medicines List Committee, 2021-2023) & ZA (Right to Care) have no interests to declare pertaining to cephalexin.

Background:
At a recent National Essential Medicines List Committee (NEMLC) meeting (August 2022), the inclusion of cephalexin for Staphylococcus Aureus skin infections was deliberated as an external comment was received to replace flucloxacillin/cephalexin with amoxicillin/clindamycin for the management of impetigo and cellulitis, without supporting evidence.

It is noted that during the 2013 review cycle a request was made to replace cloxacillin with amoxicillin. However, cloxacillin was retained. Cloxacillin supply constraints have been experienced by the Department of Health. Macrolides are included in the Standard Treatment Guidelines (STG) as an alternative for severe penicillin allergy.

A summary of the evidence used in reaching the decision to retain cephalexin on the STG was requested by NEMLC. The evidence includes two Cochrane reviews (2010 & 2012)[i],[ii] and Guidelines from the Infectious Diseases Society of America[iii].

In September 2022, an additional search brought up a protocol of a study that is still underway entitled antibiotic therapy for skin and soft tissue infections: a protocol for a systematic review and network meta-analysis (biomedcentral.com)[iv]. Remaining, studies date back to the 1990's and early 2000's. Therefore, the two Cochrane Reviews[i,ii] and IDSA guideline[iii] were reviewed and summarised here.

Meta-Analysis and Systematic Review of Interventions for cellulitis and erysipelas[i]

A Cochrane review included 25 studies (n=2488) published until May 2010 that included adults or children diagnosed with cellulitis. Treatment regimens included antibiotics or antibiotics with anti-inflammatory agents, or physical treatment (such as topical heat, cold, vibration, or elevation). The primary outcomes included symptoms rated by participant or medical practitioner, e.g., duration and intensity of fever, pain, redness of the affected area, swelling of the skin surface and subcutaneous tissue, blister formation, or proportion symptom-free ('cure'), at a time specified by the study authors; proportion with severe complications (such as severe sepsis, multi-organ failure, death) and quality of life scores (including generic and disease-specific items and return to normal activity). Data was screened and independently extracted by two authors. For studies where similar types of interventions were compared and the same primary outcome measures were used, a meta-analysis was conducted.

The age of participants from the included trials ranged from 16 to 90 years old. Of the 25 studies included 17 studies included skin and skin structure infections (such as abscess, impetigo, folliculitis (inflammation of hair follicles), furunculosis (boils), and wound infection). Cellulitis was included as a subgroup. There were eight studies included

where cellulitis or erysipelas was the main inclusion criteria. Three trials compared a cephalosporin with penicillin, six trials compared different cephalosporins and one trial compared a macrolide against a first-generation cephalosporin.

Results:

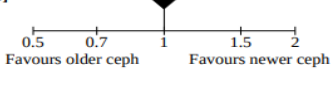
Penicillin versus a cephalosporin: None of the three studies that compared penicillin to a cephalosporin included cephalexin in the comparison. In two studies IV ampicillin/sulbactam was compared with IV cefazolin for the treatment of cellulitis. In the third study IV cefuroxime was compared with IV flucloxacillin. After accounting for heterogeneity, the two studies that reviewed the 1st generation cephalosporins showed no strong evidence of an effect (RR 1.17, 0.91 to 1.50). Similarly, the evidence from the one study using a third-generation cephalosporin also showed no strong effect (RR 0.7, 95% CI 0.48 to 1.00).

Cephalosporin versus cephalosporin

Symptoms rated by participant or medical practitioner (Cure at the end of treatment): Six trials (n=538) compared one cephalosporin with another. Four of these six trials included cephalexin in the comparison. In the meta-analysis comparisons were labelled as new vs old cephalosporin. Overall, no significant differences in treatment effect were noted between the cephalosporins (RR 1.00, 95% CI 0.94 to 1.06).

