2. Fusidic acid in skin and soft-tissue infections

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Topical antibacterial therapy is an important component in managing skin and soft-tissue infections (SSTIs). Fusidic acid, a narrow-spectrum antibiotic active against Staphylococcus aureus, has shown good skin permeability and low allergenic potential. The resistance rate in S. aureus remains low, as shown in a study of Canadian hospitals from 1999 to 2005. In treating primary skin infections, including impetigo, fusidic acid cream and ointment provided similar response rates and equal/better tolerability compared with other topical and oral antibiotics. Fusidic acid and mupirocin are equally or more efficacious than oral treatment in localized impetigo, and may be similarly efficacious in extensive impetigo, according to a recent Cochrane review. In clinical practice, mupirocin is often reserved for methicillin-resistant S. aureus infections. Studies of oral fusidic acid forms in SSTI have shown that: tablets are as effective as comparator antibiotics; they have fewer side-effects; a suspension achieves high cure rates, and is suitable for paediatric use. Fusidic acid, both topical and systemic, is an effective treatment for SSTI with few adverse reactions.

INTRODUCTION

Superficial skin and soft tissue infections (SSTIs) are common presentations in clinical practice. These may manifest either as primary infections or as secondary to some other cutaneous problem. Primary SSTIs, such as impetigo contagiosa, bullous impetigo, folliculitis, furuncles, carbuncles and cellulitis, are frequent occurrences, in addition to secondary SSTIs, for example, secondarily infected wounds or secondarily infected dermatoses of different types such as atopic dermatitis, contact dermatitis, prurigo and neurodermatitis.

The majority of primary and secondary skin infections are caused by either *S. aureus* or *Streptococcus pyogenes*. Primary skin infections caused by Gram-negative organisms are infrequent but may occur in patients who are immunocompromised or diabetic. Chronic wound infections are more likely to be colonized by Gram-negative organisms, although initial colonization is usually by Gram-positive organisms.

Topical antibacterial therapy is an important component of therapeutic management. There are various classes of topical antibacterial therapy, both antibiotic and non-antibiotic, which may have beneficial results on the overall therapeutic outcome. Culture should ideally be carried out and a microbiological diagnosis obtained before instituting any form of therapy, but this may not be possible in a given clinical situation. Antibiotic treatment may subsequently require modification once the culture results become available.

Topical antibacterials have a distinct advantage over systemic agents, in that they can be applied to the affected area and therefore high local concentrations of the agent may be achieved. With selection of the appropriate agent, interaction with normal flora can be avoided. The ideal topical antibiotic should:

- have a selective effect on one (or at least very few) organisms of the same class, therefore minimizing the development of cross-resistance to other organisms;
- not cause allergic reactions or potential cross-allergic reactions with other medications of the same class or individual components of these, such as preservatives;
- be safe, efficacious and ideally penetrate the skin in sufficiently high concentrations to kill bacteria efficiently;
- be available in different formulations in order to meet patients' preferences and needs, as this will increase compliance with treatment and thus improve therapeutic outcomes.

The obvious limitation to topical antibacterial therapy is that the infections must be limited or localized in area and must, for the most part, be superficial.

Classes of topical antibiotics used for superficial SSTIs are shown in Table I. Fusidic acid is an antibiotic that has all of the features listed above for an ideal topical antibacterial treatment. This article reviews the clinical evidence on the efficacy and safety of fusidic acid in primary skin infections. A review of the use of fusidic acid in secondary skin infections appears elsewhere in this supplement (1).

