A systematic review and meta-analysis of treatments for impetigo

Ajay George and Greg Rubin

SUMMARY

Background: *Impetigo is a common clinical problem seen in general practice. Uncertainty exists as to the most effective treatment, or indeed if treatment is necessary.*

Aim: *To determine the most effective treatment for impetigo in a systemically well patient.*

Design of study: *Systematic review and meta-analysis.*

Method: *Databases were searched for relevant studies. The Cochrane highly sensitive randomised controlled trial (RCT) search string was employed and combined with the word 'impetigo' as the MeSH term and keyword. The bibliographies of relevant articles were searched for additional references. RCTs that were either double- or observer-blind, and involved systemically well patients of any age in either primary or secondary care settings, were included. Studies that selected patients on the basis of skin swab results were excluded, as were studies that were not in English. Cure or improvement of impetigo reported at seven to 14 days from start of treatment was the primary outcome measure. Meta-analysis was performed on homogeneous studies.*

Results: *Three hundred and fifty-nine studies were identified, of which 16 met the inclusion criteria. Meta-analysis demonstrated that topical antibiotics are more effective than placebo (odds ratio [OR] = 2.69, 95% confidence interval [CI] = 1.49 to 4.86). There is weak evidence for the superiority of topical antibiotics over some oral antibiotics, such as erythromycin (OR = 0.48, 95% CI = 0.23 to 1.00). There is no significant difference between the effects of mupirocin and fusidic acid (OR = 1.76, 95% CI = 0.77 to 4.03).*

Conclusion: *This review found limited high-quality evidence to inform the treatment of impetigo. From that which is available, we would recommend the use of a topical antibiotic for a period of seven days in a systemically well patient with limited disease. Further research is needed on the role of flucloxacillin and non-antibiotic treatments for impetigo.*

Keywords: *impetigo; antibiotics; systematic review; meta-analysis.*

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Introduction

IMPETIGO is a common bacterial skin infection that particularly affects children. In the United Kingdom (UK) the annual incidence in children up to four years old is 2.8%, and for five to 15-year-olds it is 1.6%.[1] Impetigo was described in 1864 by Tilbury Fox as a disease characterised by 'circular, umbilicated quasi-bullous spots which increase centrifugally, and become covered by yellow flat crusts which cover over superficial ulceration'.[2] It is generally a minor illness, causing few systemic ill effects. Less than 1% of cases lead to post-streptococcal glomerulonephritis and treatment of the impetigo lesions does not seem to stop susceptible individuals developing this complication.[3] Impetigo is a contagious infection and schools are advised to exclude affected children until lesions have healed/crusted over or until they have received at least two days of treatment.[4]

Impetigo can occur as a primary infection or secondary to pre-existing skin conditions, such as eczema or scabies. It has two forms: bullous and non-bullous, and over 70% of cases are the latter.[5] *Staphylococcus aureus* has become the main bacteriological agent involved in the non-bullous form, either alone or with *S. pyogenes* (Lancefield group A).[6,7] It tends to affect exposed areas, such as the face and extremities. The bullous form, in which the blisters are usually less than 3 cm in diameter, is always caused by *S. aureus*.[8,9] Its usual distribution involves the face, buttocks, trunk and perineum.

There is some uncertainty regarding the optimal treatment of impetigo. Advice ranges from the use of oral flucloxacillin, erythromycin, penicillin or cephalosporins to topical treatment with fusidic acid, mupirocin, neomycin or bacitracin.[10-13] The *British National Formulary* (*BNF*) recommends topical fusidic acid or mupirocin, and oral flucloxacillin or erythromycin for widespread disease.[13] It is unclear whether topical or oral antibiotics are more effective, or indeed whether specific treatment is indicated. Other treatments that have been advocated include topical antifungal preparations (with or without corticosteroids),[14,15] antiseptic washes,[16] and even topical treatments containing tea.[17] The question of whether an antibiotic is necessary at all, and if so which one, also has implications in current thinking about limiting antibiotic use.[18,19]

The diagnosis of impetigo is a clinical one and treatment decisions are rarely based on the results of skin swabs. Skin swabs do not reliably differentiate between infection and colonisation[20] and if samples are not taken correctly results may be unrepresentative.[21] It is therefore important to look at evidence that is based on the clinical appearance of impetigo, rather than bacteriological results. Rapid clinical recovery is important to patients and some authors have suggested that patients should be re-examined after seven days.[5,9,22] For this reason evaluation of treatment effect with-

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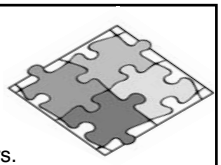

What do we know?

