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SUMMARY WITH CRITICAL APPRAISAL

Topical Antibiotics for Impetigo: A Review of the Clinical Effectiveness and Guidelines

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Context and Policy Issues

Impetigo is a common, often self-limiting, superficial infection of the skin in which systemic symptoms are rare.[1] Presentations often consist of blister-like sores filled with pus, or non-bullous forms with erosions covered with yellowish-brown or honey-coloured crusts.[1,2] Impetigo is contagious and scratching often spreads the infection. It is the most common childhood skin infection encountered in a primary care setting.[2]

Impetigo is a bacterial infection where the causative organism is not routinely identified, however an epidemiological shift from *S. pyrogenes* to *S. aureus* has been observed.[3] *S. aureus* is the dominant pathogen in non-bullous impetigo and is also usually involved in secondary impetigo, a complication of many other dermatological conditions.[2] Changes in the incidence of particular causative organisms or the status of any emerging impetigo pathogens, and the prevalence of antibiotic resistant impetigo are not well known.[4]

Antibiotic treatments of impetigo are indicated for faster symptom resolution and to reduce disease spread and transmission.[5] While treatment practices differ widely, topical antibiotics are widely used for this indication.[2] Oral antibiotics are also used, especially for patients with numerous and/or extensive lesions that may be associated with a systemic infection.[6] Topical antibiotics applied directly to the infection can minimize systemic side-effects and the potential for resistance associated with oral antibiotic use.[3]

The purpose of this report is to retrieve and review the existing clinical effectiveness evidence on the treatment of patients with impetigo with the topical antibiotics: polymyxin B sulfate-bacitracin (Polysporin ointment), polymyxin B sulfate-gramicidin (Polysporin cream), polymyxin B sulfate-bacitracin-gramicidin (Polysporin triple ointment), bacitracin (Bacitin ointment), mupirocin (Bactroban cream/ointment), silver sufadiazine (Flamazine cream), fusidic acid/fusidate sodium (Fucidin cream/ointment), and fusidic acid 2% with hydrocortisone (Fucidin H), compared to each other, placebo or oral antibiotics. Additionally, this report aims to retrieve and review evidence-based guidelines for the treatment of impetigo using topical antibiotics.

Research Questions

1. What is the clinical effectiveness of topical antibiotics for patients with impetigo?

2. What are the evidence-based guidelines regarding the use of topical antibiotics for the treatment of impetigo?

Key Findings

The evidence identified in this report supports the clinical efficacy of topical antibiotics, specifically mupirocin and fusidic acid, for the treatment of impetigo. Insufficient evidence was identified to support the clinical efficacy of bacitracin and a lack of evidence was identified on other topical antibiotics of interest. Evidence from randomized controlled trials of comparative clinical efficacy was lacking or did not support the superiority of mupirocin, fusidic acid, or bacitracin as compared to each other or to other topical antibiotics for the treatment of impetigo. The evidence

identified in this report on systemic antibiotic treatment of impetigo supports mupirocin as superior to erythromycin however the evidence also suggests existing local antimicrobial resistance patterns may strongly influence this comparative efficacy. Insufficient evidence was identified on side-effects of the interventions of interest. No Canadian guidelines were identified, however guidelines from Australia and the United States both contained impetigo treatment recommendations for the use of topical mupirocin and topical fusidic acid consistent with the identified clinical evidence.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval to study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and January 23, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with impetigo
Intervention	Topical Antibiotics: Polymyxin B sulfate-bacitracin (Polysporin ointment) Polymyxin B sulfate-gramicidin (Polysporin cream) Poymyxin B sulfate-bacitracin-gramicidin (Polysporin triple ointment) Bacitracin (Bacitin ointment) Mupirocin (Bactroban cream/ointment) Silver sufadiazine (Flamazine cream) Fusidic acid/fusidate sodium (Fucidin cream/ointment) Fusidic acid 2% plus hydrocortisone (Fucidin H)
Comparator	Placebo, topical antimicrobials compared to each other, oral antibiotics
Outcomes	Clinical effectiveness (symptom reduction), safety and harms, antimicrobial resistance, evidence-based guidelines.
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2007.

Critical Appraisal of Individual Studies

The included systematic review, meta-analysis and health technology assessment (HTA) were critically appraised using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool,[7] while guidelines were assessed with the AGREE II instrument.[8] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 132 citations were identified in the literature search. Following screening of titles and abstracts, 124 citations were excluded and eight potentially relevant reports from the electronic search were retrieved for full-text review. Ten potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 13 publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The literature included in this report consists of a systematic review (SR),[4] a meta-analysis (MA),[2] one health technology assessment (HTA),[9] and two guidelines.[10,11] A tabulated summary of study characteristics is provided in Appendix 2.

Study Design

The MA from The Cochrane Collaboration identified 68 RCTs, and is an update from a 2004 MA from the same author that included 57 RCTs on interventions for impetigo. This MA identified literature published as early as 1938. Among the 68 included RCTs, 31 presented data that were relevant to the patient population and interventions of interest for this report.[2] Pangilinan et al. published an SR in 2009 that identified 29 RCTs in on topical antibiotic treatments for skin infections, 11 of which were for impetigo. All of the relevant RCTs included in this SR were also included in the MA, however two additional efficacy outcomes not reported in the Cochrane review[2] were reported in this SR.[4] An HTA from Provider Synergies published in 2009 on topical antibiotics was identified which cited evidence for the treatment of impetigo, in addition to FDA approved topical antibiotic indications and microorganism indications. The HTA found five relevant reports on topical antibiotics for the treatment of impetigo, three of which were included in the MA and SR. The two which were not also included were sources from product package inserts which were both described as randomized, double-blind trials. It was unclear if these studies were published elsewhere.[9] The SR and MA only included evidence from RCTs,[2,4] while the HTA included RCTs, SRs, and MAs.[9]