Table I. *Examples of topical antibiotics commonly used for superficial skin and soft tissue infections*

Generic name	Class	Mechanism of action
Fusidic acid	Fusidanes	Inhibits protein synthesis
Mupirocin	Unique	Inhibits protein synthesis
Neomycin	Aminoglycoside	Inhibits protein synthesis
Gentamicin	Aminoglycoside	Inhibits protein synthesis
Bacitracin	Cyclic polypeptide	Inhibits cell wall synthesis
Polymyxin B	Cyclic lipopeptide	Increases cell membrane permeability
Sulfacetamide sodium	Sulfonamide	Inhibits folic acid synthesis
Silver sulfadiazine	Sulfonamide	Inhibits folic acid synthesis Silver – inhibits cell wall synthesis
Erythromycin	Macrolide	Inhibits protein synthesis
Clindamycin	Lincosamide	Inhibits protein synthesis
Retapamulin	Pleuromutilin	Inhibits protein synthesis

WHY USE FUSIDIC ACID?

Fusidic acid is available in different topical formulations: fusidic acid (Fucidin® cream; LEO Pharma A/S, Ballerup, Denmark) and sodium fusidate (Fucidin® ointment; LEO Pharma A/S). There are also oral formulations in the form of tablets and a suspension. Following absorption, fusidic acid and sodium fusidate ionize into the same molecule, fusidate; thus, in this article the term fusidic acid will be used to refer to the therapeutic agents in all Fucidin® formulations. Combinations of fusidic acid with corticosteroids are covered elsewhere in this supplement (1).

Fusidic acid has a steroid-like structure but no steroid side-effects (2). In topical form, its penetration is time-related and is comparable to glucocorticoids in diseased skin (3, 4). The normal skin horny layer offers marked resistance to outside agents unless it is damaged or removed, but fusidic acid does still penetrate intact skin to some extent (3, 5). Because of its significant absorption qualities, topical administration of fusidic acid results in much higher local concentrations than can be achieved with systemic administration, even at deeper layers of the epidermis or dermis (6). It is indicated for use in the treatment of mild to moderately severe primary and secondary skin infections caused by sensitive strains of *S. aureus,* Streptococcus species and *Corynebacterium minutissimum*. Fusidic acid has some activity against other corynebacteria and strains of *Clostridium*. It is virtually inactive against Gram-negative bacteria because of a difference in cell wall permeability; however, it has demonstrated good *in vitro* activity against strains of *Neisseria* and *Bacteroides*.

Policies designed to limit the development of antibiotic resistance recommend that, in any therapeutic situation, the optimal antibiotic with the narrowest spectrum should be used. As fusidic acid targets the common pathogens in skin infection, a broader-spectrum antibiotic should not be necessary. This therefore limits the development of antibiotic resistance, cross-resistance and cross-allergic reactions with other medications.

Clinical disease states that would be expected to respond to the topical use of fusidic acid are impetigo contagiosa, bullous impetigo, folliculitis, sycosis barbae, furuncles, carbuncles, ecthyma, acute paronychia, erythrasma, infected wound and burns, and secondarily infected dermatoses such as eczema.

CLINICAL STUDIES ON TOPICAL FUSIDIC ACID

A number of studies have examined the use of fusidic acid cream and ointment in the treatment of superficial skin infections (Table II) (7–19). These studies varied in design with regard to randomization, blinding and use of comparator. Nearly all studies included children. These will be looked at with respect to speed of action, efficacy, safety and outcome compared with other topical therapies and systemic antibiotics in various disease states.

Comparison of fusidic acid cream and ointment

Two studies have compared fusidic acid cream and ointment (Table II) (7–8). In a study by Pakrooh (7), the use of these 2 formulations was compared in 101 patients with SSTI, specifically abscess/boil, paronychia and infected wounds. Each preparation was applied 2 or 3 times a day or once daily if a dressing was applied. *S. aureus* was the most frequently isolated pathogen. Both preparations were effective treatments, with mean healing times being similar: 7.7 days for the ointment and 7.9 days for the cream. Both preparations were well tolerated and there were no complaints of side-effects.

A larger multicentre study by Baldwin & Cranfield (8), involving 487 patients with skin infections (abscess/boil, impetigo, paronychia, wounds and burns), compared the use of these 2 formulations applied 3 times daily or once daily with a dressing. An excellent or good response to treatment was observed in over 90% of patients, with mean healing times of 7.1 days for patients treated with the ointment and 7.7 days for those using the cream. Both preparations were well tolerated: only one patient complained of a mild skin reaction with the ointment, which was not severe enough to discontinue treatment. Subsequent treatment with fusidic acid cream elicited no reaction.

