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Current options for the treatment of impetigo in children

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Impetigo contagiosa is a common, superficial, bacterial infection of the skin characterised by an inflamed and infected epidermis caused by *Staphylococcus aureus, Streptococcus pyogenes* or both. The less common bullous impetigo is characterised by fragile fluid-filled vesicles and flaccid blisters, and is invariably caused by pathogenic strains of *S. aureus*. In bullous impetigo, exfoliative toxins are produced, although these are restricted to the area of infection and bacteria can be cultured from the blister contents. In the rare variant, staphylococcal scalded skin syndrome, the exfoliative toxins are spread haematogenously from a localised source causing widespread epidermal damage at distant sites.

Keywords: fusidic acid, impetigo, mupirocin, *Staphylococcus aureus*

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1. Introductory overview of the disease

Cutaneous staphylococcal and streptococcal infections are important and common in children. They cause a wide spectrum of illness depending on the location of infection, organism type and host immunity.

Impetigo is a superficial bacterial infection of the skin characterised by a localised, inflamed and infected epidermis with golden coloured crusts. It is the third most common skin disease in children, after eczema and viral warts, with peak incidence at 2 – 6 years of age [1]. Lesions are highly contagious and can spread rapidly. Nasal carriage of organisms may predispose the patient to recurrent infection.

Impetigo can occur either as a primary infection of previously normal skin or secondary to another disease, such as eczema or scabies, which has disrupted the skin barrier.

There are two main clinical forms of impetigo. Impetigo contagiosa is the more common crusted form and is caused by staphylococci, streptococci or by both together. This is clinically distinguishable from bullous impetigo (BI), which is characterised by fragile, fluid-filled vesicles and blisters (bullae), and is invariably caused by pathogenic strains of *Staphylococcus aureus*. Both are highly contagious.

BI represents the mild end of a spectrum of blistering skin diseases due to a toxin produced by *S. aureus* that, at the other extreme, is represented by the widespread painful blistering and superficial denudation characteristic of staphylococcal scalded skin syndrome (SSSS).

2. Pathophysiology

Staphylococcal infections are one of the most important and common clinical problems in both paediatric and adult dermatology. These infections cause a remarkable spectrum of illness in children depending on the bacterial strain involved, the location of the infection and prevailing host immunity [2].

The normal human skin is colonised in early life by a number of bacteria that live commensally on the skin and its appendages. *S. aureus* is part of this flora. Carriage may be intermittent and transient with 30 – 50% of healthy adults harbouring the organism at any given time [3]. Up to 84% of individuals have nasal *S. aureus* that is

detectable in the anterior nares [4]. Staphylococcal nasal carriage appears to predispose patients to the development of impetigo [5].

Patients with atopic dermatitis, diabetes mellitus, on dialysis and intravenous drug abusers are predisposed to *S. aureus* carriage. Pathological reactions (the staphylococcal pyodermas) may occur when nasally carried *S. aureus* is transferred onto the skin and enters via breaks in the epidermis to cause superficial infections [3].

The pathogenesis of impetigo involves the interaction of bacterial virulence factors with host immune factors.

Bacterial virulence factors include a number of different enzymes produced by the bacterium. The most important of these enzymes are catalases and hyaluronidase. Catalases affect phagocytosis by interfering with host peroxide metabolism. Hyaluronidase destroys host tissue and promotes bacterial spread. Additional exoproducts known as exfoliative toxins (ETs) cause generalised disease when disseminated through the blood from localised foci of infection.

Host immune factors include atopy, immunosuppression and diabetes. A postulated deficiency in the expression of cutaneous antimicrobial peptides in patients with atopic dermatitis may predispose them to this susceptibility of skin infection with *S. aureus* [6]. BI occurs more commonly in infants and neonates because of both a lack of specific immunity to ETs produced by the infection, and insufficient renal function to adequately clear them. This leads to a higher risk of developing the disease [7].

In BI and SSSS two distinct ETs, ET-A and ET-B, are responsible for epidermolysis. ET-A acts as a trypsin-like serine protease and produces skin separation by specifically cleaving desmoglein 1 [8], a protein involved in the integrity of the upper epidermis. This leads to splitting through the epidermal granular cell layer [9] and the separation of this layer from the underlying epidermis.

In addition, both ET-A and ET-B stimulate T cell proliferation. They may act as superantigens with the unique ability to activate a specific subgroup of V-β bearing T cells [10]. ETs may also elicit an immune response by producing neutralising antibodies. The postulated super antigenic activity of ETs is distinct from their ability to cause exfoliation.

Minor skin infections with ET-producing strains may cause SSSS in infants who lack ET immunity. However, adults and older children with ET immunity usually develop only localised BI when infected with the same bacterial strain.

2.1 Impetigo contagiosa

Although staphylococcal toxins, especially ET-A, are known mediators of BI in children, it was not previously clear whether this was also true for the non-bullous impetigo contagiosa. A study from The Netherlands [5] found that, in wound and nasal swabs from children with impetigo contagiosa, the *S. aureus* strains isolated harboured the ET-B gene (*ETB*) as a specific virulence factor. Interestingly both the number and size of lesion were increased in patients infected with an *ETB*-positive strain. This suggests that a combination of staphylococcal virulence and resistance genes, rather than a single gene, determines the development and course of non-bullous impetigo contagiosa.