Analysis 3.1. Comparison 3: Newer vs older generation cephalosporin, Outcome 1: Symptom-free/reduced at the end of treatment

Study or Subgroup	Newer cephalosporin Events	Total	Older cephalosporin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 2nd vs 1st generation						
Iannini 1985	31	35	9	10	6.5%	0.98 [0.78 , 1.25]
Subtotal (95% CI)		**35**		**10**	**6.5%**	**0.98 [0.78 , 1.25]**
Total events:	31		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
3.1.2 3rd vs 1st generation						
Bucko 2002 part 2	50	56	55	66	18.7%	1.07 [0.93 , 1.23]
Grayson 2002	51	59	51	59	18.2%	1.00 [0.87 , 1.15]
Tack 1998	13	17	14	17	3.2%	0.93 [0.66 , 1.31]
Subtotal (95% CI)		**132**		**142**	**40.0%**	**1.03 [0.93 , 1.13]**
Total events:	114		120			
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
3.1.3 3rd vs 2nd generation						
Bucko 2002 part 1	54	66	69	79	18.6%	0.94 [0.81 , 1.08]
Subtotal (95% CI)		**66**		**79**	**18.6%**	**0.94 [0.81 , 1.08]**
Total events:	54		69			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.37)						
3.1.4 4th vs 3rd generation						
Schwartz 1996	49	51	22	23	34.8%	1.00 [0.91 , 1.11]
Subtotal (95% CI)		**51**		**23**	**34.8%**	**1.00 [0.91 , 1.11]**
Total events:	49		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
Total (95% CI)		**284**		**254**	**100.0%**	**1.00 [0.94 , 1.06]**
Total events:	248		220			
Heterogeneity: Tau² = 0.00; Chi² = 1.97, df = 5 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.97)						
Test for subgroup differences: Chi² = 1.13, df = 3 (P = 0.77), I² = 0%						



Miscellaneous (Other) antibiotics: One study which provided an analysis for a cellulitis subgroup showed failure rates of 1/24 (4%) for azithromycin vs 1/23 for cephalexin (4%). In this study oral azithromycin was administered as 1 x 500 mg on day 1 and 250 mg once a day on days 2 to 5. Oral cephalexin was dosed 500 mg 2 times a day for 10 days.

Refer to Appendix 1A for AMSTAR review.

Interventions for impetigo (Review)[ii]

Initially 57 trials were included in the review. Following the update of the review, 1 trial was excluded and 12 new trials added. Therefore, the updated review included 68 trials (n=5578), reporting on 50 different treatments, including placebo.

Participants included were diagnosed with impetigo or impetigo contagiosa (preferably confirmed by bacterial culture). Treatments included topical or systemic (oral, intramuscular, or intravenous) antibiotics, disinfectants, or any other intervention for impetigo, such as 'awaiting natural response'. Studies that compared different dosages of the same medicine were excluded. Primary outcomes included (1) clearance of crusts, blisters, and redness (i.e., cure as assessed by the investigator), and (2) relief of symptoms such as pain, itching, and soreness as assessed by the participant in the trial.

Topical antibiotics vs oral (systemic) antibiotics (overall n=16 studies, 17 comparisons; n=1 study relevant to cephalexin)

No significant differences were noted between mupirocin and dicloxacillin (n=1 study), cephalexin (n=1 study), or ampicillin (n=1 study). Bacitracin was significantly worse than oral cephalexin in this one small study[v] (n=26 participants), which consisted of three arms.

In this study, cephalexin was reviewed at a dose of 50 mg/kg/day orally in three divided doses (maximum 500mg per dose) plus 30 g of a placebo topical ointment (petrolatum plus glycerin) to be applied to affected areas three times daily in 10 patients, mupirocin ointment 2%, 3 times a day plus an oral liquid placebo matched to oral cephalexin to be given in a dosage comparable with that of cephalexin in 7 patients and bacitracin ointment 500 units/g, three times a day plus an oral liquid placebo matched to oral cephalexin to be given in a dosage comparable with that of cephalexin in three divided daily doses in 9 patients.