Impetigo is a common bacterial skin infection presenting to general practitioners. Uncertainty exists as to the best treatment for the condition, or even if treatment is necessary.

What does this paper add?

There is a lack of high quality evidence for the treatment of impetigo. The available evidence indicates that topical antibiotics are more effective than placebo, with a number needed to treat of five. Topical antibiotics may be more effective than some oral antibiotics, though the evidence for this is weak. Treatment duration of seven days is sufficient and there is no difference in effectiveness between mupirocin and fusidic acid. Further studies are required to examine the role of flucloxacillin and non-antibiotic treatments for impetigo.

in seven to 14 days was a criterion for inclusion.

Method

Strategy

The Cochrane highly sensitive randomised controlled trial (RCT) search string[23] was employed and combined with the word 'impetigo' as the MeSH term and keyword. Databases were searched in August 2002. They included MEDLINE (1966–2002), EMBASE (1980–2002), CINHAL (1982–2002), and the Cochrane Controlled Trials Register as well as the NHS National Research Register, the NHS R&D register, *Clinical Evidence*, *Bandolier*, and *Drugs and Therapeutics Bulletin*. The bibliographies of relevant articles were searched for additional references. Pharmaceutical companies were also contacted to obtain additional unpublished data.

Study selection

Randomised controlled trials of treatments of bullous or non-bullous impetigo, irrespective of extent of disease, were included in this review. Included studies had to be double- or observer-blind and had to be conducted on systemically well patients of any age in either primary or secondary care. Studies were included if they were not exclusively about impetigo (for example, pyoderma or bacterial skin infections), but contained discrete data on impetigo. They had to report cure or improvement of the condition within seven to 14 days of starting treatment. Studies that selected patients for entry by bacteriology (skin swabs), or that excluded patients from final analysis if swab culture proved negative, were excluded. Non-English studies were also excluded. One author (AG) checked the titles and abstracts of all studies identified in the search process and selected relevant articles. The full reports of these studies were scrutinised and further studies excluded based on the inclusion criteria. Both authors independently reviewed the remaining articles and the final selection of studies was agreed by discussion.

Assessment of methodological quality

Both authors independently scored selected papers for methodological quality using the Jadad scale[24] (Table 1). This scale scores for randomisation, blinding, and patient attrition. Further marks can be added or subtracted based on an assessment of the appropriateness of the randomisation and double-blinding methods. The scale ranges from zero to five, with a score of three or more suggestive of a 'good' paper.

Data extraction and statistical methods

Data from included studies was extracted using a structured pro-forma. This was done independently by both authors. Data was entered into RevMan MetaView software (version 4.1)[25] and analysis performed using the Mantel–Haenszel fixed-effects model. Quantitative analyses of outcomes were performed on an intention-to treat basis where possible, and results expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical heterogeneity was calculated as a χ^2 value with κ–1 degrees of freedom and significance at the 5% level.

Results

The search strategy identified a total of 359 titles. Of these, 112 titles appeared to meet the inclusion criteria and their full texts were examined. After further selection, 40 of the 112 papers were assessed independently by both authors (Figure 1). After discussion, a final selection of 16 papers was made[6,7,14,15,26-37] (Table 2). Writing to pharmaceutical companies identified no additional data that met the inclusion criteria. Of the 16 trials included, 12 had a Jadad score of three or more, with six of the studies scoring five. The four studies deemed to be of poor quality (i.e. a score of less than three) were either not double-blinded in design[28,29,34] or inappropriately blinded (comparing an ointment with a cream[35]). One study[36] had a score of three despite being single-blind because it adequately described its randomisation procedure. For 12 of the 16 studies, sufficient data were available to enable calculation of outcomes on an intention-to-treat basis. For the remaining four, data are presented here as completely as possible.[28,29,35,36]

Five studies commented on the extent of impetigo (mild, moderate or severe), either defining it in terms of the size of the affected area,[27,29] the number of lesions,[33] or not defining the term.[34,35] However, outcomes were not reported in relation to these categories. Two studies explicitly excluded patients with widespread disease.[6,7] Most of the studies excluded patients who were systemically unwell or who were taking topical or systemic antibiotics.