2.2 Bullous impetigo

BI represents a localised version of the SSSS with splitting or lysis of the upper epidermis. It is caused by phage group II *S. aureus*, particularly strains 55 and 71, in virtually all cases. In BI, the ETs are localised to the area of infection and, in contrast to the generalised flaccid blisters and erosions in SSSS, bacteria can be cultured from the blister contents.

Minor skin trauma, including scratches or insect bites, is usually an important antecedent for the development of impetigo. Infected children may be the reservoir for their own infection. Nasal or throat *S. aureus* colonisation rates of 51% have been reported in normal individuals with 79% of cultures growing the same strain from both skin and nasal/throat sites [11].

3. Epidemiology

Impetigo contagiosa has a peak incidence at 3 – 6 years of age whereas BI occurs more commonly in children < 5 years of age and particularly in neonates. Lesions are highly contagious and spread rapidly through a family, nursery or school class [12]. Impetigo is more common in tropical climates and under conditions of crowding and poor hygiene. Organisms are spread by direct contact [13] and often by medical personnel or carers [14].

4. Clinical features

4.1 Impetigo contagiosa

Impetigo contagiosa is the most common form. Lesions begin as small red macules, which develop into transient vesicles or pustules. These rapidly evolve into a weeping eroded lesion from which serous fluid forms crusted plaques with the characteristic honey colour. Individual lesions can enlarge to 2 cm in diameter, which then coalesce and become surrounded by satellite lesions. Lesions typically affect the face, especially around the month and nose but the extremities and buttocks can be involved. Local adenopathy appears to be a more common manifestation of streptococcal rather than staphylococcal impetigo [2]. The lesions heal without scarring. Constitutional symptoms are absent and satellite lesions may occur due to autoinoculation [1].

4.2 Bullous impetigo

The initial lesion is a faint red macule, which rapidly develops into a distinct small blister that may enlarge and remain intact to form a true bulla (blister). These bullae are thin walled, flaccid and clear, and usually arise on areas of grossly normal skin. They may contain pus before rupturing to leave an extending area of exudation and yellowish crusting. These

areas are often sharply demarcated, annular and with central erythema that is initially glistening but which dry and scale rapidly. Lesions are often multiple, particularly around the orifices of the mouth and nose, and grouped in body folds. A superficial folliculitis is sometimes associated [2]. The lesions may be more characteristically bullous in infants. Neonatal BI also tends to occur in the inguinal area and on the buttocks.

4.3 Staphylococcal scalded skin syndrome

In children, the ET-producing strain of *S. aureus* is usually found in a commensal site such as the conjunctiva, perineum, axilla, umbilicus, or at an infective site such as an abscess, wound or furuncle. There is a swift onset of painful, tender and red skin and this is often accentuated in flexural and periorifical areas. After 24 – 48 h, flaccid blisters and erosions develop and large areas of the overlying epidermis loosen and peel like a scald. These areas are sterile on bacterial culture. Conjunctival inflammation, perioral erythema and crusting, and lip fissuring are characteristic at this stage, although mucosal lesions are rare. Important physical signs include skin tenderness, denudation in areas of skin stress and Nikolsky's sign (separation of the outer epidermal layer of the skin from the underlying dermis on gentle rubbing) [9].

The diagnosis is usually made on clinical grounds. Swabs should be taken but treatment must not be delayed by waiting for culture results. If there is any doubt about the diagnosis, especially in the more severe variants, then a biopsy of the lesion or microscopy of the blister roof can provide a definitive diagnosis and exclude other differential diagnoses.

5. Differential diagnoses

The differential diagnoses of impetigo [15] that should be considered at initial presentation include impetiginised eczema, herpes simplex infection, immuno-bullous disease and erythema multiforme [16].

Children with impetigo may have a preceding history of atopic dermatitis [17]. As the skin in atopic dermatitis is often heavily colonised by *S. aureus*, bacteriological swabs of the affected skin should be performed before commencing treatment. Recurrent impetigo of the head and neck should prompt a search for head lice or scalp ringworm (tinea capitis).

Herpes simplex virus (HSV), either *per se* or as an antecedent trigger for the development of erythema multiforme (EM), is an important differential diagnosis particularly as HSV can become secondarily infected with *S. aureus*. HSV can be detected by electron microscopy or the culture of any intact blister fluid. Serology for herpes simplex antibodies in the early stages of the illness and after a 10-day interval is diagnostic but treatment should not be withheld during this period. Immunobullous disorders are rare and can be excluded by histopathological examination or direct immunofluorescence of the skin. Circulating antiepidermal antibodies are sometimes found. EM is suggested by the clinical appearance of indurated annular lesions of the hands and feet, some with central clearing and some appearing as characteristic 'target' lesions. In the rare bullous variant these lesions then evolve into flaccid bullae. Histological findings of marked dermal oedema, overlying epidermal oedema (spongiosis) and necrosis with degeneration of the basal cells of the epidermis are highly suggestive of EM. Antinuclear antibodies and antibodies to extractable nuclear antigens may be found in the rare bullous variants of lupus that occasionally mimic EM.