S. aureus was cultured from all 22 of 26 patients who had cultures performed of their lesions.

An improvement was noted in 1/10 (1%) participant in the cephalexin group vs 1/7 (14%) in the mupirocin group vs none (n=9 participants) in the bacitracin group. Nine of 10 participants (90%) on cephalexin were cured vs 6/7 (86%) in the mupirocin group vs 3/9 (33%) in the bacitracin group. No treatment failures (0%) were noted for cephalexin and mupirocin groups. However, 6/9 (67%) participants were noted as failing in the bacitracin group.

Comparison of the three treatment groups (Taken from Bass, 1997[v])

Treatment	Initial Lesion(s) Size (cm^2)	Duration of Lesions (Days)	Type of Lesion(s)	Culture Results	Outcome Failure/Improved/ Cured
Cephalexin	6.9 ± 1.8*	7.5 ± 1.8	HC 9, B 1	SA 9	0/1/9
Mupirocin	8.0 ± 3.8	6.1 ± 3.0	HC 4, HC + B1, B1, P1	SA 3, SA + GABHS 2	0/1/6
Bacitracin	4.4 ± 0.9	7.2 ± 1.6	HC 5, HC + B 1, P + B 1, B 2	SA 7, SA + GABHS 1	6/0/3
	6.3 ± 1.3	7.0 ± 1.2	Totals HC 18, HC + B 2, P + B 1, B 4, P 1	Totals SA 19, SA + GABHS 3	Totals 6/2/18

*Mean ± SE.
HC, honey-crusted; NA, not available; GABHS, group A beta-hemolytic streptococci; SA, *Staphylococcus aureus*; B, bullous; S, sensitive; P, pustular; R, resistent.

THE PEDIATRIC INFECTIOUS DISEASE JOURNAL

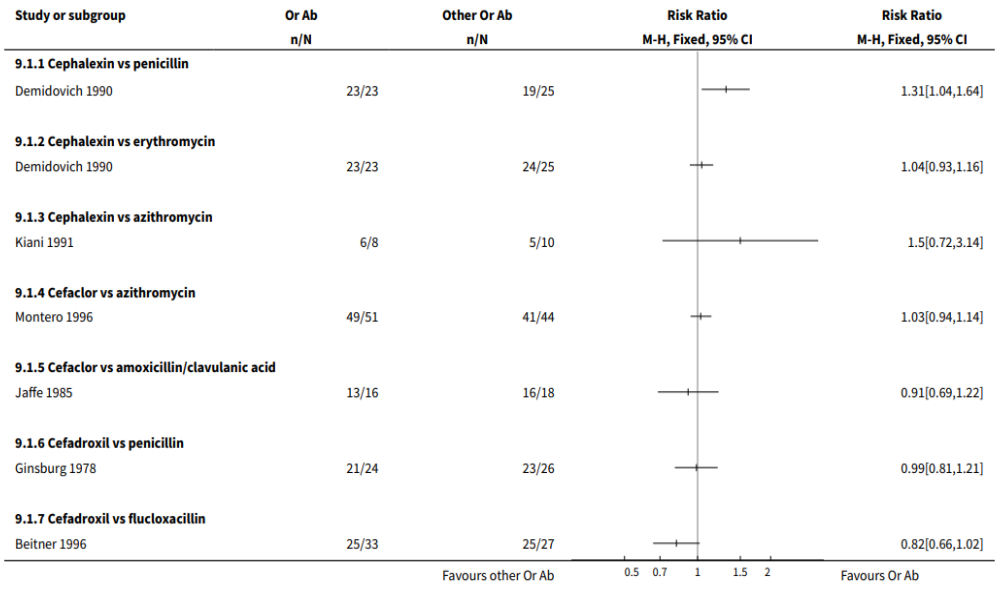
Adverse effects were not reported in the study.