Skin infections

Further studies using either fusidic acid cream or ointment have shown that there is fast and effective healing of SSTIs (Table II) (9–14). Studies in mainly primary skin infections, such as impetigo, abscesses/boils, folliculitis and paronychia, and including a few cases of infected wounds and other secondary infections (9, 10, 12–14), have demonstrated response rates of between 86% and 100%, with treatment duration or mean healing time varying between 4 and 7.1 days. Adverse events have been infrequent, with most related to application site irritation.

A study by Pakrooh (10) examined the clinical efficacy of topical fusidic acid ointment applied once daily compared with that of 3 oral antibiotics given for 5 days: 150 mg clindamycin, 250 mg flucloxacillin or 250 mg of erythromycin 4 times daily plus placebo ointment. A total of 90 patients suffering from SSTIs, including infected wounds, paronychia and abscesses/boils, were included. The mean healing time in patients receiving oral antibiotics was grouped and compared with that in patients using fusidic acid ointment. A significantly more rapid healing time in soft tissue infections was

Table II. *Studies of topical fusidic acid in skin infections in general, and impetigo. The studies shown under "Skin infections" were mainly of primary skin infections (including impetigo), but some infected wounds and other secondary infections were included*

Reference	Fucidin® formulation		Comparator	
	n	Response rate[a] (%) Mean healing time or treatment duration (days)	*n*	Response rate[a] (%) Mean healing time or treatment duration (days)
Skin infections				
Pakrooh, 1980 (7)	Ointment *n*=51	91% 7.7	Fusidic acid cream *n*=50	98% 7.9
Baldwin & Cranfield, 1981 (8)	Ointment *n*=249	90% 7.1	Fusidic acid cream *n*=238	92% 7.7
Jackson et al., 1966 (9)	Ointment *n*=101	93% 6.8	Oral/i.m. penicillin *n*=58	96% (oral), 94% (i.m.) 5.3 (oral) 4.9 (i.m.)
Pakrooh, 1977 (10)	Ointment *n*=49	100% 7.1	Oral antibiotics[b] *n*=41	83% 9.7
Zelvelder, 1984 (11)	Ointment *n*=30	NR 4–7[d]	Oral amoxicillin *n*=30	NR 4–7[d]
Morley & Munot, 1988 (12)	Ointment *n*=191	86% 7[e]	Mupirocin *n*=163	86% 7[e]
Langdon & Mahapatra, 1990 (13)	Cream *n*=104	95% 7[e]	Mupirocin *n*=102	98% 7[e]
Jasuja et al., 2001 (14)	Ointment *n*=50	84% 7[e]	Mupirocin *n*=50	90% 7[e]
Impetigo				
Jackson et al., 1966 (9)	Ointment *n*=32	100% 5.9	None	–
Cassels-Brown, 1981 (15)	Ointment *n*=52	100% 7[e]	Neomycin/bacitracin *n*=58	90% 7[e]
Morley & Munot, 1988 (12)	Cream *n*=51	88% 7[e]	Mupirocin *n*=38	84% 7[e]
Sutton, 1992 (16)	Ointment *n*=93	97% 7[e]	Mupirocin *n*=84	98% 7[e]
Christensen & Anehus, 1994 (17)	Cream *n*=128	82% Up to 3 weeks[e]	Hydrogen peroxide cream *n*=128	72% Up to 3 weeks[e]
Koning et al., 2002 (18)	Cream + povidone-iodine *n*=78	87% 7	Placebo cream + povidone-iodine *n*=82	59% 7
Oranje et al., 2007 (19)	Ointment *n*=172	90% 7	Retapamulin *n*=345	95% 5

[a]As defined in each study, to include cure or cure/improvement.
[b]Clindamycin, erythromycin, or flucloxacillin.
[c]Study included a fusidic acid/amoxicillin combination arm, not reported here.
[d]Reported time to improvement or healing.
[e]Duration of treatment (healing time not stated).
i.m.: intramuscular; NR: overall rate not reported.

shown for fusidic acid ointment compared with the oral antibiotics (7.1 days vs. 9.7 days; $p < 0.0002$). There were no adverse events in the fusidic acid ointment treatment group, whereas gastrointestinal events were reported in the oral antibiotic group.