6. Prognosis and complications

Although there is a perception that impetigo contagiosa is a mild disease with a favourable natural course and early spontaneous resolution, the evidence for this is scarce. There is a large variation in the rate of resolution of impetigo in the placebo arms of controlled studies [18,19]. Although impetigo contagiosa and BI may clear slowly even without treatment, untreated disease tends to spread and persist on the skin [18,19] and can act as a source of infection to others. Complications such as glomerulonephritis are rare in Europe and the US [18,19].

7. Summary of available therapeutic/ diagnostic approaches

7.1 Diagnosis

Gram staining of exudates from BI reveals Gram-positive cocci in characteristic clusters or 'bunches of grapes'. Phage group II *S. aureus* can be cultured from aspirates of intact bullae.

A skin biopsy is not usually necessary but may be useful in severe cases where there is diagnostic doubt, or where there is a poor response to the appropriate antibacterial therapy. In BI the histopathological changes are of vesicles in the granular layer of the epidermis with occasional free (acantholytic) cells in the blister cavity. There is oedema of both the epidermis (spongiosis) and dermis, with a mixed infiltrate of lymphocytes and neutrophils around superficial dermal blood vessels. The rare autoimmune disorder, pemphigus foliaceous, causes similar histopathological changes to BI. In BI there is a split high in the epidermis with a low-grade inflammatory infiltrate.

7.2 Therapy

Data on the natural course of impetigo are lacking; placebo-controlled trials are scarce, and there is no standard therapy and guidelines for treatment differ widely [18,19].

In clinically minor cases of impetigo, mild topical antiseptics such as povidine iodine can be used to soften crusts and clear exudates. In early cases of impetigo, topical therapy with specific antibacterials may be all that is needed to abort disease progression. In order to minimise the development of resistant organisms it is preferable to limit the use of antibiotics used topically to those that are not used systemically.

7.2.1 *Fusidic acid*

Fusidic acid is a narrow spectrum antibiotic indicated for penicillin-resistant staphylococci in osteomyelitis and staphylococcal

endocarditis. However, as it is only occasionally used systemically, topical fusidic acid has become a useful agent in the management of staphylococcal skin infections.

Fusidic acid has been shown to be superior to placebo in the treatment of children with impetigo in primary care in a randomised placebo-controlled trial. In addition, more children in the placebo group were non-compliant, received extra antibiotic treatment and reported adverse effects [20].

The drug is applied as a 2% preparation in the form of gel, cream or ointment. The cream formulation is recommended in wet or weeping lesions. Excipients include butylated hydroxyanisole and cetyl alcohol in the cream, parabens (hydroxybenzoates) and polysorbate 80 in the gel and cetyl alcohol and wool fat in the ointment. Patients with known hypersensitivities to these agents should be prescribed an alternative formulation.

7.2.2 *Mupirocin (pseudomonic acid)*

Mupirocin is a topical antibiotic that was introduced into UK clinical practice in 1985. It is extremely effective at treating skin infections and one of the most successful topical antibiotics for the clearance of nasal *S. aureus* isolates including those resistant to methicillin [21]. Mupirocin produces an excellent response in impetigo and may have comparable efficacy to oral erythromycin [22]. It is not related to any other antibacterial in current clinical use. It is effective for a range of skin infections especially those caused by Gram-positive organisms and is as efficacious as fusidic acid [18,19]. Although *S. aureus* strains with low-level resistance to mupirocin are emerging [23], it remains useful in infections resistant to other antibacterials. It is available as a 2% formulation as either cream or ointment. The former is recommended in wet weeping lesions but contains the excipients benzyl alcohol, cetyl alcohol and stearyl alcohol. Individuals with known sensitivities to these excipients (who are usually older and often have pre-existing chronic skin disease) should, therefore, be prescribed the ointment instead. Use should be restricted to 10 days to minimise the risk of resistance and it should be avoided for hospital usage if possible.

There is good evidence that both topical mupirocin and topical fusidic acid are equally, or more effective, than oral treatment for children with limited impetigo [18,19].

7.2.3 *Neomycin and bacitracin*

Neomycin and bacitracin are both used in impetigo but are associated with significant rates of cutaneous sensitisation and can cause subsequent allergic reactions if used topically and systemically [24,25].

For cases of impetigo with more than a handful of scattered localised lesions, or where the patient has systemic symptoms, oral antibiotic therapy should be considered in addition to topical therapy [26]. Intravenous antibiotics are usually only needed in SSSS, where increased bioavailability and eradication of *S. aureus* from the primary focus of infection is important. Even then, oral antibiotics can be substituted after only a few days as clinical improvement occurs.

7.2.4 *Flucloxacillin*

Flucloxacillin, a semisynthetic penicillinase (β-lactamase)-resistant penicillin, is the treatment of choice for impetigo [11], and is superior to penicillin [18,19]. It is resistant to hydrolysis by gastric acid and is well absorbed when given orally. However, food interferes with its absorption, which is incomplete even in the fasting state, so it can be given parenterally in severe infections such as SSSS. Cholestatic jaundice can rarely occur up to several weeks after the administration of flucloxacillin, therefore, courses of > 2 weeks are not recommended, especially in the very young.