Oral antibiotic vs another oral antibiotic: cephalosporin vs another antibiotic (n=6 studies)

Only one comparison, cephalexin versus penicillin, showed a significant difference in the treatment of non-bullous impetigo (RR 1.31, 95% CI 1.04 to 1.64), favouring cephalexin. Treatment failure occurred in 6/25 (24%) treated with penicillin, 1/25 (4%) treated with erythromycin, and 0/23 (0%) treated with cephalexin. Results showed that *S aureus* was the most common cause of impetigo in this paediatric study population and cephalexin was the most effective treatment. Additionally, erythromycin estolate was nearly equally effective as cephalexin but penicillin was considered

inadequate for treatment of non-bullous impetigo.[vi] There were concerns around randomization, blinding and selective reporting on outcome data and other biases in this study.

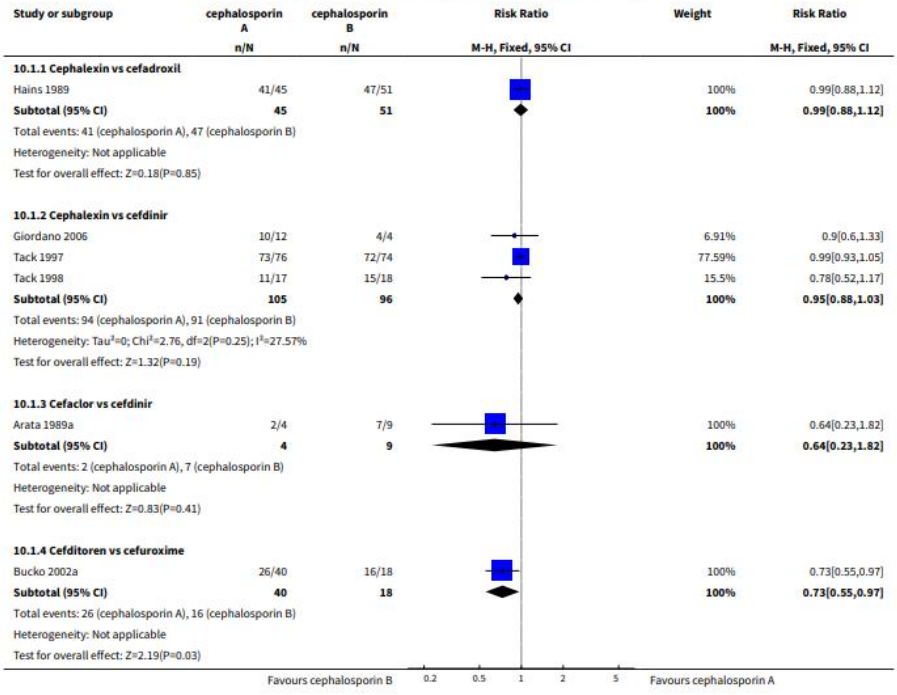
Analysis 9.1. Comparison 9 Non-bullous impetigo: oral (Or) antibiotic (Ab) (cephalosporin) vs another oral (Or) antibiotic (Ab), Outcome 1 Cure/improvement.



Oral antibiotic vs another oral antibiotic: one cephalosporin vs another cephalosporin (n=7 studies)

No significant differences were noted between cephalexin and cefadroxil, cephalexin vs cefdinir, cefaclor vs cefdinir, or cefditoren vs cefadroxil. The only significant difference for the cephalosporins was noted in the comparison of cefditoren vs cefuroxime, where cefuroxime was more effective (RR 0.73, 99% CI 0.55 to 0.97).

Analysis 10.1. Comparison 10 Non-bullous impetigo: oral (Or) cephalosporin vs other oral (Or) cephalosporin, Outcome 1 Cure/improvement.