Topical treatment versus placebo

Three trials compared topical treatment with placebo.[7,31,37] The combined number of patients in the three trials with impetigo was 233 and most were children. One excluded patients with widespread lesions (covering more than 5% of the skin surface area).[7] Meta-analysis of these studies shows that topical treatment is more effective than placebo (OR = 2.69, 95% CI = 1.49 to 4.86). This equates to an absolute benefit increase of 0.20 or a number needed to

Table 1. Quality assessment of included studies.

Study	Randomisation (appropriate)	Double-blind (appropriate)	Withdrawals and dropouts	Total
Bass *et al* 1997[26]	1 (1)	1 (1)	1	5
Britton *et al* 1990[26]	1 (1)	1 (1)	1	5
Cassels-Brown 1981[28]	1 (0)	0 (0)	1	2
Dagan *et al* 1992[6]	1 (0)	1 (1)	1	4
Demidovich *et al* 1990[29]	1 (0)	0 (0)	1	2
Eells *et al* 1986[30]	1 (1)	1 (1)	1	5
Gilbert 1989[31]	1 (0)	1 (0)	1	3
Jaffe *et al* 1985[32]	1 (0)	1 (1)	1	4
Jaffe *et al* 1986[14]	1 (0)	1 (1)	1	4
Koning *et al* 2002[7]	1 (1)	1 (1)	1	5
Koranyi *et al* 1976[33]	1 (1)	1 (1)	1	5
Morley *et al* 1988[34]	1 (0)	0 (0)	1	2
Nolting 1988[15]	1 (1)	1 (1)	1	5
Sutton *et al* 1992[35]	1 (0)	1 (-1)	1	2
White *et al* 1989[36]	1 (1)	0 (0)	1	3
Zaynoun *et al* 1974[37]	1 (0)	1 (1)	1	4

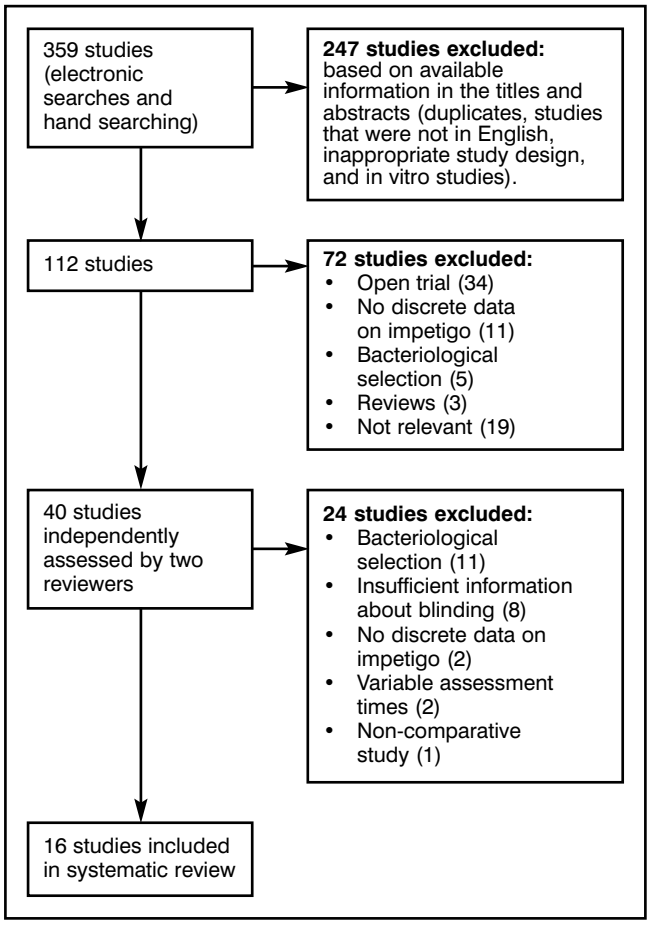

Figure 1. Flow diagram of study selection.

treat of five (Figure 2).