The most recent guidelines were published in June of 2016 by The Joanna Briggs Institute.[11] One other set of guidelines was identified, published in 2010 from the National Athletic Trainers' Association.[10] Neither guideline provided information on the clinical study designs included as evidence for supporting the formulated recommendations.[10,11] The target audience of the guidelines from the Joanna Briggs Institute was not specifically stated,[11] while guidelines from the National Athletic

Trainers' Association stated a target audience of certified athletic trainers and others in athletic health care.[10]

Country of Origin

Four publications included in this report originated in the USA,[2,4,9,10] and one from Australia.[11] The SR, MA, and the HTA included in this report did not limit systematic literature searches to any particular country, however they only included English language publications.[2,4] The guidelines did not provide information on literature search limitations.[10,11]

Patient Population

Koning et al. examined evidence on the treatment of impetigo and identified RCTs that examined bullous impetigo, both bullous and non-bullous impetigo, secondary impetigo, both primary and secondary impetigo, and mixed skin infections. Studies on patients with mixed skin infections were included only if the primary outcome measure was presented separately for the subgroup of patients with impetigo. Sample sizes of most of the included RCTs were small, with an average of 82 and a median of 60.5 patients.[2] The SR from Pangilinan et al. focused on patients with uncomplicated skin infections including impetigo, infected wounds, and infected dermatitis.[4] All FDA-approved indications for topical antibiotics were included in the HTA from Provider Synergies.[9] The HTA also provided some information on topical antibiotics for pediatric and pregnant patient populations.[9]

The guidelines from the Joanna Briggs Institute include evidence that examined patients with seasonal/perennial conjunctivitis, dermatitis, scabies, athlete's foot and fungal infections of the toenails, cutaneous warts, acute musculoskeletal pain, osteoarthritic pain, neuropathic pain, wound healing, actinic keratoses, rosacea, in addition to impetigo.[11] Guidelines from the National Athletic Trainers' Association presented recommendations for skin diseases of fungal, viral, and bacterial etiologies that included impetigo for athlete patients in training.[10]

Interventions and Comparators

The MA identified 50 different treatments for impetigo including 24 topical treatments. The interventions of interest identified in this MA were polymyxin B, bacitracin, mupirocin, and fusidic acid. This MA included comparative RCTs and placebo controlled RCTs.[2] Placebo controlled studies for impetigo were identified for mupirocin (3 RCTs), fusidic acid (1 RCT), and bacitracin (1 RCT). RCTs that compared muciprocin to rigamycin (1 RCT), neomycin (1 RCT), dicloxacillin (1 RCT), cephalexin (1 RCT), ampicillin (1 RCT), chlortetracycline (1 RCT), and erythromycin (10 RCTs) were included. Fusidic acid was compared to chloramphenicol, erythromycin, and retapamulin in one included RCT for each comparative trial on impetigo patients. Bacitracin was compared to erythromycin (1 RCT), penicillin (1 RCT), and cephalexin (1 RCT), and also compared to erythromycin (1 RCT) and chloramphenicol (1 RCT) as a combined treatment with neomycin for impetigo. RCT evidence from direct comparison studies of interventions of interest included mupirocin vs fusidic acid (4 RCTs), mupirocin vs polymyxinB/neomycin (1 RCT), fusidic acid vs neomycin/bacitracin (2 RCTs), fucidic acid vs tetracycline/polymyxin B (1 RCT).[2] The SR from Pangilinan et al. identified RCTs that investigated several interventions for impetigo including the topical antibiotics of interest mupirocin (8 RCTs), and fusidic acid (2 RCTs). Comparators in the identified RCTs included placebo, erythromycin,

and retapamulin.[4] The HTA included RCTs on FDA-approved topical antibiotics including mupirocin, bacitracin, cephalexin, triple antibiotic ointments, sulfadiazine, gentamycin, and retapamulin for a wide variety of indications.[9] RCTs of interest included mupirocin vs placebo (1 RCT), and mupirocin vs erythromycin (2 RCTs).[9] Relevant recommendations from both of the published guidelines included in this report include recommendations for the use of topical mupirocin and fusidic acid for the treatment of impetigo.[10,11] No literature on other interventions of interest was identified.

Outcomes

Koning et al. included RCTs that reported primary outcomes of cure and relief of symptoms in addition to secondary outcomes of recurrence, adverse events, and development of bacterial resistance. Cure was defined as clearance of crusts, blisters, and redness as assessed by the investigator.[2] Pangilinan tabulated outcomes identified in the included RCTs as clinical failure and micro-biologic failure which were not defined.[4] Other outcomes were also reported narratively and included symptom relief or clinical improvement, recurrence, adverse events, and bacterial resistance.[4] The HTA from Provider Synergies did not predefine examined outcomes from included evidence but also reported outcomes of cure, bacterial culture, various measures of clinical improvement, adverse events, and bacterial resistance.[9]

Evidence Levels and Grades of Recommendations

The guidelines published in 2016 from the Joanna Briggs Institute listed evidence on topical medications with the supporting evidence level. Evidence from studies with experimental designs were assigned the highest evidence level of 1. Quasi-experimental design evidence was assigned level 2, observational evidence from an analytical designed study was assigned level 3, observational evidence from a descriptive study was assigned level 4, and expert opinion and bench research were assigned the lowest evidence level of 5. Recommendations from these guidelines were assigned grades of either strong or weak. A strong recommendation was defined as having clear benefits that outweigh the undesirable effects and supported by evidence of adequate quality. Additionally, a strong recommendation had a benefit or no impact on resource use, as well as taking into account the values, preferences, and experience of the patient. A weak recommendation was defined as being supported by evidence of less quality, with a potential impact on resource use, and/or less consideration given to the values, preferences, and experience of the patient.[11]

The guidelines from the National Athletic Trainers' Association provided recommendations graded as evidence category A, B, or C. Recommendations assigned an evidence category A were based upon well-designed experimental, clinical, or epidemiological evidence, whereas a theoretical rationale for recommendations assigned an evidence category B were based upon experimental, clinical or epidemiologic studies. Evidence category C was assigned to recommendations based upon anecdotal evidence.[10]

Summary of Critical Appraisal

A tabulated critical appraisal summary of the included publications is provided in Appendix 3.