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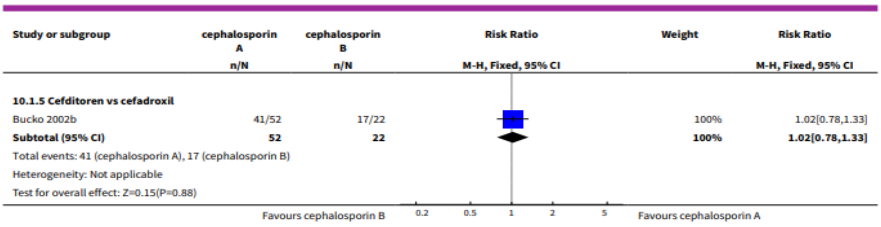

Oral antibiotic versus another oral antibiotic (n=1 study)

No significant difference was noted between cephalexin (50 mg/kg/day in 2 divided doses) and dicloxacillin (15 mg/kg/day in 4 divided doses) (RR 1.17, 95% CI 0.95 to 1.45) in the treatment of bullous impetigo.

Topical antibiotic versus oral antibiotic (n=1 study)

No significant difference was noted for cure or improvement between topical mupirocin (44/77 (57%) cured or improved) vs oral cephalexin (52/82; 63%) (RR 1.11, 95% CI 0.86 to 1.43).

Oral antibiotics

In a very small study (n=10), no significant difference was detected between cephalexin and enoxacin for either cure or improvement in secondary impetigo cases (RR 0.75, 96% CI 0.24 to 2.33).

Refer to Appendix 1B for AMSTAR review.

Guidelines

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America[iii] recommend the following regarding cephalexin and *S Aureus Skin* Infections:

Therapy for Typical Cases of Cellulitis:

- Should include an antibiotic active against streptococci.

- A large percentage of patients can receive oral medications from the start for typical cellulitis, and suitable antibiotics for most patients include penicillin, amoxicillin, amoxicillin-clavulanate, dicloxacillin, cephalexin, or clindamycin.
- In cases of uncomplicated cellulitis, a 5-day course of antimicrobial therapy is as effective as a 10-day course, if clinical improvement has occurred by 5 days
- If coverage for both streptococci and Methicillin-resistant Staphylococcus aureus (MRSA) is desired for oral therapy, options include clindamycin alone or the combination of either sulfamethoxazole and trimethoprim (SMX-TMP) or doxycycline with a β-lactam (e.g., penicillin, cephalexin, or amoxicillin)
- The guidelines mention that a double-blind study showed that a combination of SMX-TMP plus cephalexin was no more efficacious than cephalexin alone in pure cellulitis

Evaluation and Treatment of Impetigo and Ecthyma:

- Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible dicloxacillin or cephalexin is recommended

Impetigo (Staphylococcus and Streptococcus):

- Adults: Cephalexin - 250mg QID po
- Children 25-50mg/kg/d in 3-4 divided doses po

***Methicillin-Sensitive Staphylococcus. Aureus Skin and soft tissue infections* (*MSSA SSTI)*:** (For penicillin allergic patients except those with immediate hypersensitivity reactions. Availability of a suspension and requirement for less frequent dosing)

- Adults: Cephalexin - 500mg QID po
- Children 25-50mg/kg/d in 4 divided doses po

***Streptococcal skin infections*:**

- Adults: Cephalexin 500 mg every 6 h po

***Antibiotics for Treatment of Incisional Surgical Site Infection*:**

- *Surgery of trunk or extremity away from axilla or perineum:* Cephalexin 500 mg every 6 h po

Refer to Appendix 2 for AGREE II Appraisal.

Conclusions

The Cochrane reviews could not definitively recommend one antibiotic treatment over another, and it was unclear if oral antibiotics are superior to topical antibiotics for the management of impetigo. However, penicillin was not as effective as other antibiotics as an intervention for the management of impetigo. Mostly there was no significant difference between cephalexin and other treatments and cephalexin was the most effective treatment (significantly different versus penicillin) in the treatment of non-bullous impetigo. In this case *S aureus* was the most common cause of impetigo in a paediatric population and cephalexin was the most effective treatment. Previously, also due to supply issues, cephalexin was recommended for S aureus skin infections.

