

4. Antibacterial/steroid combination therapy in infected eczema

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Infection with Staphylococcus aureus is common in all forms of eczema. Production of superantigens by S. aureus increases skin inflammation in eczema; antibacterial treatment is thus pivotal. Poor patient compliance is a major cause of treatment failure; combination preparations that contain an antibacterial and a topical steroid and that work quickly can improve compliance and thus treatment outcome. Fusidic acid has advantages over other available topical antibacterial agents – neomycin, gentamicin, clioquinol, chlortetracycline, and the anti-fungal agent miconazole. The clinical efficacy, antibacterial activity and cosmetic acceptability of fusidic acid/corticosteroid combinations are similar to or better than those of comparator combinations. Fusidic acid/steroid combinations work quickly with observable improvement within the first week. Studies have shown that short-term (2 weeks) use of fusidic acid/corticosteroid combinations does not increase the development of resistance. A new formulation of fusidic acid with betamethasone valerate in a lipid cream also addresses xerosis in eczema.

INTRODUCTION

Staphylococcus aureus is often implicated in different forms of eczema. It has been shown to produce superantigens that exacerbate the inflammatory response in eczema (1–3) and induce corticosteroid insensitivity (4). Anti-staphylococcal agents are thus pivotal agents in our treatment of eczema. A number of topical antibacterial agents are commercially available. A combination product that contains both an antibacterial agent and a topical steroid in one preparation has obvious advantages over 2 different products each containing one active agent, as the combination preparation will increase patient compliance and thus improve therapeutic outcome.

This paper briefly describes the importance of *S. aureus* in eczema, examines the rationale for the use of combination antibacterial/steroid preparations, compares the characteristics of those available, and suggests management strategies for the optimal use of these agents.

S. AUREUS AND ECZEMA

S. aureus is commonly found in all types of eczema (5). This may manifest as obvious infection with impetiginization or cellulitis, but may also be more cryptic, presenting as excoriations, increased erythema, or fissuring of the skin. Even when overt infection is not

present, the use of anti-staphylococcal agents with topical corticosteroids has been shown to produce greater clinical improvement than topical corticosteroids alone (6, 7). These findings are in keeping with the demonstration that *S. aureus* can be isolated from more than 90% of atopic eczema skin lesions (8); in one study, it was isolated from 100% of lesional skin and 79% of normal skin in patients with atopic eczema (9).

We observed similar rates of infection in a prospective audit at the Hammersmith Hospital, in which all new patients referred with atopic eczema were evaluated. In a 2-month period, 30 patients were referred (22 children and 8 adults). The reason given by the primary health physician for referral in 29 was failure to respond to prescribed treatment, and one patient was referred because the parents wanted a consultant opinion. In 90% of the patients there was clinical evidence of infection; in 87% swabs from lesional skin were highly positive for *S. aureus*; and 93% showed marked improvement within one week of treatment with topical fusidic acid/corticosteroid combinations and emollients, with or without a systemic antibiotic.

These findings are compelling arguments for the general use of anti-staphylococcal agents in the management of all patients with eczema.

IS TREATMENT OF *S. AUREUS* SUFFICIENT TO TREAT ECZEMA?

S. aureus is very important in the pathophysiology of eczema, but is its eradication sufficient to control eczema? In a randomized, double-blind, prospective, parallel-group study, Ramsay et al. (10) compared topical 2% fusidic acid, 1% hydrocortisone, or a combination of 2% fusidic acid with 1% hydrocortisone in the treatment of atopic eczema. One group of patients was treated with hydrocortisone or the fusidic acid/hydrocortisone combination, and the second with fusidic acid or the fusidic acid/hydrocortisone combination. As expected, the fusidic acid-containing preparations were superior in eradicating *S. aureus* and beta haemolytic streptococci, with eradication rates of 100% for fusidic acid cream and 98% for fusidic acid/hydrocortisone cream vs. 53% for the hydrocortisone cream (Fig. 1). When the results of all the patients were pooled, the 3 preparations were found to be statistically significantly different in achieving >50% improvement in total signs and symptoms, and in reduction of sign and symptom scores after 2 weeks' treatment. Fusidic acid/hydrocortisone cream gave the best results, followed by hydrocortisone cream and then fusidic acid cream.