The well-conducted MA from Koning et al.[2] had a number of strengths that the SR of Pangilinan et al.[4] and the HTA from Provider Synergies did not.[9] The MA included duplicate screening of literature, a critical appraisal of included studies, and a table of excluded study characteristics. As an MA, Koning et al. also described a data extraction methodology, statistical methodology, conducted a sensitivity analysis, and examined statistical heterogeneity. The data extraction utilized a data extraction form and was done in duplicate. The statistical heterogeneity indicated the data was pooled appropriately and in cases of substantial heterogeneity ($I^2 > 50\%$) a random-effects model was used instead of a fixed-effect model. Some pooled results of interest had substantial heterogeneity. The critical appraisal of the MA reported an unclear risk of bias in random sequence generation, allocation concealment, selective reporting, and other biases due to insufficient reporting in a majority of the included RCTs. Over 75% of the included RCTs were reported as having a high or unclear risk of performance and detection bias.[2] The MA however did not provide an assessment of publication bias.[2] The MA, SR, and HTA included a sufficient literature search methodology, literature inclusion and exclusion criteria, and reporting of adverse event observations.[2,4,9] A defined research objective was formulated for the MA and SR,[2,9] but was lacking in the HTA.[9] The HTA contained some unique information on FDA-approval, special patient populations, and available dosage formats.[9] An assessment of bias was reported in the HTA however it was a general statement about the collective risk of bias,[9] and there was no critical appraisal as part of the included SR.[4] The HTA did not tabulate information on study characteristics, provide data extraction methodology, or a conflict of interest (COI) statement.[9] COI statements from both the MA and the SR suggested the potential for a COI.[2,4]

The included guidelines provide graded recommendations for topical antibiotic treatment of impetigo.[10,11] Strengths of the guidelines issued by the Joanna Briggs Institute also include an evidence level assigned to statements that support the recommendations.[11] Strengths of the guidelines issued by the National Athletic Trainers' Association include recommendations explicitly linked to supporting evidence, and a focus on a specific patient population.[10] These guidelines share some significant quality limitations including very little methodological information on the literature search, broad focus and research question, no information on stakeholder involvement, and no COI statement.[10,11] Guidelines from the Joanna Briggs Institute also had no information on recommendation implementation or guideline updating, and the meaning of recommendation grades and levels of evidence were only available from a separate uncited source.[11]

Summary of Findings

What is the clinical effectiveness of topical antibiotics for patients with impetigo?

The clinical effectiveness findings of the included SR, MA, and HTA, are summarized in Appendix 4, Table 1.

The MA identified in this report summarized RCT evidence on the clinical effectiveness of mupirocin treatment of non-bullous impetigo as compared to placebo, rifamycin, neomycin, bacitracin, chlortetracycline, polymyxin B/Neomycin, fusidic acid, erythromycin, dicloxacillin, cephalexin, and ampicillin in outcomes of cure or clinical improvement. Statistically significant differences ($P < 0.05$) favoring mupirocin were

identified in pooled data from three RCTs with a total of 173 patients that compared mupirocin to placebo, and pooled data from ten RCTs with 581 patients that compared mupirocin to erythromycin. Two RCTs (total 137 patients) identified in the MA assessed topical mupirocin and erythromycin and had blinded outcome assessments. When data from these two RCTs was pooled, there was substantial statistical heterogeneity (79%) and the statistical difference in cure/clinical improvement outcomes between topical mupirocin and erythromycin was no longer observed. All other mupirocin comparative RCT evidence in this MA was from single trials including comparisons to the interventions of interest bacitracin and polymyxin B/neomycin. None of the other comparative RCTs, including comparisons of interventions of interest, revealed statistically significant differences in clinical effectiveness with mupirocin. Four RCTs were identified in the MA and the pooled data from 440 patients with non-bullous impetigo did not demonstrate a statistically significant difference between mupirocin and fusidic acid in cure rates.

The MA identified in this report also summarized RCT evidence on the clinical effectiveness of fusidic acid for the treatment of non-bullous impetigo as compared to placebo, neomycin/bacitracin, tetracycline/polymyxin B, chloramphenicol, erythromycin, and retapamulin. All identified comparisons were from single RCTs. One RCT of 517 non-bullous impetigo patients did not find a statistically significant difference between fusidic acid and retapamulin.[2,4] A statistically significant superiority with fusidic acid treatment in outcomes of cure or clinical improvement was identified over placebo in an RCT examining 156 patients but none of the other comparator trials.[2]

Koning et al. also identified relatively small single RCTs comparing bacitracin to placebo, erythromycin, penicillin, and cephalexin for the treatment of non-bullous impetigo. In one identified RCT bacitracin demonstrated inferior clinical efficacy to cephalexin in an outcome reported as cure or clinical improvement. No other statistically significant differences were identified in the other comparisons with bacitracin, including no significant difference from placebo in one RCT.