Topical versus systemic antibiotics

Four studies compared topical antibiotics with systemic antibiotics. One study concluded that oral antibiotics were significantly better than topical antibiotics[26] while another study, which specifically excluded patients with widespread lesions, came to the opposite conclusion.[6] The remaining two trials could not detect significant differences in effect between treatments.[27,33] Differences existed, both in terms of patient groups and interventions. Three studies compared oral erythromycin with topical antibiotics (mupirocin,[6,27] bacitracin[33]). There was no evidence of statistical heterogeneity (χ^2 = 4.59, df [degrees of freedom] = 2, P = 0.1). Meta-analysis favoured topical treatment and tended towards significance (OR = 0.48, 95% CI = 0.23 to 1.00) (Figure 3). Inclusion of the fourth study,[26] which compared cephalexin with mupirocin and bacitracin, resulted in significant statistical heterogeneity (χ^2 = 12.05, df = 3, P = 0.0072). Meta-analysis again favoured topical treatment (OR = 1.20, 95% CI = 0.64 to 2.26) but was not significant.

Mupirocin versus fusidic acid

The *BNF* advises use of mupirocin or fusidic acid as topical treatment for impetigo.[13] Of the four studies comparing these two treatments, one showed 100% cure or improvement in both groups[31] and one favoured fusidic acid,[34] while the other two favoured mupirocin[35,36] (with only one of these showing mupirocin to be significantly better than fusidic acid). The three studies that showed differences in treatment effects were all set in UK general practice. There was no strong evidence of statistical heterogeneity (χ^2 = 5.94, df = 2, P = 0.051) and meta-analysis shows no difference between the two treatments, (OR = 1.76, 95% CI = 0.77 to 4.03) (Figure 4).

Oral antibiotics

Two trials compared the effects of different oral antibiotics. One, comparing co-amoxiclav with cefaclor, included 36 patients aged between six months and 12 years with impetigo.[32] No difference between the two treatments was detected. The second study[29] compared penicillin, erythromycin, and cephalexin in children. It concluded that cephalexin was the most effective, with erythromycin almost as effective, but that penicillin was inadequate for treating impetigo.

Table 2. Description of included studies.

Author, year	Setting	Patients	Treatments	Duration of treatment	Time of assessment (measured from start of treatment)	Outcome
Topical versus oral treatment						
Bass *et al* 1997[26]	Paediatric clinic, USA	32 children	Cephalexin three times daily with topical placebo, mupirocin 2% three times daily with oral placebo, bacitracin 500 u/g three times daily with oral placebo	10 days	8–10 days	Cured, improved, failed according to lesion character and size
Britton *et al* 1990[27]	Hospital outpatient department, USA	54 children aged 2 months to 11 years	Erythromycin four times daily with topical placebo, mupirocin 2% three times daily with oral placebo	10 days	10 days	Complete resolution or clinical improvement to the point that further antibiotic therapy was not required
Dagan *et al* 1992[6]	Paediatric clinics, Israel	102 infants and children aged under 16 years	Erythromycin three times daily with topical placebo, mupirocin 2% three times daily with oral placebo	7 days	7–8 days	Cured or improved, worse
Koranyi *et al* 1976[33]	Paediatric outpatient clinic, USA	30 children aged 2 months to 15 years	Bacitracin ointment (500 u/g) four times daily with oral placebo, erythromycin four times daily with topical placebo	6 days	7 days	Responses grouped as excellent, satisfactory or failure
Topical versus topical treatment						
Cassels-Brown 1981[28]	General practice, UK	113 patients	Fucidin ointment, Cicatrin cream	Treatment continued until lesions had healed	7 days	Healed, improved, no change or worse
Gilbert 1989[31]	Dermatology clinic, Canada	70 patients (19 had impetigo)	Mupirocin 2% ointment three times daily, fusidic acid 2% ointment three times daily	7 days	8 days	Cure, improvement, failure (lack of improvement, or deterioration)
Jaffe *et al* 1986[14]	General practice, UK	119 patients aged 1-83 years (43 with impetigo)	Hydrocortisone 1%/potassium hydroxyquinoline sulphate 0.5% twice daily, hydrocortisone 1%/miconazole nitrate 2% twice daily	14 days	14 days	Cured, improved, same, worse
Morley *et al* 1988[34]	General practice, UK	354 patients (89 with impetigo)	Fusidic acid ointment 2% three times daily, mupirocin 2% three times daily	7 days	6–8 days	Satisfactory response (excellent or good), unsatisfactory (fair or poor)
Nolting *et al* 1988[15]	Unclear, Germany	80 patients (66 had impetigo)	Sulconazole nitrate 1% cream twice daily, miconazole nitrate 2% cream twice daily	14 days	14 days	Excellent, very good, good, fair, poor, none or worse
Sutton 1992[35]	General practice, UK	201 patients	Fusidic acid cream 2% three times daily, mupirocin ointment 2% three times daily	7 days	7 days	Cured or improved
White *et al* 1989[36]	General practice, UK	413 patients aged 11 months to 84 years (165 had impetigo)	Fusidic acid ointment 2% three times daily, mupirocin ointment 2% twice daily	7 days	10–11 days	Successful outcome (healed or improved), unchanged, worse or failed
Oral versus oral treatment						
Demidovich *et al* 1990[29]	Paediatric clinic, USA	75 children aged 5 months to 15 years	Penicillin V three times daily, cephalexin three times daily, erythromycin three times daily	10 days	8–10 days	Cured or improved, treatment failure