A double-blind 3-arm comparative study by Zelvelder (11) compared the effects of fusidic acid ointment plus placebo amoxicillin, placebo fusidic acid ointment plus amoxicillin, or fusidic acid ointment plus amoxicillin in 90 patients in the treatment of furuncles, carbuncles, impetigo and infected wounds. Fusidic acid ointment was as effective as amoxicillin, and there was no further improvement in clinical outcome when the treatments were used in combination.

Fusidic acid ointment is as effective as mupirocin ointment but has superior patient acceptability. In a study by Morley & Munot (12), 354 patients with primary or secondary skin infections were randomized to receive either medication 3 times daily for up to 7 days. There was no difference between the two preparations in outcome in either primary or secondary infections. However, adverse events were reported in 1.0% of the fusidic acid ointment group, compared with 7.4% of those using mupirocin ointment. The greasy, messy or sticky nature of mupirocin ointment accounted for the majority of complaints. A study by Langdon & Mahapatra (13) obtained similar results, while comparing fusidic acid cream and mupirocin ointment.

Impetigo

Impetigo, a contagious superficial bacterial infection frequently seen in children, is one of the most common conditions for which the use of topical fusidic acid is appropriate. Impetigo may be primary, with direct bacterial invasion of normal skin, or secondary to another skin condition such as atopic dermatitis, insect bites or scabies. Non-bullous impetigo is the most common form of impetigo and is typically caused by *S. aureus* but occasionally by *Streptococcus pyogenes* or a combination of both. Bullous impetigo is always caused by *S. aureus*. Complications of impetigo are generally rare, but local and systemic spread can occur, resulting in cellulitis, lymphangitis or septicaemia, and non-infectious complications of *S. pyogenes* include guttate psoriasis, scarlet fever and glomerulonephritis. The natural history of impetigo is not well documented. It is thought that spontaneous resolution may occur in a few weeks but that treatment will hasten recovery.

Studies of the use of topical fusidic acid specifically in impetigo (or subgroups of patients with impetigo from larger studies) are shown in Table II (9, 12, 15–19). A study by Koning et al. in 2002 (18) examined the effect of twice-daily povidone-iodine shampoo with either fusidic acid cream or placebo cream applied 3 times daily for up to 14 days in the treatment of impetigo. Treatment with fusidic acid cream plus povidone-iodine shampoo was found to be more effective than the placebo cream/povidone-iodine combination, with the size of the affected area in the placebo group actually increasing in size after one week of treatment. Interestingly, at treatment week 2, the percentage reduction in size was 90% for the fusidic acid group and 38% for the placebo combination group. However, at follow-up at week 4, the percentage reduction was comparable for both groups, 99% for the fusidic acid group and 95% for the placebo group, probably representing the natural course of resolution of the disease.

A recent Cochrane Review on interventions for impetigo examined 57 trials, including 3533 participants in total, studying 20 different oral and 18 different topical treatments (20). The reviewers conclude that data on the natural course of the disease are lacking. Cure rates for placebo creams range from 8% to 42% at 7–10 days. Topical antibiotics showed better cure rates than placebo (pooled odds ratio (OR) 6.49, 95% confidence interval (CI) 3.93–10.73). There was no clearly superior topical antibiotic. Fusidic acid and mupirocin are of similar efficacy (OR of mupirocin vs. fusidic acid 1.76, 95% CI 0.69–2.16). According to the review, there is good evidence that topical fusidic acid and mupirocin are equally or more efficacious than oral treatment for patients with localized disease, and it could not be demonstrated that therapy with oral antibiotics was su-

perior to topical antibiotics for extensive impetigo (20). In fact, in clinical practice, mupirocin is often reserved for methicillin-resistant *S. aureus* (MRSA) infections.