7.2.5 *Erythromycin*

Erythromycin (and the macrolides clarithromycin and azithromycin) has an antibacterial action that is similar to penicillin. However, it is active against many penicillin-resistant staphylococci and is superior to penicillin in treating impetigo [18,19]. It is, therefore, suitable for penicillin-allergic patients but its use is now limited because erythromycin resistance is becoming more common. In some patients, erythromycin causes nausea, vomiting and diarrhoea. These symptoms can be ameliorated by reducing the drug dose by 50% or, in severe infections requiring high-drug doses, changing to clarithromycin or azithromycin.

Erythromycin and the macrolides interact with many drugs. They enhance the effect of warfarin, digoxin and theophylline. They also increase the potential for side effects in several drugs commonly used in dermatological practice, such as itraconazole, ciclosporin and systemic tacrolimus. Erythromycin and clarithromycin inhibit the metabolism of terfenadine and are associated with a risk of developing hazardous arrhythmias. They may also increase the concentration of loratidine and mizolastine. As sedating antihistamines are frequently used in children with chronic pruritic skin disease, such as atopic dermatitis, clinicians must take care when prescribing erythromycin in this patient group. A single daily dose of oral azithromycin has been shown to be equally effective as dicloxacillin [27].

7.2.6 *Cephalexin (cefalexin), cefaclor and cefprozil*

The cephalosporins are broad spectrum antibiotics with similar pharmacological properties to penicillins. Their principal side effect is hypersensitivity and 10% of penicillin-sensitive patients will also react to the cephalosporins. The orally active first- (cefalexin) and second-generation (cefaclor and cefprozil) cephalosporins have similar antimicrobial activity. Cefaclor has rarely been associated with protracted skin reactions, especially in children, but otherwise it has a good safety profile and few important interactions. For impetigo caused by erythromycin-resistant *S. aureus*, cephalexin, cefaclor, or cefprozil, amoxicillin plus clavulanic acid, or clindamycin are equally effective.

Third-generation cephalosporins (cefotaxime, ceftazidime and ceftriaxone) are more active than second-generation cephalosporins against Gram-negative bacteria but are less active against Gram-positive organisms such as *S. aureus*. In addition, their broad antibacterial range may encourage super infection with resistant bacteria. Therefore, the authors do not recommend their use in treating childhood impetigo.

7.2.7 Co-amoxiclav

Co-amoxiclav (amoxicillin and the β-lactamase inhibitor clavulanic acid) is effective in infections with β-lactamase-producing bacterial strains, including resistant strains of *S. aureus*. It should be reserved for infections known to be caused by amoxicillin-resistant β-lactamase-producing strains. Once again, a swab for bacteriological culture is important before changing therapy to this drug. Co-amoxiclav has been reported as having a higher risk of acute liver toxicity with the development of cholestatic jaundice. This is more common in the elderly and is rare in children. It is self-limiting and rarely fatal but treatment should not exceed 14 days in children.

7.2.8 Clindamycin

Clindamycin is active against Gram-positive cocci including penicillin-resistant staphylococci. However, systemic clindamycin is associated with severe side effects, including antibiotic-associated colitis. In addition, clindamycin injection contains the preservative benzyl alcohol, which has been associated with a rare and fatal toxic shock syndrome in premature infants. Clindamycin is, therefore, not recommended in neonates.

7.2.9 Rifampicin

Rifampicin may be useful in resistant staphylococcal infections when used as adjunctive therapy [28].

7.2.10 Supportive skin care

Supportive skin care and fluid balance are important in cases where there is extensive skin involvement, such as severe BI and SSSS. The child should be nursed in a side room and staff should observe the measures described below to avoid the spread of infection. Fluid input and output should be monitored, as insensible water loss can occur through inflamed or denuded skin especially in smaller infants. Large areas of skin loss can also affect thermoregulation. Regular adequate analgesia is important and careful nursing should be observed as further skin involvement can occur during the acute stage of the disease. Adhesive dressings should not be used.

7.3 Eradication of staphylococcal carriage

Asymptomatic nasal carriage of *S. aureus* is an important source of infection especially in neonatal units. Strict control measures should be applied. These include isolation of affected patients, barrier nursing and chlorhexidine hand washing by both staff and visitors to the unit. Triclosan 0.3% is reported to be highly effective in controlling and preventing outbreaks in a neonatal nursery [29]. Family members and healthcare staff should be screened by nasal swabs to determine the source of any outbreak. Positive swabs should be treated with the local application of an antistaphylococcal agent. In the UK a cream containing chlorhexidine and neomycin can be used. It is applied four-times daily for 10 days to the anterior nares, although recolonisation frequently occurs.

Mupirocin is indicated for primary and secondary skin infections. It is also used for the eradication of nasal colonisation of *S. aureus*, particularly methicillin-resistant *S. aureus* (MRSA). Following > 15 years of use, short courses of treatment, even when repeated, are associated with little resistance and it is argued that this resistance is unlikely to be clinically significant [30].