Table 2 continued over page

Table 2 (continued). Description of included studies.

Author, year	Setting	Patients	Treatments	Duration of treatment	Time of assessment (measured from start of treatment)	Outcome
Jaffe *et al* 1985[32]	Paediatric outpatient clinic, USA	43 children aged 6 months to 12 years (36 had impetigo)	Augmentin (amoxicillin 125mg and clavulanic acid 30 mg per 5 ml) three times daily, cefaclor three times daily	10 days	9–11 days	Cure, fail
Topical treatment versus placebo (vehicle)						
Eells *et al* 1986[30]	Unclear, Puerto Rico	52 children aged 7 months to 13 years (50 patients had impetigo, 2 had ecthyma)	Mupirocin 2% three times daily, placebo three times daily	7–9 days (up to 12 days if unable to attend follow-up at 7–9 days	7–9 days (up to 12 days if unable to attend follow-up at 7–9 days	Cured, improved, failed, unevaluable (e.g. if lost to follow-up, assessed too late to be included)
Koning *et al* 2002[7]	General practice, the Netherlands	160 children aged 0–12 years	Fusidic acid cream 2% three times daily, placebo cream three times daily. (Both groups washed lesions with povidone-iodine shampoo, 75 mg/ml twice daily)	14 days	7 days	Cure, improvement, failure
Zaynoun 1974[37]	Hospital outpatient department, Lebanon	46 patients aged 4 months to 65 years (mostly children) (23 had impetigo)	Gentamicin 0.1% cream twice daily, placebo twice daily	7 days	7 days	Excellent (complete cure), moderate (improved), poor (minimal or no improvement)

Discussion

This systematic review demonstrates that topical antibiotics are more effective than placebo in achieving clinical improvement or resolution of impetigo at seven to 12 days. Topical antibiotics may also be more effective than some oral antibiotics, though the evidence for this is weak. This could have implications for practice, as topical antibiotics are likely to have a better systemic side-effect profile than oral antibiotics [38] and may achieve better compliance with treatment. The greater effectiveness of topical therapy in skin conditions in general is plausible, and there is evidence from *in vivo* animal[39] and human[40] studies that drug concentrations at the site of disease are higher than with systemic drug administration. There is a lack of information on the effectiveness of oral antibiotics in general, and flucloxacillin in particular. The most commonly studied topical antibiotics are mupirocin and fusidic acid and meta-analysis shows that there is no difference between them. Treatment duration of seven days appears to be effective for impetigo. The studies in this review were selected because inclusion was based on clinical diagnosis, making its findings directly applicable to routine clinical practice.

There is a lack of high quality evidence on the most effective treatment of impetigo. Of the 359 studies identified, only 16 were included in the final review. Many were rejected during the initial stages because of lack of randomisation, blinding, and comparative groups. Most of the studies were small (nine studies had fewer than 100 patients) and not all patients included had impetigo. The largest study had 201 patients with impetigo.[35] Topical treatment appears to be effective in comparison with placebo. There were no trials of oral antibiotic against placebo that fulfilled the inclusion criteria. Some studies assessing the benefits of non-antibiotic treatments, such as disinfectant soaps, were identified, but again these did not fulfill the criteria for inclusion.