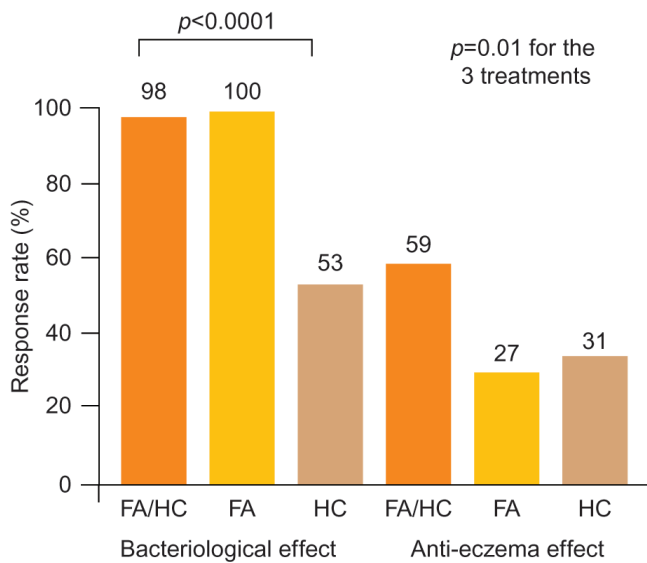


Fig. 1. Results of treating patients with infected atopic eczema with topical 2% fusidic acid (FA), 1% hydrocortisone (HC), or a combination of 2% fusidic acid with 1% hydrocortisone (FA/HC) for 2 weeks (data from Ramsay et al. (10)). The graph shows bacteriological response (eradication of bacteria) and anti-eczema effect (expressed as a percentage of patients who did not fail treatment) for patients with bacteria present at baseline. Results are combined results for 2 parallel studies comparing hydrocortisone with the combination ($n=73$), or fusidic acid with the combination ($n=32$).

This study demonstrates that eradication of pathogenic bacteria from eczema is not sufficient to treat eczema. An important finding, however, was that the combination of an antibacterial with a topical corticosteroid improved the outcome compared with the topical corticosteroid by itself. This shows the importance of also using antibacterial therapy when treating eczema.

TREATMENT FAILURE IN ECZEMA

To treat eczema effectively, the 3 principal problems need to be targeted: dryness of the skin (xerosis); inflammation; and infection (see Fig. 3 by Leung in this supplement, p. 25) (3). These can be individually targeted by the use of, respectively, emollients and moisturizers; appropriate strength topical steroid or topical immune response modifiers; and topical or systemic antibacterial agents.

Treatment failure is complex, but the major cause is failure to adhere to therapy. There are a number of possible reasons for this, including: lack of understanding of the topical agents prescribed, complex regimens comprising a number of different topical agents, fear of real or imaginary side-effects of topical agents, slow response to treatment, under-prescribing by the physician, failure to renew prescriptions, child refusal of topical agents, adult unwillingness to use the treatment prescribed, and poor cosmetic acceptability (11, 12). The ideal treatment in eczema is one that addresses all the problems in a single preparation, works quickly, is

free of side-effects, and is cosmetically acceptable. Few preparations match this ideal.

It is of major importance to discuss with patients the treatments prescribed to ensure appropriate usage. The importance of providing patients or carers with information is illustrated by a study that showed parents' lack of knowledge and incorrect perceptions concerning commonly prescribed topical corticosteroids (11). Among the parents or carers of 100 children attending paediatric outpatient clinics, 44% of those who had been prescribed 1% hydrocortisone for their children's eczema graded it as moderately potent; 42% of those who had used betamethasone valerate 0.1% did not grade it as potent; and the fusidic acid 2%/hydrocortisone 1% combination was graded as moderately potent by 56% and potent by 32%. Such misunderstanding increases the anxiety of patients about the risks of using steroids and leads to avoidance where use would help to control the eczema.