In hospitals, mupirocin nasal ointment should be reserved for the elimination of nasal MRSA. It is applied to the nares three-times daily for 5 days and a repeat swab is taken at 7 days to confirm clearance. The course can be repeated once if a second swab is positive and the throat is not colonised. Although MRSA eradication by the treatment of wounds or anterior nares with mupirocin decreases *S. aureus* colonisation, it may not necessarily decrease transmission [31].

A rigorous 'search and destroy' policy, based on the screening of staff and patients and the isolation of identified patients, is now being increasingly advocated in UK healthcare settings [32,33]. The eradication of *S. aureus* by oral therapy is not usually needed in patients with impetigo. Oral rifampicin for 10 days may eradicate nasal staphylococcal carriage for up to 12 weeks and can be used in resistant cases of impetigo [28]. However, rifampicin-resistant strains can be rapidly selected out following such therapy. The addition of a second drug has been advocated to decrease rifampicin resistance. Dicloxacillin can be used for methicillin-sensitive strains or trimethoprim-sulfamethoxazole, ciprofloxacin or minocycline in MRSA [3].

A recent Cochrane review of trials of antimicrobial drugs for the eradication of MRSA colonisation concluded that there was no demonstrated superiority of either topical or systemic therapy. Evidence for treatment was insufficient, and systemic side effects were common with systemic therapy. All trials reported the development of resistance to the antimicrobial agents used [34].

8. Drug resistance

Hospitalisation for > 3 days, with or without antimicrobial therapy, is associated with increased antimicrobial resistance in colonising *Staphylococcus. epidermidis* [35], this also appears to be the case for *S. aureus.*

8.1 Fusidic acid

Fusidic acid acts by binding to bacterial elongation factor G (EF-G), a protein involved in ribosomal protein synthesis [36]. All bacterial populations produce spontaneous mutations in the gene encoding EF-G [37]. Fusidic acid resistance in *S. aureus* has been shown to result from point mutations

within the chromosomal *fusA* gene encoding EF-G. In addition, the introduction of mutant *fusA* alleles on plasmids into the fusidic acid-susceptible *S. aureus* strains causes a fusidic acid-resistant phenotype [38].

Studies examining the rates of fusidic acid resistance in staphylococci initially showed low levels of resistance. Studies where high levels of resistance were seen were from hospitals in which cross-infection is common. Rates of resistance were thought to have been slightly higher in methicillin-resistant strains of *S. aureus* [36]. However, strains of MRSA, by their clonal nature, distort this data [39].

Internationally, the reported size of the increase in resistance to fusidic acid has been varied. In a study of antimicrobial resistance of *S. aureus* isolated from impetigo patients between 1994 and 2000 in Japan, there were no strains of *S. aureus* resistant to vancomycin or fusidic acid [40]. However, a study performed in African hospitals found that only 46% of 59 MRSA strains analysed were susceptible to fusidic acid [41]. A large Korean study of clinical *S. aureus* isolates showed rifampicin and fusidic acid to have superior *in vitro* activity against MRSA isolates. No isolates were resistant to quinupristin–dalfopristin or linezolid and none showed reduced susceptibility to vancomycin [42].

More recently, fusidic acid-resistant epidemic *S. aureus* strains causing BI have been reported in Scandinavia [43,44]. These strains form part of a European epidemic clonotype that carries a *fusB* determinant. In contrast, resistance to fusidic acid in non-epidemic strains results primarily from mutations in *fusA* [45].

Prescriptions for fusidic acid and the level of resistance to fusidic acid among community methicillin-susceptible *S. aureus* (MSSA) isolates in the UK have both doubled over the past 6 years [46]. A statistically significant association has been found between these fusidic acid-resistant MSSA isolates and exposure to topical fusidic acid at the individual patient level. This supports the argument that resistance is causally associated with the increased use of topical fusidic acid [47].

Children with atopic dermatitis commonly have impetigo or secondary staphylococcal infection. Repeated, and perhaps prolonged, treatment with fusidic acid may contribute to resistance. Children with atopic dermatitis can be colonised with fusidic acid-resistant *S. aureus* [17].

Topical antibiotics are widely used for dermatological problems [48], and this may be leading to the emergence of resistant bacteria. One UK study showed that 50% of *S. aureus* isolates from dermatology patients were resistant to fusidic acid. This figure rose to 78% in patients with atopic eczema. Of patients with fusidic acid-resistant *S. aureus* isolates, 96% had used a fusidic acid-containing preparation within the previous 6 months. By comparison, the level of fusidic acid resistance in *S. aureus* samples cultured from non-dermatology patients in this study was only 9.6% [49].

A study in Cambridge also demonstrated higher rates of fusidic acid resistance among *S. aureus* isolates from dermatology out-patients compared with isolates from hospital in-patients (6.9%) [50]. Among dermatology out-patients, resistance was more common in younger patients. This was probably because of their increased exposure to topical fusidic acid used to treat chronically infected eczema [50]. These findings have been reproduced in other centres in the UK [51].