Oral antibiotic interventions did not demonstrate a statistically significant difference in outcomes of cure or clinical improvement for impetigo compared to mupirocin or fusidic acid in the identified data from individual RCTs.[2] In two small RCTs bacitracin demonstrated inferiority to systemic antibiotics, including one RCT where cephalexin was superior in the treatment of non-bullous impetigo, and one RCT where erythromycin demonstrated statistically significant superiority ($P = 0.049$) to neomycin/bacitracin in the treatment of bullous impetigo.[2] One small RCT did not observe a difference between neomycin/bacitracin and chloramphenicol for the treatment of bullous impetigo. Koning et al. made three concluding statements that good evidence supported topical mupirocin and fusidic acid as equally or potentially more effective than oral antibiotics while also demonstrating fewer side-effects.[2]

The HTA from Provider Synergies identified three RCTs that examined topical antibiotics for the treatment of impetigo and the findings were reported without statistical analysis of significance. One double-blind RCT of 100 impetigo patients over two months old reported a clinical efficacy of 71% for mupirocin and 35% for a placebo control for treatment of eight to twelve days. Additionally, this RCT observed pathogen eradication rates of 94% for mupirocin and 62% for placebo with no

reported adverse events. Another open-label RCT of 62 impetigo patients, between the ages of five months and 13 years, found that 100% of mupirocin patients had a 75 to 100% reduction in lesion size as compared to 93% of erythromycin patients seven days after eight days of therapy. An unreported frequency of mild diarrhea occurred in the erythromycin treated patients and no additional adverse events were reported in the HTA. The third RCT identified in the HTA was a double-blind RCT of 102 patients, conducted in Israel, which compared mupirocin to erythromycin in order to examine the prevalence of erythromycin-resistant strains of *S. aureus* in impetigo. In 88% of impetigo patients *S. aureus* was isolated, 28% of those isolates were erythromycin resistant while none were resistant to mupirocin. Erythromycin treated patients with erythromycin-resistant *S. aureus* impetigo had a much higher treatment failure rate of 47% as compared to 8% patients with erythromycin-sensitive *S. aureus* impetigo. Development of erythromycin resistance occurred in 4% of patients during the study. The authors of the HTA cited guidelines from the Infectious Diseases Society of America from 2005 that recommended mupirocin for topical antibiotic therapy of impetigo, and also reported there is a lack of evidence comparing mupirocin to retapamulin for this indication.[9]

The SR identified ten relevant RCTs and categorized outcomes as either clinical failure or micro-biologic failure, with some additional outcomes summarized narratively. Clinical failure outcomes were reported from seven RCTs that compared mupirocin to erythromycin. Six of the seven RCTs reported higher clinical failure rates in erythromycin treated patients although no statistical analysis was presented. Three of these RCTs also reported an outcome that the SR classified as micro-biologic failure. Two of these three RCTs reported higher failure rates for erythromycin with one RCT additionally reporting a higher recurrence rate at one month follow-up for patients treated with erythromycin. One identified RCT reported a higher clinical failure rate of 15% for placebo as compared to 0% for mupirocin and a micro-biologic failure rate of 62% for placebo and 10% for mupirocin. Another identified placebo controlled RCT found a clinical failure rate of 13% for fusidic acid and 41% for placebo, and a micro-biologic failure rate of 0% for fusidic acid and 68% for placebo. Both differences in failure rates were statistically significant ($P < 0.05$). One larger RCT included 517 impetigo patients treated with fusidic acid or retapamulin. Clinical and micro-biologic treatment failure rates were lower in retapamulin treated patients however no statistical anlaysis was presented. Pangilinan et al. offered conclusions suggesting that mupirocin and erythromycin were at least comparable for the treatment of impetigo and significantly better than placebo. The authors also suggest that while topical agents should be preferred due to better tolerability, there is no evidence to support their use for highly virulent strains of MRSA.[4]

What are the evidence-based guidelines regarding the use of topical antibiotics for the treatment of impetigo?

The relevant recommendations and supporting evidence statements from the identified guidelines included in this report are directly quoted in Appendix 4, Table 2. Guidelines published in 2016 from the Joanna Briggs Institute provided an evidence statement of level 1, and a recommendation of grade A, which both stated that topical mupirocin and topical fusidic acid were equally, or more effective than oral treatments for non-extensive impetigo.[11] The National Athletic Trainers' Association had two statements assigned an evidence category of B; a treatment and a diagnosis

statement. Topical mupirocin, fusidic acid, and retapamulin were reported as being effective in the treatment of impetigo. The treatment statement also suggested that culture and sensitivity of suspicious lesions dictate the treatment for all bacterial infections. The diagnosis statement regarding impetigo also suggested that specimens for culture and antimicrobial susceptibility should be obtained from questionable lesions.[10]

Limitations

Over representation of RCT evidence that was included in more than one of the HTA, SR, and MA included in this report may give the appearance of a greater quantity of evidence than has been identified. Evidence was not identified for all interventions and comparators of interest. The SR conducted a critical appraisal of the majority of the evidence included in this report and reported an unclear risk of bias for many assessed items due to a lack of methodology reporting. No Canadian guidelines were identified which may limit applicability to a Canadian healthcare setting, particularly with regard to local antibiotic resistance patterns.

Conclusions and Implications for Decision or Policy Making

The evidence on topical antibiotics for the treatment of impetigo identified and included in this report consists of one SR,[4] one HTA,[9] and one high quality MA published in 2012.[2] Interventions of interest for which clinical evidence was identified were mupirocin,[2,4,9] fusidic acid,[2,4] polymyxin B,[2] and bacitracin.[2] All of the identified literature reported consistent evidence for the clinical efficacy of mupirocin for impetigo indications over placebo.[2,4,9] The SR and the MA also reported consistent RCT evidence of a statistically significant increase in the clinical efficacy of fusidic acid over a placebo control for the treatment of impetigo.[2,4] One final placebo controlled RCT of 36 patients identified in the MA found that bacitracin and placebo had no statistically significant differences in rate of non-bullous impetigo cures.[2] Collectively this evidence supports the clinical efficacy of mupirocin and fusidic acid for the treatment of impetigo. Insufficient evidence was identified to support the clinical efficacy of bacitracin.