TOPICAL ANTIBACTERIAL/STEROID COMBINATIONS

A number of antibacterial/steroid topical combinations are commercially available. These include combinations with 1% hydrocortisone or with a potent topical corticosteroid such as betamethasone valerate 0.1% (Table I).

Fusidic acid has major advantages over other available topical antimicrobial agents. It shows very good penetration into the skin (13, 14). High *in vitro* skin permeability to both the fusidic acid and betamethasone valerate components of the combination product formulation has also been documented (15). Furthermore, fusidic acid has high anti-staphylococcal activity even against methicillin-resistant *S. aureus* (MRSA) (16). Unlike neomycin and gentamicin, it has a very low potential to sensitize and induce contact allergic dermatitis (17). It also has very good cosmetic acceptability, unlike clioquinol and chlortetracycline, which can mark clothes and bedding.

Sensitization by topical antibacterials

The major advantage of using topical antibiotics is the ability to achieve a high concentration of the antibiotic in the skin where it is needed, without the side-effects inherent with the use of systemic antibiotics. When used on eczematous skin, where the skin barrier function is impaired, there is an increased risk of cutaneous sensitization. Antibiotics such as neomycin are contained in over-the-counter products in Europe, some deodorants, and a number of topical prescription drugs used on the skin and in the eyes. Sensitization to neomycin is a well recognized problem and many dermatologists avoid topical neomycin for this reason.

Two recent studies have examined patch test results from Departments of Dermatology participating in the Information Network of Departments of Dermatology in

Table I. Antimicrobial agents available as combination preparations with topical corticosteroids, showing some of their characteristics

Agent	Available in combination with	Sensitization potential	Formulation ^a	Cosmetic acceptability
Fusidic acid	Hydrocortisone 1%	Low	Cream, ointment	Good
	Betamethasone valerate 0.1%		Cream, lipid cream	
Neomycin	Betamethasone valerate 0.1%	High	Cream, ointment	Good
Gentamicin	Betamethasone valerate 0.05%	High	Cream, ointment	Good
Clioquinol	Betamethasone valerate 0.1%	Medium	Cream, ointment	Poor
Chlortetracycline	Triamcinolone acetonide 0.1%	Low	Ointment	Poor
Miconazole ^b	Hydrocortisone 1%	Low	Cream, ointment	Good

^aAvailability of formulations varies by country.

^bAlthough an antifungal compound, miconazole, is included here, as it has been used in the treatment of atopic eczema.

Germany (18, 19). In the first study, 8532 patients with atopic eczema were subjected to aimed testing for suspected allergic contact dermatitis over a 4-year period. Among those tested, 2.1% were sensitive to neomycin ($n=7619$ tested), 2.11% were sensitive to gentamicin ($n=1635$), and 0.31% were sensitive to clioquinol ($n=1177$), compared with 0% sensitive to fusidic acid ($n=48$) (18). The second study estimated the incidence of contact allergy to topical drugs in the overall German population, based on patch tests performed during 2000 to 2004, as 2.2% for neomycin, 3.2% for gentamicin, and 0.8% for fusidic acid (19).

Cosmetic acceptability

The majority of topical antibiotics available in combination with topical corticosteroids are cosmetically acceptable. Notable exceptions are chlortetracycline, which is yellow and can mark clothing, and clioquinol. Clioquinol is initially colourless, but when exposed to air it turns yellow, and if applied to clothing it will turn brown: this often discourages use.

Efficacy of fusidic acid/steroid combination products

A number of randomized clinical trials have compared the efficacy of different topical antimicrobial/corticosteroid preparations with fusidic acid/corticosteroid preparations in infected eczema (Table II) (5, 20–24).