Higher rates of resistance to fusidic acid appear to relate to chronic skin infections [52]. A retrospective study from Wales noted a rise in the incidence of fusidic acid resistance, particularly among paediatric patients presenting with infected eczema and impetigo. Worryingly, the fusidic acid-resistant isolates of *S. aureus* were typically from patients with impetigo. These isolates fell into a single clonal group, whereas isolates from other skin disease, such as eczema, were usually susceptible to fusidic acid and were polyclonal [53].

Fusidic acid-resistant strains may be overrepresented in observational studies because swabs from resistant cases are more likely to be sent to the laboratory. Even so, resistance rates in laboratory isolates of *S. aureus* have increased by 200% in the last 10 years [37].

In acute skin infection, short courses of fusidic acid have been associated with very low rates of developing resistance [36]. There are calls for fusidic acid not to be used outside hospitals [37]. Others suggest that fusidic acid should be used only to treat acute primary impetigo and not for secondary impetiginised atopic dermatitis [18,19]. The Swedish Medical Products Agency has recommended that neither fusidic acid nor mupirocin should be used topically at all [54].

8.2 Mupirocin

Strains of mupirocin-resistant *S. aureus* were described after its initial introduction. Many of these cases occurred after long-term use in a hospital setting. In one series, mupirocin was used as topical prophylaxis to reduce colonisation of central venous catheters in a neonatal intensive care unit. Mupirocin resistance was recorded in 42% of clinical isolates of coagulase-negative staphylococci and decreased to 13% during a mupirocin-free interval of 12 months [55]. In an earlier study, which involved long-term treatment of patients with epidermolysis bullosa with mupirocin, 5 out of 47 patients grew cultures of *S. aureus* resistance to mupirocin [56]. In a hospital outbreak of mupirocin-resistant staphylococci in Poland, almost all the mupirocin-resistant staphylococci were also resistant to methicillin. The mupirocin-resistant *S. aureus* were found to represent a single epidemic strain, which was clonally disseminated. The outbreak was attributed to frequent and inappropriate use of mupirocin and the dermatological formulation of the drug was withdrawn [57]. In a study of mupirocin resistance in staphylococci from 19 European hospitals, methicillin sensitivity was found in 72% of *S. aureus*. High-level mupirocin resistance was detected in 1.6% of *S. aureus* isolates and low-level mupirocin resistance in 2.3%. Among *S. aureus*, methicillin-resistant isolates were twice as likely to have mupirocin resistance [58]. Similar studies in the US have confirmed the emerging pattern of mupirocin resistance and that this resistance can be plasmid mediated [59].

The appropriate use of this topical agent as outlined above is important to minimise the ongoing development of resistance. Local surveillance for emerging mupirocin resistance seems to be warranted [59].

8.3 Methicillin-resistant *Staphylococcus aureus*

β-Lactam antibiotic agents are the most common treatment for bacterial infections. These agents include penicillins (flucloxacillin, methicillin, amoxicillin, piperacillin), cephalosporins, carbepenems (imipenem) and monobactams (aztreonam). Production of β-lactamases remain the most common mechanism of bacterial resistance [60]. There are many variants of these enzymes and they are increasing in number. They mutate continuously in response to the pressure of antibiotic therapy, which consequently leads to increasingly severe infections. This has resulted in the emergence of the extended spectrum β-lactamases by organisms such as *Klebsiella pneumoniae* and *Escherichia coli* [61].

The emergence of strains of staphylococcus producing β-lactamase has first led to resistance to penicillin and then to semisynthetic penicillinase-resistant penicillins. MRSA has caused major problems in the treatment of the staphylococcal infections, as methicillin was the first penicillin resistant to destruction by staphylococcal β-lactamase. The recent emergence of vancomycin-resistant strains has further complicated treatment. While the prevalence of *S. aureus* infection has not changed, the proportion of infections with MRSA strains has increased dramatically. In England and Wales, MRSA as a proportion of the total *S. aureus* bacteraemias rose from < 2% in 1990 to 42% in 2000 (one of the highest rates in Europe) [62]. In the UK, MRSA reservoirs are predominantly thought to be hospital healthcare workers and patients, with transmission occuring through direct contact [63]. MRSA strains causing BI and SSSS have previously been uncommon and, therefore, disease management was relatively straightforward. However, there are now reports of emerging clonal groups of ET-producing MRSA [64].

Community-acquired MRSA (CA-MRSA), which has a predilection for skin and soft tissues in children, has recently been reported. CA-MRSA, in contrast to hospital-acquired MRSA (HA-MRSA), is not associated with exposure to multiple antibiotic treatments, surgery, dialysis or prolonged hospitalisation [65]. A therapeutic challenge arises because current recommendations for empiric treatment of CA-MRSA include clindamycin and co-trimoxazole [66], and these drugs should not be used for first-line therapy for HA-MRSA.

In addition, *in vitro* resistance has been demonstrated in strains of CA-MRSA after exposure to rifampicin and gentamicin, and in some strains after fusidic acid exposure, independent of methicillin-resistance phenotype [67].