The SR,[4] MA,[2] and HTA[9] also identified comparative clinical efficacy evidence for the treatment of impetigo. Evidence of efficacy between topical antibiotics consisted of mupirocin as compared to rifamycin,[2] neomycin,[2] bacitracin,[2] chlortetracycline,[2] polymyxin B/neomycin,[2] and fusidic acid.[2] The RCT evidence of comparative clinical efficacy was lacking or did not support the superiority of mupirocin, fusidic acid, or bacitracin as compared to each other or to the other investigated topical antibiotics for the treatment of impetigo.

The SR,[4] MA[2] and HTA[9] also identified clinical efficacy evidence that compared topical antibiotics of interest to systemic antibiotic therapies. Evidence of comparative efficacy was identified for mupirocin as compared to erythromycin,[2,4,9] dicloxacillin,[2] cephalexin,[2] and ampicillin.[2] The evidence identified in this report suggests that mupirocin may be superior to erythromycin for the treatment of impetigo however these results may be dependent upon local antimicrobial resistance patterns. The HTA, SR, and MA did not report any incidences of topical antibiotic-resistance and it is unclear if any included RCT tested for topical antibiotic resistance. Evidence suggests that fusidic acid may be as effective as chloramphenicol and erythromycin in the treatment of impetigo however this evidence is from small RCTs.[2]

Limited comparative evidence on side-effects was identified. An unreported greater frequency of mild diarrhea in impetigo patients treated with erythromycin as compared to mupirocin was found in one RCT.[9] Koning et al. concluded that, ”In general, oral antibiotics have more side-effects than topical antibiotics, especially gastrointestinal side-effects.”[2]

The identified guidelines had methodological limitations however both guidelines provided graded recommendations based upon cited evidence which generally agree with the clinical effectiveness evidence included in this report. Both guidelines recommend treatment of impetigo with topical antibiotics, specifically mupirocin and fusidic acid.[10,11] One guideline also recommends antimicrobial susceptibility testing to guide treatment options.[10] See Appendix 4, table 2 to read the complete relevant recommendations in their full context.

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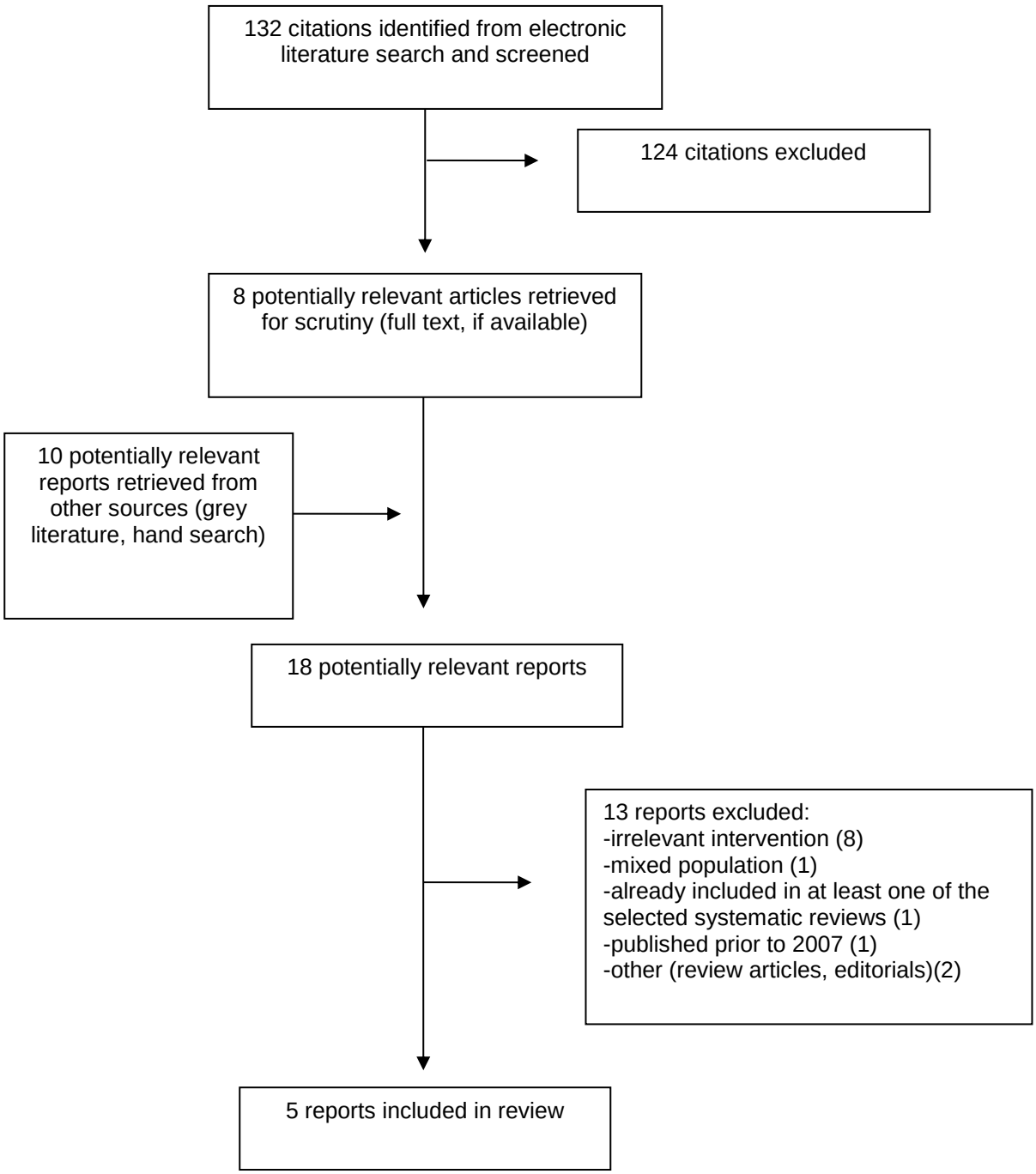
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table A1: Characteristics of Included Publications