Appendix 1 A: Evaluating the methodological quality of the Kilburn et al (2010)[1] systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[2])

LOW QUALITY REVIEW

No.	Criteria	Yes/ Partial Yes/ No	Comment
1	Research questions and inclusion criteria for the review included the components of PICO	No	Comparators were not explicitly explained (grouped with interventions)
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Yes	Report listed deviations from the protocol
3	Review authors explained selection of the study designs for inclusion in the review	Yes	The authors mention that they included studies that allocated participants to groups using randomisation in order to reduce bias.
4*	Review authors used a comprehensive literature search strategy	Partial yes	The authors did not include/consult content experts in the field where relevant
5	Review authors perform study selection in duplicate	Yes	-
6	Review authors perform data extraction in duplicate	Yes	-
7*	Review authors provided a list of excluded studies and justify the exclusions	Yes	-
8	Review authors described the included studies in adequate detail	Partial yes	Comparators included as interventions
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Yes	Risk of bias assessed using Cochrane methods – no graphical representation provided
10	Review authors reported on the sources of funding for the studies included in the review.	No	Only mention that a number of drug-company-sponsored studies excluded participants where the bacteria isolated were not sensitive to study antibiotics
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	Yes	-
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	Yes	The authors mention that they were not able to conduct sensitivity analyses due to the small number of trials available within each category
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes	-
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes	There was heterogeneity in the results
15*	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	No	
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	The authors had no conflicts of interest to disclose

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

- *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

[1] Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. Cochrane Database Syst Rev. 2010 Jun 16;2010(6):CD004299. doi: 10.1002/14651858.CD004299.pub2. PMID: 20556757; PMCID: PMC8693180.

[2] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. https://pubmed.ncbi.nlm.nih.gov/28935701/

Appendix 1 B: Evaluating the methodological quality of the Koning et al (2012)[3] systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[4])

MODERATE QUALITY REVIEW

No.	Criteria	Yes/ Partial Yes/ No	Comment
1	Research questions and inclusion criteria for the review included the components of PICO	No	Comparators were not explicitly explained (grouped with interventions)
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Yes	Report listed deviations from the protocol Inclusion and exclusion were not explicitly stated in the methods but assessed in the results and summary provided in tables
3	Review authors explained selection of the study designs for inclusion in the review	No	The authors mentioned that they included randomized controlled trials but do not provide an explanation
4*	Review authors used a comprehensive literature search strategy	Partial yes	The authors did not apply any language restrictions. Conducted search on 27 July 2010 and published in 2012
5	Review authors perform study selection in duplicate	Yes	-
6	Review authors perform data extraction in duplicate	Yes	-
7*	Review authors provided a list of excluded studies and justify the exclusions	Yes	-
8	Review authors described the included studies in adequate detail	Partial yes	Comparators included as interventions
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Yes	Risk of bias assessed using Cochrane methods
10	Review authors reported on the sources of funding for the studies included in the review.	Yes	
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	No meta-analyses conducted	Did not conduct meta-analyses
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	No meta-analyses conducted	Did not conduct meta-analyses
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes	-
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes	
15*	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	No meta-analyses conducted	
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	Where there was conflict of interest declared, the authors explained how funds from sponsors were used

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

[3] Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, Butler CC, Berger M, van der Wouden JC. Interventions for impetigo. Cochrane Database Syst Rev. 2012 Jan 18;1(1):CD003261. doi: 10.1002/14651858.CD003261.pub3. PMID: 22258953; PMCID: PMC7025440.