In the UK, there has been a rapid rise in both fusidic acid resistance and MRSA. However, the two observations are not directly related. The predominant strains of MRSA remain fusidic acid-sensitive, although a new fusidic acid-resistant epidemic strain (EMRSA-17) has recently been identified [37].

9. New therapies

The antibiotic linezolid, a member of the novel oxazolidinone class, is as effective as clarithromycin in uncomplicated skin infections [68] and as effective as vancomycin in the treatment of MRSA infections [69]. Quinupristin–dalfopristin is a combination of two semisynthetic agents that demonstrate synergistic activity when used in combination. It is indicated for complicated skin infections caused by MRSA and is administered parenterally. The combination is valuable because resistance is rare and it has a long postantibiotic effect [70]. Daptomycin has been re-evaluated and is effective in the treatment of both MRSA and MSSA [71].

Aminoacyl-tRNA synthetases are a family of enzymes essential for protein synthesis and have become promising targets of new antimicrobials. Indolmycin, a secondary metabolite of *Streptomyces griseus* is a selective inhibitor of prokaryotic (bacterial) tryptophanyl-tRNA synthetase. Indolmycin is a potent antistaphylococcal agent, which exhibits activity against mupirocin- and fusidic acid-resistant strains. It is bacteriostatic and demonstrates good activity against MSSA, MRSA and vancomycin-intermediate *S. aureus* (VISA), including strains resistant to mupirocin or fusidic acid [72].

In recent studies, plant-based therapies have been used to treat MRSA. These include small laboratory-based studies of allicin extracts [73] and isoflavanone [74], and a randomised, controlled clinical trial of topical tea tree preparations [75]. However, more research is needed before this vogue for plant-based therapies can be recommended.

10. Optimal therapy

Treatment options for impetigo include topical antiseptics, topical antibiotics and systemic antibiotics. Although there is no clear evidence to support their role [18,19], topical antiseptics help to soften crusts and clear exudate in mild disease. They may be a useful adjunct to antibiotic therapy in more severe cases.

There is firm evidence from systematic reviews that topical mupirocin and fusidic acid are safe and effective treatments for mild cases of impetigo. In these mild cases, they are probably as effective as oral antibiotics [18,19]. In order to minimise the development of resistant organisms, it is preferable to limit the use of topical antibiotics to those used solely as topical preparations (which are unavailable in systemic preparations) [1].

Flucloxacillin is considered the treatment of choice for impetigo. Cephalosporins, macrolides and co-amoxiclav are also effective but there is limited supportive randomised trial data because the studies have not been performed. The selection of systemic antibiotic is determined by factors such as local epidemiology of antibiotic resistance, patient allergy or intolerance to antibiotics and proven bacterial sensitivity following microbiological assessment. The authors would recommend a 7-day course of flucloxacillin as first-line

treatment. In cases of penicillin allergy, erythromycin (or similar macrolide antibiotic) is suitable but this causes nausea and diarrhoea in some patients, and resistance to erythromycin is increasing. For impetigo caused by erythromycin-resistant organisms, cephalosporins (e.g., cephalexin) are effective, although 10% of penicillin-sensitive patients also react to cephalosporins. Co-amoxiclav (amoxicillin and the β-lactamase inhibitor clavulanic acid) is effective in infections with β-lactamase-producing bacterial strains, including resistant strains of *S. aureus*. It should be reserved for infections known to be caused by amoxicillin-resistant β-lactamase-producing strains. A swab for bacteriological culture is important before changing therapy to co-amoxiclav.

Oral antibiotics may be more effective than topical antibiotics for more serious/extensive disease. They are easier to use in extensive disease but have more side effects than topical agents.

The authors suggest using topical mupirocin or fusidic acid for 7 days in clinically mild (limited) impetigo. Oral antibiotics should be reserved for recalcitrant, extensive, systemic disease.

To determine the source of an outbreak, nasal swabs should be performed to screen family members and healthcare staff.

10.1 Evidence-based therapy

A recent Cochrane review [18,19] of evidence-based interventions for impetigo included 57 trials totalling 3533 patients and studied 20 different oral and 18 different topical treatments. It found that topical antibiotics showed better cure rates than placebo but no topical antibiotic was superior. Fusidic acid and mupirocin were shown to be of similar efficacy. The study confirmed that topical mupirocin is superior to oral erythromycin and that penicillin is inferior to both erythromycin and flucloxacillin. The reported number of side effects was low and, as may be expected, oral antibiotic treatment caused more side effects, especially gastrointestinal, than topical treatment.

11. Summary and conclusions

Impetigo is a common superficial bacterial infection of the skin characterised by inflamed, crusted and infected epidermis. The rarer variant, BI, is characterised by fragile fluid-filled vesicles and flaccid blisters, and is invariably caused by pathogenic strains of *S. aureus*. BI is at the mild end of a spectrum of blistering skin diseases due to a staphylococcal exotoxin that, at the other extreme, is represented by the widespread painful blistering and superficial denudation characteristic of SSSS. Impetigo occurs more commonly in children < 6 years of age. It is important to swab the skin for bacteriological confirmation and sensitivities and, in SSSS, to identify the primary focus of infection.