Author, Publication Date	Study Design	Population	Intervention	Comparator(s)	Outcomes
Koning, 2012[2]	SR of 68 RCTs	5578 patients with non-bullous, bullous, primary, and secondary impetigo	50 different treatments including oral and topical antibiotics and disinfecting treatments Of interest: Polymyxin B Bacitracin Mupirocin Fusidic acid	Placebo controls Comparisons to different interventions listed	• Cure • Symptom relief • Recurrence • Adverse events • Bacterial resistance
Provider Synergies, 2010[9]	HTA	Patients with skin and soft tissue bacterial infections	Mupirocin Bacitracin Cephalexin Triple antibiotic ointment Sulfadiazine Gentamycin Retapamulin	Placebo controls White petrolatum Comparisons to other interventions listed	• Cure • Culture • Clinical improvement - various measures • Adverse events • Bacterial resistance
Pangilinan, 2009[4]	SR of 29 RCTs	Patients with secondarily infected traumatic lesions, cellulitis or abscesses, secondarily infected dermatoses, impetigo, and carbuncles or furunculosis	Mupirocin Erythromycin Flucloxacillin Fusidic acid Retapamulin Cephalexin Neosporin Tetracycline Bacitracin Chlorhexidine Povidone iodine Triple antibiotic ointment	Placebo controls Comparisons to different interventions listed	• Cure • Culture • Symptom relief (clinical improvement) • Recurrence • Adverse events • Bacterial resistance

HTA = health technology assessment; RCT = randomized controlled trial; SR = systematic review

Table A2: Characteristics of Included Guidelines

Origin, Publication Date	Interventions of Interest	Evidence Levels and Recommendation Grading	Target Population
The Joanna Briggs Institute, USA, 2016[11]	Topical mupirocin, and fusidic acid	Evidence Levels: **1**: Experimental Designs **2**: Quasi-experimental Designs **3**: Observational - Analytic Designs **4**: Observational - Descriptive Studies **5**: Expert Opinion and Bench Research	Not specifically stated

Origin, Publication Date	Interventions of Interest	Evidence Levels and Recommendation Grading	Target Population
		Grades of Recommendation: **A**: Strong Recommendation: Clear benefits outweigh undesirable effects Evidence of adequate quality support recommendation Benefit or no impact on resource use Values, preferences, and patient experience has been considered **B**: Weak Recommendation: Desirable effects appear to outweigh undesirable effects, although this is not clear Evidence supports use but may not be of high quality Benefit, no impact, or minimal impact on resource use Values, preferences, and patient experience may not have been considered	
National Athletic Trainers' Association, USA, 2010[10]	Topical mupirocin, and fusidic acid	Evidence Categories: **A**: Well designed experimental, clinical, or epidemiological studies support the recommendation **B**: Experimental, clinical, or epidemiologic studies provide theoretical rationale for recommendation **C**: Recommendation is currently based largely upon anecdotal evidence	Certified athletic trainers and others in athletic health care

Appendix 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and HTA using the AMSTAR tool[7]

Strengths	Limitations
Koning, 2012[2]	
• Defined research objective • Literature search selection/inclusion/exclusion methodology outlined • Literature screened in duplicate • Table of included study characteristics • Table of excluded study characteristics • Critical appraisal of included literature • COI statement provided • Data extraction methodology described • Statistical methods outlined • Sensitivity analysis conducted • Statistical heterogeneity tested • Examination of reported adverse events	• Potential COI • No assessment of publication bias • No quantified summary of adverse events
Provider Synergies, 2010[9]	
• Literature search selection/inclusion/exclusion methodology outlined • Examination of reported adverse events • Includes information on FDA-approval, special populations, and available formats for dosages	• Lacks defined research objective • No table of included study characteristics • Studies assessed for bias but not reported for each included study - only general statements about the collective evidence quality • No COI statement provided - unclear funding • No data extraction methodology
Pangilinan, 2009[4]	
• Defined research objective • Literature search selection/inclusion/exclusion methodology outlined • Table of included study characteristics • COI statement provided • Limited reporting of adverse event observations	• No critical appraisal of included studies • Potential COI

COI = conflict of interest

Table A4: Strengths and Limitations of Guidelines using AGREE II8

Strengths	Limitations
The Joanna Briggs Institute, 2016[11]	
• Recommendations graded • Evidence level assigned to supporting statements	• Very limited methodology reported • No guideline implementation or updating information • Recommendations and supporting evidence not clearly linked • No information on literature search methodology • Meaning of recommendation grades and levels of evidence in separate source • Broad focus and research question • No information on stakeholder involvement or potential COIs
National Athletic Trainers' Association, 2010[10]	
• Recommendations and supporting evidence linked • Recommendations graded based upon evidence level • Focus on specific patient population	• Broad focus and research question • Very limited methodology reported • Unclear if literature search was systematic • No information on stakeholder involvement or potential COIs

COI = conflict of interest

Appendix 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included SRs and HTA