Limitations of this review

Clinical heterogeneity between studies made meta-analysis difficult. There was variation in how cure of impetigo was reported and in the advice given to patients on preparation of skin before treatment (for example, advice to remove crusts, wash with soap or disinfectant). Some studies did not describe the extent of impetigo, though the exclusion of patients who were taking, or had recently taken, systemic antibiotics might mean that less widespread disease was being studied. The review was not designed to look at the side effects of treatments or to examine the effects of antibiotic treatment on bacterial resistance. Studies that were not in English were excluded and as a result some important findings may have been missed, though there is some evidence to suggest that studies not in English contribute small numbers to the totals and this has little effect on treatment estimates.[41] In this case, the meta-analyses involve small numbers and their inclusion may have influenced the results. Only one study not in English[42] was included in a previously published review,[43] suggesting that its inclusion here would not have greatly influenced the results.

One of the problems identified by this and other system-

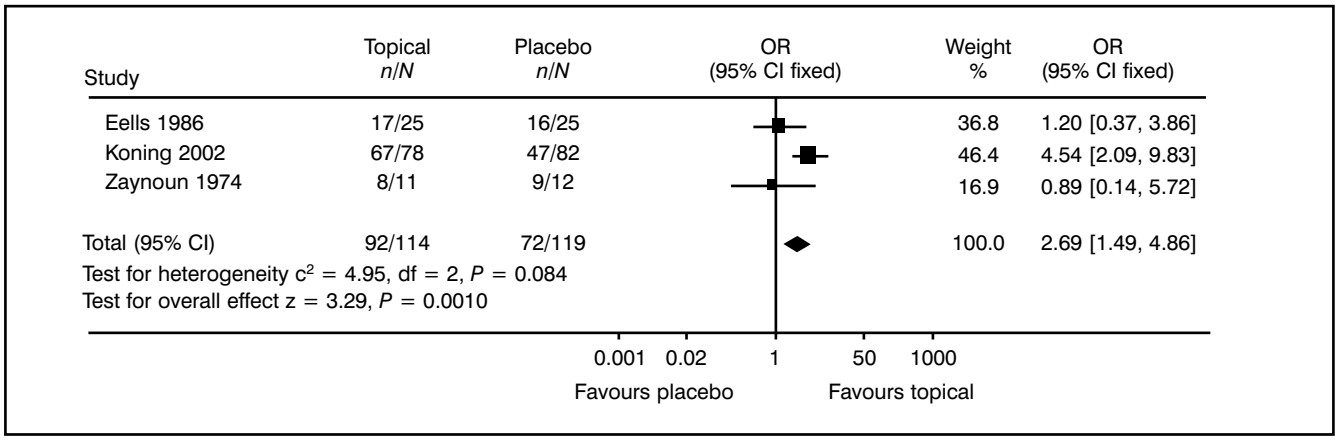

Figure 2. Topical treatment versus placebo (vehicle). Outcome = cure or improvement at 7–12 days.

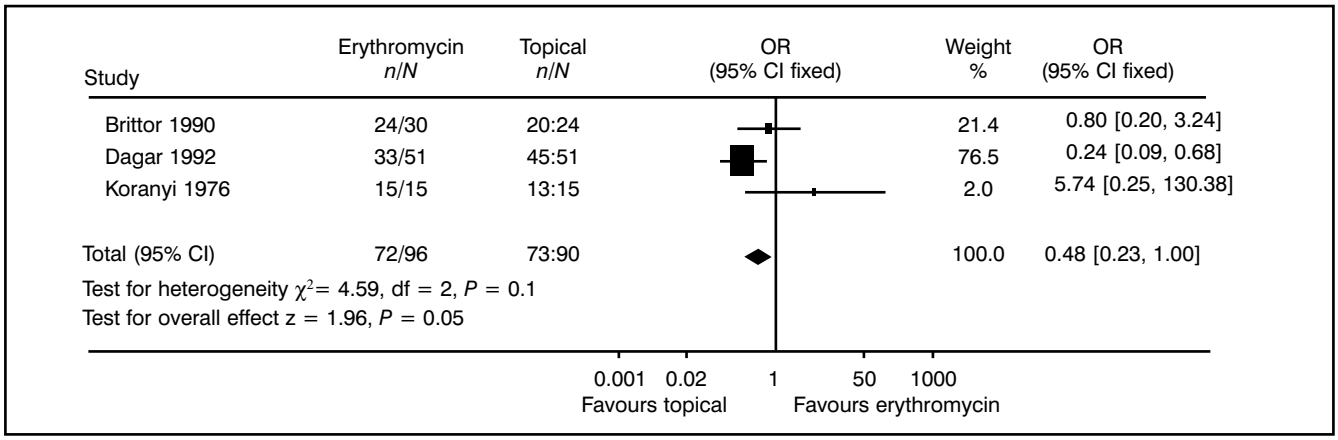

Figure 3. Erythromycin versus topical treatment. Outcome = cure or improvement at 7–10 days.