[4] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. https://pubmed.ncbi.nlm.nih.gov/28935701/

Appendix 2: AGREE II Score Sheet - Evidence-Based Guideline: Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America[iii]

		Reviewer 1 (1 to 7 – Strongly Disagree to Strongly Agree)	Reviewer 2 (1 to 7 – Strongly Disagree to Strongly Agree)
Domain 1	**Scope and purpose**		
Item 1	The overall objective(s) of the guideline is (are) described	5	6
Item 2	The health question(s) covered by the guideline is (are) specifically described	7	7
Item 3	The population (patients, public, etc) to whom the guideline is meant to apply is specifically described	7	4
Domain 2	**Stakeholder involvement**		
Item 4	The guideline development group includes individuals from all relevant professional groups.	6	6
Item 5	The views and preferences of the target population (patients, public, etc.) have been sought.	1	1
Item 6	The target users of the guideline are clearly defined	2	3
Domain 3	**Rigour of development**		
Item 7	Systematic methods were used to search for evidence	4	3
Item 8	The criteria for selecting the evidence are clearly described	4	1
Item 9	The strengths and limitations of the body of evidence are clearly described	3	1
Item 10	The methods for formulating the recommendations are clearly described	6	5
Item 11	The health benefits, side effects, and risks have been considered in formulating the recommendations	4	1
Item 12	There is an explicit link between the recommendations and the supporting evidence	6	6
Item 13	The guideline has been externally reviewed by experts prior to its publication	4	3
Item 14	A procedure for updating the guideline is provided	7	7
Domain 4	**Clarity of presentation**		
Item 15	The recommendations are specific and unambiguous	6	5

		Reviewer 1 (1 to 7 – Strongly Disagree to Strongly Agree)	Reviewer 2 (1 to 7 – Strongly Disagree to Strongly Agree)
Item 16	The different options for management of the condition or health issue are clearly presented	6	5
Item 17	Key recommendations are easily identifiable	6	6
Domain 5	**Applicability**		
Item 18	The guideline describes facilitators and barriers to its applications	1	1
Item 19	The guideline provides advice and/or tools on how the recommendations can be put into practice	4	3
Item 20	The potential resource implications of applying the recommendations have been considered	1	1
Item 21	The guideline presents monitoring and/or auditing criteria	1	1
Domain 6	**Editorial independence**		
Item 22	The views of the funding body have not influenced the content of the guideline	4	4
Item 23	Competing interests of guideline development group members have been recorded and addressed	6	6
Overall assessment	**Assessment**		
	Rate the overall quality of the guideline	5	4
	I would recommend this guideline for use (yes/with modifications/no	Yes, with Modifications	Yes, with Modifications

Appendix 4: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	The Cochrane reviews could not definitively recommend one antibiotic treatment over another for cellulitis. One comparison, cephalexin versus penicillin, showed a significant difference in the treatment of non-bullous impetigo (RR 1.31, 95% CI 1.04 to 1.64), favouring cephalexin Recommendations are based on one trial
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	Overall, no significant differences in treatment effect were noted between the cephalosporins (RR 1.00, 95% CI 0.94 to 1.06). 6 trials (n=538) – only 4 included cephalexin One comparison, cephalexin versus penicillin, showed a significant difference in the treatment of non-bullous impetigo (RR 1.31, 95% CI 1.04 to 1.64), favouring cephalexin (n=1 trial). No significant differences between: • mupirocin, dicloxacillin, cephalexin & ampicillin (n=1 study) • topical mupirocin vs oral cephalexin • cephalexin and enoxacin • cephalosporins
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Failure rates of 1/23 for cephalexin (4%) – 1 trial Concerns around randomization, blinding and selective reporting on outcome data and other biases in the study that favoured cephalexin over penicillin.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☐ None ☐	Unknown - Most trials did not consider adverse effects.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	Most likely favours intervention – as no significant differences with other oral antibiotics and topical treatments. One comparison showed that cephalexin performed significantly better in the treatment of non-bullous impetigo (*S aureus*) compared to penicillin.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	In March/April 2022 – there were some supply challenges experienced with cephalexin syrup. No supply challenges with cephalexin capsules May 2022 – no supply issues noted for cephalexin suspension or capsules