Main Study Findings	Author's Conclusion
Koning et al., 2012[2]	
Mupirocin for non-bullous impetigo Cure/Improvement (RR > 1 favours Mupirocin) Mupirocin vs Placebo (3 RCTs, n = 173) (*P* < 0.00001) RR (95% CI): 2.18 (1.58, 3.00) (I^2 = 0.0%) Mupirocin vs Rifamycin (1 RCT, n = 17) (*P* = 0.069) RR (95% CI): 1.72 (0.96, 3.07) Mupirocin vs Neomycin (1 RCT, n = 32) (*P* = 0.074) RR (95% CI): 1.29 (0.98, 1.71) Mupirocin vs Bacitracin (1 RCT, n = 16) (*P* = 0.057) RR (95% CI): 2.57 (0.97, 6.80) Mupirocin vs Chlortetracycline (1 RCT, n = 14) (*P* = 0.55) RR (95% CI): 1.11 (0.78, 1.59) Mupirocin vs Polymyxin B/Neomycin (1 RCT, n = 8) (*P* = 0.86) RR (95% CI): 1.06 (0.56, 2.01) Mupirocin vs Fusidic acid (4 RCTs, n = 440) (*P* = 0.51) RR (95% CI): 1.03 (0.95, 1.11) (I^2 = 0.0%) Mupirocin vs Erythromycin (10 RCTs, n = 581) (*P* = 0.032) RR (95% CI): 1.07 (1.01, 1.13) (I^2 = 11%) Mupirocin vs Erythromycin (2 outcome assessment blinded RCTs, n = 137) (*P* = 0.39) RR (95% CI): 1.12 (0.86, 1.46) (I^2 = 79%) Mupirocin vs Dicloxacillin (1 RCT, n = 53) (*P* = 0.49) RR (95% CI): 1.04 (0.94, 1.15) Mupirocin vs Cephalexin (1 RCT, n = 17) (*P* = 0.79) RR (95% CI): 0.95 (0.66, 1.37) Mupirocin vs Ampicillin (1 RCT, n = 13) (*P* = 0.26) RR (95% CI): 1.78 (0.65, 4.87) Mupirocin for secondary impetigo Cure/Improvement (RR > 1 favours Mupirocin) Mupirocin calcium vs Cephalexin (1 RCT, n = 159) (*P* = NR) RR (95% CI): 1.11 (0.86, 1.43) Fusidic acid for non-bullous impetigo Cure/Improvement (RR > 1 favours Fusidic Acid)	"There is good evidence that topical mupirocin and topical fusidic acid are equally, or more, effective than oral treatment. Due to the lack of studies in people with extensive impetigo, it is unclear if oral antibiotics are superior to topical antibiotics in this group. Fusidic acid and mupirocin are of similar efficacy." (pp. 2) "Topical antibiotic treatment showed better cure rates than placebo (pooled risk ratio (RR) 2. 24, 95% confidence interval (CI) 1.61 to 3.13) in 6 studies with 575 participants. In 4 studies with 440 participants, there was no clear evidence that either of the most commonly studied topical antibiotics (mupirocin and fusidic acid) was more effective than the other (RR 1.03, 95% CI 0.95 to 1.11). In 10 studies with 581 participants, topical mupirocin was shown to be slightly superior to oral erythromycin (pooled RR 1.07, 95% CI 1.01 to 1.13). There were no significant differences in cure rates from treatment with topical versus other oral antibiotics." (pp. 2) "Worldwide, bacteria causing impetigo show growing resistance rates for commonly used antibiotics." (pp. 2) "There is good evidence that the topical antibiotics mupirocin and fusidic acid are equal to, or possibly more effective than, oral treatment for people with limited disease. Fusidic acid, mupirocin, and retapamulin are probably equally effective; other topical antibiotics seem less effective. In general, oral antibiotics have more side-effects than topical antibiotics, especially gastrointestinal side-effects." (pp. 16)

Main Study Findings	Author's Conclusion
Fusidic acid vs Placebo (1 RCT, n = 156) (*P* < 0.00001) RR (95% CI): 4.42 (2.39, 8.17) Fusidic acid vs Neomycin/bacitracin (1 RCT, n = 84) (*P* = 0.61) RR (95% CI): 0.92 (0.66, 1.27) Fusidic acid vs Tetracycline/polymyxin B (1 RCT, n = 87) (*P* = 0.73) RR (95% CI): 1.06 (0.75, 1.52) Fusidic acid vs Neomycin/bacitracin (1 RCT, n = 12) (*P* = NR) RR (95% CI): 10.00 (1.51, 66.43) Fusidic acid vs Chloramphenicol (1 RCT, n = 12) (*P* = NR) RR (95% CI): 5.00 (1.38, 18.17) Fusidic acid vs Erythromycin (1 RCT, n = 24) (*P* = 0.20) RR (95% CI): 1.43 (0.83, 2.45) Fusidic acid for non-bullous impetigo Cure/Improvement (RR < 1 favours Fusidic Acid) Retapamulin vs Fusidic acid (1 RCT, n = 517) (*P* = 0.074) RR (95% CI): 1.05 (1.00, 1.11) Bacitracin for non-bullous impetigo Cure/Improvement (RR < 1 favours Bacitracin) Bacitracin vs Placebo (1 RCT, n = 36) (*P* = 0.41) RR (95% CI): 3.71 (0.16, 85.29) Bacitracin vs Erythromycin (1 RCT, n = 30) (*P* = 0.090) RR (95% CI): 0.50 (0.22, 1.11) Bacitracin vs Penicillin (1 RCT, n = 34) (*P* = 0.37) RR (95% CI): 0.38 (0.04, 3.25) Bacitracin vs Cephalexin (1 RCT, n = 19) (*P* = 0.040) RR (95% CI): 0.37 (0.14, 0.95) Bacitracin for bullous impetigo Cure/Improvement (RR < 1 favours Bacitracin) Chloramphenicol vs Neomycin/bacitracin (1 RCT, n = 12) (*P* = NR) RR (95% CI): 2.00 (0.21, 19.23) Cure/Improvement (RR > 1 favours Bacitracin) Neomycin/bacitracin vs Erythromycin (1 RCT, n = 24) (*P* = 0.049) RR (95% CI): 0.14 (0.02, 0.99)	
Provider Synergies, 2010[9]	
Mupirocin for impetigo Clinical efficacy rate Mupirocin (Bactroban ointment) vs placebo (1 RCT, n = 100)	"The Infectious Diseases Society of America (IDSA) 2005 practice guidelines for the diagnosis and management of skin and soft-tissue infections recommend mupirocin (Bactroban)