Topical therapy should constitute either fusidic acid as first-line or mupirocin in proven cases of bacterial resistance. First-line systemic therapy is oral flucloxacillin. Nasal swabs of the patient and immediate relatives should be performed to identify asymptomatic nasal carriers of *S aureus*. In the case of outbreaks on wards and in nurseries, healthcare professionals should also be swabbed. Topical antibiotics should be used prudently and in short courses to minimise the development of resistance. These key issues regarding impetigo are summarised in Box 1.

Box 1. Key issues.

- Impetigo, bullous impetigo and SSSS occur more commonly in children < 6 years of age.
- It is important to swab the skin for bacteriological confirmation and, in the SSSS, identify the primary focus of infection.
- Topical therapy should include either fusidic acid or mupirocin.
- First-line systemic therapy is flucloxacillin.
- Nasal swabs of patient and immediate relatives should be performed to identify asymptomatic nasal carriers of *Staphylococcus aureus.*
- In the case of outbreaks, healthcare professionals should also be swabbed.
- Resistance to both fusidic acid and mupirocin is rising.
- Topical therapy should be restricted to short courses.
- The presence of methicillin-resistant *Staphylococcus aureus* causing impetigo is being increasingly recognised.

SSSS: Staphylococcal scaled skin syndrome.

12. Expert opinion

Recommendations for clinical strategies and drug products are detailed above and constitute the best current treatment regimen. The rising rate of resistance to fusidic acid is a cause for concern. One author has suggested that fusidic acid be used only in acute primary impetigo [20]. Another, suggests that fusidic acid and mupirocin should not be used topically at all [54]. However, as there is no currently available useful evidence-based topical alternative, Johnston and colleagues suggest that fusidic acid should be used prudently and in short courses.

To maintain the relatively low prevalence of mupirocin resistance in Europe amongst *S. aureus*, mupirocin should also be used prudently. Some authorities suggest usage restricted to infection-control strategies [58], and to emphasise the importance of local surveillance for emerging mupirocin resistance [59].

The identification of asymptomatic carriers both in the family (to prevent further cases in the community) and in healthcare professionals (to prevent hospital-acquired outbreaks) may be the gold standard in disease prevention but would require significant resources. A successful outcome in terms of disease eradication and limitation of spread of resistant strains would be in no way guaranteed [62]. A rise in the prevalence of ET-producing MRSA [64] has important implications in the future management of those ET-related diseases that currently respond effectively to appropriate antibacterial therapy.

13. 5-year view

Impetigo contagiosa is currently easily treatable and there is good evidence available to guide this treatment. The rise of antibiotic-resistant *S.aureus* threatens to change this picture. Fusidic acid resistance, in particular, will become a problem because this drug is so well established in the treatment of infected atopic dermatitis. Unless treatment is guided by microbiological investigations and information is readily available on local resistance patterns, the rise of multi-resistant *S. aureus* will continue. Mupirocin should maintain its valuable place in the treatment of staphylococcal skin infections but stricter prescribing limits may have to be introduced eventually to preserve this place in the treatment of primary impetigo contagiosa.

Most cases of BI and SSSS will require hospital-based treatment, particularly as the majority of cases occur in the very young. As hospitals and healthcare providers are the main source of resistant staphylococci, it is likely that the current rise in rates of MRSA infection will soon be followed by a corresponding rise in ET-producing MRSA. This will necessitate a change in treatment protocol. The current optimal therapy of topical fusidic acid and oral/intravenous flucloxacillin is relatively safe, clinically and cost-effective. However, in the future, new antibiotics effective against MRSA and ET-producing MRSA, which (unlike agents such as vancomycin) can be given orally in milder or early cases and do not require monitoring, will be needed. In 5-years time, the incidence of BI and SSSS may be similar but the treatment may well be very different and far less straightforward. The possibility of the development of a *S. aureus* ET inhibitor [76] would decrease the morbidity and mortality of this disease even in the absence of effective antimicrobial therapy.

Clindamycin and the oxazolidinones, protein synthesis inhibitors that have a novel mode of action, have been shown *in vitro* to be more effective in treating severe staphylococcal infections than other more susceptible antimicrobial treatments [77]. They may have a future role in severe SSSS. Quinupristin–dalfopristin may be particularly useful for community-acquired or nosocomial skin infections, and daptomycin has a role in cases of resistant *S. aureus* [71]. Newer novel agents including oritavancin and dalbavancin may be a future option in the management of Gram-positive skin infections [71]. In addition, the fluoroquinolones moxifloxacin and gatifloxacin, with their tolerability and once-daily dosing, remain valuable agents.

Indolmycin, because of its potent antistaphylococcal action and its activity against mupirocin- and fusidic acid-resistant strains, may become key in the future treatment of staphylococcal skin infections. The fact that indolmycin demonstrates good activity against MSSA, MRSA and VISA will enhance this position. Indolmycin may be a candidate for development as a topical agent in the treatment of staphylococcal infections and nasal carriage of MRSA [72].

The use of other antimicrobials with some antibacterial action, such as antifungals, has not been promising [78].

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