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td></td><td></td><td>June 22 – supply issues on cephalexin suspension

July 2022 – No serious supply issues noted on suspension or capsules</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive: [ ] Less intensive: [x] Uncertain: [ ]</td><td>Price of medicines/ month
<table><tr><th>Medicine</th><th>Price (ZAR)*</th></tr><tr><td>Cefalexin; 250mg; Capsule; 20 Capsules</td><td>14.95</td></tr><tr><td>Cefalexin; 500mg; Capsule; 20 Capsules</td><td>25.88</td></tr><tr><td>Cefalexin; 125mg/5ml; Suspension; 100 ml</td><td>13.69</td></tr><tr><td>Cefalexin; 250mg/5ml; Suspension; 100 ml</td><td>22.68</td></tr></table>Medicine Procurement Catalogue – September 2022</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor: [ ] Major: [ ] Uncertain: [x]

Is the option acceptable to key stakeholders?
Yes: [x] No: [ ] Uncertain: [ ]</td><td>It is uncertain how people value the option. However, cephalexin is available on tender and is used in the public health sector.</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes: [ ] No: [x] Uncertain: [ ]</td><td></td></tr>
</table>

<table>
<tr><th colspan="6">PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:</th></tr>
<tr><td>Type of recommendation</td><td>We recommend against the option and for the alternative (strong)</td><td>We suggest not to use the option (conditional)</td><td>We suggest using either the option or the alternative (conditional)</td><td>We suggest using the option (conditional)</td><td>We recommend the option (strong)</td></tr>
<tr><td></td><td></td><td></td><td></td><td>X</td><td></td></tr>
<tr><td colspan="6"><u>PHC/AHL Recommendation: (29 September 2022):</u> The committee suggests that cephalexin be used for management of impetigo as a therapeutic alternative to oral flucloxacillin.
Rationale: Limited evidence showing similar efficacy to alternative antibiotics
Level of Evidence: Low
Review indicator: Completion of an updated Cochrane Review</td></tr>
<tr><td colspan="6"><u>NEMLC RECOMMENDATION: 20 OCTOBER 2022</u>
• The committee suggests that cephalexin be used for management of skin and soft tissue infections as a therapeutic alternative to oral flucloxacillin.</td></tr>
<tr><td colspan="6">Monitoring and evaluation considerations</td></tr>
<tr><td colspan="6">Research priorities</td></tr>
</table>

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	8 September 2022	MR, HD, ZA	**Cephalexin be used for management of impetigo as a therapeutic alternative to oral flucloxacillin.** *Rationale:* **Limited evidence showing similar efficacy to alternative antibiotics**

References

[i] Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. Cochrane Database Syst Rev. 2010 Jun 16;2010(6):CD004299. doi: 10.1002/14651858.CD004299.pub2. PMID: 20556757; PMCID: PMC8693180.

[ii] Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, Butler CC, Berger M, van der Wouden JC. Interventions for impetigo. Cochrane Database Syst Rev. 2012 Jan 18;1(1):CD003261. doi: 10.1002/14651858.CD003261.pub3. PMID: 22258953; PMCID: PMC7025440

[iii] Intravenous antibiotics (severe cellulitis and erysipelas): 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.idsociety.org/practice-guideline/skin-and-soft-tissue-infections/

[iv] Bartoszko JJ, Mertz D, Thabane L, Loeb M. Antibiotic therapy for skin and soft tissue infections: a protocol for a systematic review and network meta-analysis. Syst Rev. 2018 Sep 11;7(1):138. doi: 10.1186/s13643-018-0804-8. PMID: 30205844; PMCID: PMC6134765.

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