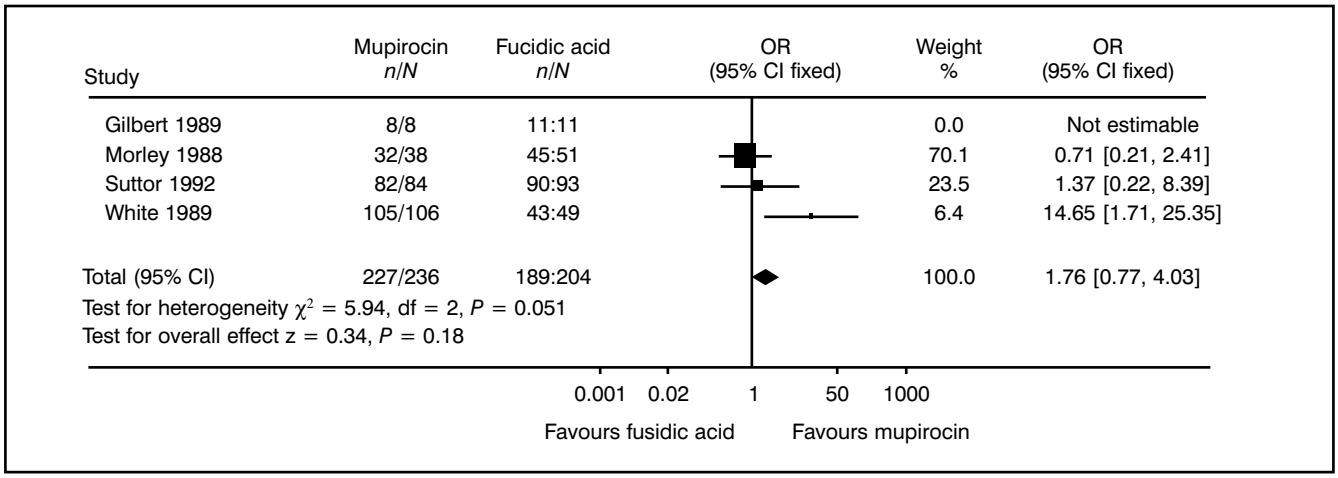

Figure 4. Mupirocin versus fusidic acid. Outcome = cure or improvement at 7–11 days.

atic reviews is the difficulty in assessing the quality of studies. Several assessment scales have been devised; each with its limitations. That described by Jadad[24] is a widely used scale and can be applied to different settings. It focuses on three dimensions of internal validity — randomisation, blinding, and withdrawals. One criticism is that it gives more weight to the quality of reporting rather than to actual methodological quality[44] and studies may be graded inaccurately as a result. Though some studies scored highly on the Jadad scale, the overall quality of the majority of research identified was poor.

Previous work

One systematic review has previously been published in a Dutch language primary care journal.[43] This review contained 21 studies and included studies that selected patients on the basis of positive bacteriology. It also included studies

that did not specify a time limit on the treatment or specify the timing of the assessment of treatment effects. This makes its findings less applicable to routine clinical practice.

Implications for practice

Topical treatment for localised impetigo appears to be effective and there is little difference between the two most commonly used treatments. None of the studies identified in this review specifically evaluated the treatment of widespread impetigo, either as a primary objective or in subgroup analysis. The *BNF*[13] and others advocate treatment with oral antibiotics for widespread impetigo, though the term 'widespread' is not defined. In practice, limited disease is usually defined as a small number of lesions confined to a single anatomical area and widespread disease is anything else. There is a marked lack of evidence about the relative efficacy of flucloxacillin and it is therefore not possible to say whether this oral treatment is better or worse than topical treatment. There remains uncertainty about the effectiveness of non-antibiotic therapies and, though it may present methodological difficulties, further work in this area merits attention from researchers. Given the lack of evidence for the use of flucloxacillin, comparative studies of this and other oral antibiotics are also required.

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