Topical retapamulin ointment is the first drug product approved for human use in the class of antibacterials called pleuromutilins. A recent study by Chosidow et al. (19) compared retapamulin ointment twice a day for 5 days with fusidic acid 3 times a day for 7 days in a randomized phase III trial on the treatment of impetigo (21). The clinical success rates were comparable and retapamulin was well tolerated, although more patients reported adverse events with retapamulin (e.g. application site irritation was reported in 2% of patients using retapamulin); adverse events were virtually non-existent with fusidic acid. Retapamulin is not approved for use in infections due to MRSA (21).

Erythrasma

Fusidic acid is also highly effective against *Corynebacterium minutissimum*. A double-blind comparative 3-arm parallel group study of 186 patients by Hamann & Thorn (22) compared the clinical efficacy of systemic erythromycin (500 mg twice daily) and placebo cream, topical fusidic acid cream (applied twice daily) plus placebo tablets, or placebo cream plus placebo tablets in the treatment of erythrasma over a 14-day period. Fusidic acid cream was as effective as the oral antibiotic. However, there were significantly fewer side-effects with fusidic acid cream (one event) compared with systemic erythromycin (8 events, 6 of which were gastrointestinal).

RESISTANCE

A disadvantage of using topical antibiotics is the possible development of bacterial resistance. The problem of resistance to fusidic acid appears still to be limited. In 2006, a study by Rennie (23) examined susceptibility tests of fusidic acid against a sampling of Canadian hospital-based isolates from samples collected every 6 months from March 1999 to September 2005. Of the 2302 *S. aureus* strains tested, 65 (2.8%) were resistant to fusidic acid; 240 (10.4%) were methicillin-resistant (MRSA), of which 10 (4.2%) were resistant to fusidic acid. There was no trend to increasing resistance over this time period. The author concludes that the resistance rate to fusidic acid in *S. aureus* remains low, despite the fact that fusidic acid is the most prescribed topical antibiotic in Canada.

Resistance to mupirocin has proven to be more of a problem, with rates of over 20% reported in some countries (24, 25). There have been recommendations that mupirocin should be used judicially, given its importance in MRSA eradication programmes (25–27).

ALLERGENIC POTENTIAL

A further potential disadvantage of the use of topical antibiotics is the development of hypersensitivity or allergic contact dermatitis to a component of the formulation. This is more common with certain antibiotics such as gentamicin, bacitracin and neomycin. Adverse events with topical antibiotics are frequently irritant in nature, with complaints of burning or stinging.

In 2002, a study by Morris et al. (28) involved patch testing 1119 patients over 1 year to neomycin, clioquinol and fusidic acid. Positive patch test reactions to neomycin were recorded in 40 patients (3.6%), to clioquinol in 8 patients (0.7%) and to fusidic acid in 3 patients (0.3%). The authors also reviewed positive patch test reactions to fusidic acid over a 20-year period, and found that the frequency of allergic reactions to fusidic acid had decreased since the early 1980s, despite increasing use. Recently, the prevalence of positive reactions to patch tests in the general German population was estimated as 2.2% for neomycin, 3.2% for gentamicin and 0.8% for fusidic acid, based on data from a network of allergy departments (29). Post-marketing safety surveillance has shown a low rate of spontaneous reporting of adverse events for fusidic acid (30). The majority of reported events are similar to those noted in clinical studies: mild localized skin reactions at the site of application. Only 34 reports of allergic reactions have been received after up to 40 years of clinical use. Worldwide experience has shown that there is no significant difference in the safety of fusidic acid cream compared with the ointment.

SYSTEMIC ANTIBIOTIC TREATMENT

Systemic antibiotic treatment of SSTI is normally reserved for those patients having more extensive disease, deeper infections, with evidence of systemic spread of infection or septicaemia, or those who are immunocompromised or have ophthalmic-orbital or intranasal disease.