Main Study Findings	Author's Conclusion
Mupirocin 71% Placebo 35% <u>Pathogen eradication rate</u> Mupirocin (Bactroban ointment) vs placebo (1 RCT, n = 100) Mupirocin 94% Placebo 62% <u>Adverse Events</u> Mupirocin (Bactroban ointment) vs placebo (1 RCT, n = 100) Mupirocin 0% Placebo 0% <u>Cured or 75% reduction in lesion size after 8 days of treatment at 15 days follow-up</u> Mupirocin (3x per day) vs Erythromycin (40mg/kg/day) (1 RCT, n = 62) Mupirocin 100% Erythromycin 93% <u>Erythromycin resistant *S. aureus* impetigo</u> Mupirocin (2%) vs Erythromycin (50mg/kg/day) (1 RCT, n = 102) *S. aureus* isolated in 88% of cases *S. aureus* erythromycin resistant in 28% of cases *S. aureus* mupirocin susceptible in 100% of cases <u>Treatment failure rate (1 RCT, n = 102)</u> Mupirocin 2% Erythromycin-resistant strain 47% Erythromycin-sensitive Tx Erythromycin 8% Development of Erythromycin-resistance 4% <u>Adverse Events - diarrhea</u> Mupirocin (3x per day) vs Erythromycin (40mg/kg/day) (1 RCT, n = 62) Mild diarrhea in erythromycin group - frequency not reported	ointment as the topical antibacterial drug of choice in the treatment of impetigo in infants two months and older and adults." (pp. 12) "Mupirocin (Bactroban) ointment and retapamulin (Altabax) have not been studied in head to head trials in the treatment of impetigo, so it is unclear if retapamulin (Altabax) is more effective than mupirocin." (pp. 12)
Pangilinan et al., 2009[4]	
<u>Clinical Failure - treatment of impetigo</u> <u>Mupirocin vs Placebo (1 RCT)</u> Mupirocin (n = 18) 0% Placebo (n = 15) 15% <u>Fusidic acid vs Placebo (1 RCT) (*P* < 0.05)</u> Fusidic acid (n = 78) 13% Placebo (n = 82) 41% <u>Mupirocin vs Erythromycin (7 RCTs)</u> Mupirocin (n = 101) 1% Erythromycin or flucloxacillin (n = 99) 6% Mupirocin (n = 30) 0% Erythromycin (n = 32) 7%	"Use of mupirocin with impetigo was demonstrated to be comparable with oral therapy (erythromycin) in seven out of seven studies, and one of the studies showed clinical failure due to microbiological resistance to the studied oral antimicrobial."(pp. 7) "Topical agents, specifically mupirocin and retapamulin, were significantly better than placebo at producing a cure or improvement at 7–14 days in patients with impetigo, and were probably at least as effective as the oral antimicrobials erythromycin and/or flucloxacillin. Owing to better tolerability compared with oral antibiotics, topical antibiotics should be used initially in treating impetigo." (pp. 7) "Topical agents, although shown to be better than placebo in

Main Study Findings	Author's Conclusion
Mupirocin (n = 49) 4% Erythromycin (n = 48) 10% Mupirocin (n = 28) 0% Erythromycin (n = 25) 0% Mupirocin (n = 24) 9% Erythromycin (n = 30) 8% Mupirocin (n = 29) 0% Erythromycin (n = 30) 0% Mupirocin (n = 51) 2% Erythromycin (n = 51) 24% Failure associated with erythromycin resistance <u>Fusidic acid vs Retapamulin (1 RCT)</u> Fusidic acid (n = 172) 6% Retapamulin (n = 345) 0.9% MRSA 2.9% Fusidic acid resistance 5.6% Mupirocin resistance 3.8% <u>Microbiological failure - treatment of impetigo</u> <u>Mupirocin vs Placebo (1 RCT)</u> Mupirocin (n = 18) 10% Placebo (n = 15) 62% <u>Fusidic acid vs Placebo (1 RCT) (*P* < 0.05)</u> Fusidic acid (n = 78) 0% Placebo (n = 82) 68% <u>Mupirocin vs Erythromycin (3 RCTs)</u> Mupirocin (n = 49) 29% Erythromycin (n = 48) 35% Recurrence at one month follow-up Mupriocin (n = 49) 6% Erythromycin (n = 48) 19% Mupirocin (n = 28) 12% Erythromycin (n = 25) 63% Mupirocin (n = 29) 0% Erythromycin (n = 30) 0% <u>Fusidic acid vs Retapamulin (1 RCT)</u> Fusidic acid (n = 172) 6.1% Retapamulin (n = 345) 1.7%	impetigo and less serious conditions, may not be ideal when trying to provide empiric cover for highly virulent strains of MRSA." (pp. 12)

CI = confidence interval; NR = not reported; RCT = randomized clinical trial; RR = relative risk;

Table 2: Summary of Findings of Included Guidelines

Relevant Evidence and Recommendations
The Joanna Briggs Institute, 2016[11]
Evidence: For the treatment of non-extensive impetigo, there is good evidence that topical mupirocin and topical fusidic acid are equally, or more, effective than oral treatment. (Level 1) Recommendation: Topical mupirocin and topical fusidic acid may be considered to be equally, or more, effective than oral treatments of non-extensive impetigo. (Grade A)
National Athletic Trainers' Association, 2010[10]
Treatment: Culture and sensitivity of suspicious lesions will dictate treatment for all bacterial infections. Topical mupirocin (Bactroban; GlaxoSmithKline, Middlesex, United Kingdom), fusidic acid (Fucidin H; Leo Pharma, Ballerup, Denmark), and retapamulin (Altabax; GlaxoSmithKline, Middlesex, United Kingdom) have been shown effective in treating impetigo. (Evidence Category: B) Diagnosis: Specimens for culture and antimicrobial susceptibility should be obtained from any questionable lesions. (Evidence Category: B)