There are two oral forms of fusidic acid: a tablet (250 mg) and a suspension formula (50 mg/ml). The accumulation of systemic antibiotic in skin crust or avascular tissue may prevent bacterial invasion; orally administered fusidic acid has been shown to achieve concentrations in skin blister fluid that are above the minimal inhibitory concentration (MIC) of both staphylococci and streptococci (31). For an antibiotic to be effective, it must also have adequate tissue penetration and interstitial concentrations higher than MIC_{90} for the offending organism. In a recent study, concentrations of oxacillin, fusidic acid (given as fusidic acid tablets) and pristinamycin were measured in suction blisters in healthy volunteers at day 5 of a 6-day cycle of antibiotic therapy (32). After a rest period, this was repeated twice so that all volunteers had received each antibiotic. The mean antibiotic concentration in interstitial fluid was highest for fusidic acid, with C_{max} values much greater than the MIC_{90} of *S. aureus*, indicating that fusidic acid tablets would potentially be more active than the comparator antibiotics against all staphylococci.

A randomized double-blind study by Carr et al. (33) using 3 doses of fusidic acid tablets (500 mg 3 times a day, 500 mg twice a day and 250 mg twice a day) demonstrated that a dose of 250 mg twice a day was sufficient to improve and cure SSTI, and there was no significant difference in improvement with higher dosing. Furthermore, an obvious advantage of the lower dose was the occurrence of fewer gastrointestinal side-effects.

Another randomized double-blind trial by Nordin & Mobacken (34) compared the efficacy of 2 fusidic acid regimens (250 mg and 500 mg both twice a day) with flucloxacillin (500 mg 3 times a day) in 532 patients. Patients with SSTIs such as abscesses/furuncles, acute paronychia and superficial wound infections were included and were given an initial 5 days therapy followed by an additional 5 days if necessary. Significantly more patients were cured at the end of 5 days with fusidic acid 250 mg twice a day (32.2%) compared with flucloxacillin (21.1%, $p < 0.05$), but all 3 regimens had high comparable cure rates by the end of treatment. Side-effects were significantly less in the fusidic acid 250 mg group, the most common adverse event being diarrhoea.

Other studies comparing fusidic acid with pristinamycin (35), ciprofloxacin (36), flucloxacillin (37), or erythromycin (38) have all shown equal efficacy for fusidic acid, with comparable or fewer side-effects.

The suspension formulation of fusidic acid is particularly suitable for paediatric use. Two regimens of the suspension, 20 mg/kg/day twice a day vs. 50 mg/kg/day 3 times a day, were compared in 411 children aged 1–12 years with SSTI (39). Patients were treated for 5 days and for a further 5 days if the condition remained uncured. At the end of treatment, 91% of the 20 mg group and 89% of the 50 mg group were cured. Bacteriological cure, with elimination of fusidic acid-susceptible *S. aureus* and/or beta-haemolytic streptococci, was achieved in 100% and 99% of children, respectively. The lower-dose regimen had significantly better tolerability ($p = 0.025$), due to fewer gastrointestinal side-effects.

CONCLUSION

It has been well established that topical antibiotics are extremely important in the management of SSTIs, most of which are due to *S. aureus* and *Streptococcus* species. Fusidic acid (in both topical and systemic forms) has been demonstrated to be an effective treatment with a low incidence of adverse reactions when studied alone or in comparison with other topical and systemic antibacterial therapies.

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DISCUSSION

Q: Is it beneficial to combine oral and topical therapy, or two different antibiotics?

Long: No. Clearly if there is evidence of systemic infection, or if the person is developing septicaemia, a systemic antibiotic should be used. But the studies of topical fusidic acid have shown that it works well in mild-to-moderate infections and even in some severe infections. As mentioned earlier, fusidic acid penetrates the skin very well and achieves high local concentrations – greater concentrations than those achieved with systemic antibiotics. This is an advantage of topical agents. I would only use a systemic antibiotic if there is evidence of systemic or severe infection.