Fusidic acid 2%/hydrocortisone 1% cream vs. miconazole 2%/hydrocortisone 1% cream. In this study, fusidic acid/hydrocortisone cream (Fucidin® H; LEO Pharma A/S, Ballerup, Denmark) was compared with a combination of the antifungal compound miconazole with hydrocortisone (20). Both treatments were equally effective in treating clinically infected eczema, but healing was more rapid with the fusidic acid/hydrocortisone cream ($p=0.04$ in favour of fusidic acid/hydrocortisone after 1 week of treatment).

Fusidic acid 2%/betamethasone 0.1% cream vs. neomycin 0.5%/betamethasone 0.1% cream. Two clinical trials compared fusidic acid/betamethasone cream (Fucicort®, Fucibet®; LEO Pharma A/S) with neomy-

Table II. Comparative trials of fusidic acid/corticosteroid combination preparations

Reference	Fusidic acid combination	Comparator	Trial design	Condition
Poyner & Dass, 1996 (20)	Fusidic acid 2%/hydrocortisone 1% cream ($n=95$)	Miconazole 2%/hydrocortisone 1% cream ($n=102$)	Open	Mild to moderate infected eczema of the trunk or limbs
Wilkinson et al., 1985 (5)	Fusidic acid 2%/betamethasone 0.1% cream ($n=45$)	Neomycin 0.5%/betamethasone 0.1% cream ($n=46$)	Double-blind	Infected or potentially infected eczema
Javier et al., 1986 (21)	Fusidic acid 2%/betamethasone 0.1% cream ($n=27$)	Neomycin 0.5%/betamethasone 0.1% cream ($n=32$)	Double-blind	Infected or potentially infected eczema
Strategos, 1986 (22)	Fusidic acid 2%/betamethasone valerate 0.1% cream ($n=50$)	Gentamicin 0.1%/betamethasone valerate 0.1% cream ($n=49$)	Open	Infected eczema
Hill et al., 1998 (23)	Fusidic acid 2%/betamethasone 0.1% cream ($n=58$)	Clioquinol 3%/betamethasone 0.1% cream ($n=62$)	Open	Infected hand eczema
Schultz Larsen et al., 2007 (24)	Fusidic acid 2%/betamethasone 0.1% cream ($n=275$) and Fusidic acid 2%/betamethasone 0.1% lipid cream ($n=258$)	Lipid cream vehicle ($n=88$)	Double-blind	Infected atopic eczema

cin/betamethasone cream (5, 21). The two preparations showed similar high clinical efficacy. In the Wilkinson study, at 2 weeks 90% and 95% of patients using the neomycin or fusidic acid combination creams, respectively, considered their treatment beneficial, and both treatments were equally effective at eradicating *S. aureus* (5). In the study by Javier et al. (21), at 7–10 days both preparations were equally effective, with a satisfactory clinical response seen in 81% and 85% of patients using the neomycin or fusidic acid combination creams, respectively. Both preparations were equally effective in eradicating bacterial pathogens.

Fusidic acid 2%/betamethasone valerate 0.1% cream vs. gentamicin 0.1%/betamethasone valerate 0.1% cream. In this study, after 7–12 days of treatment, 74% of the fusidic acid group achieved an excellent response compared with 55% of the gentamicin group ($p=0.03$). The two treatments were equally effective in eradicating skin pathogens (22).

Fusidic acid 2%/betamethasone 0.1% cream vs. clioquinol 3%/betamethasone 0.1% cream. The study by Hill et al. (23) compared the two preparations used twice daily in the treatment of infected hand eczema for a period of up to 4 weeks. The overall clinical response was similar in both groups, with 54.8% of patients achieving a good or excellent response in the fusidic acid group and 53.4% in the clioquinol group. Overall cosmetic acceptability, however, was significantly different in the two groups: 29.6% of the clioquinol group and 90.6% of the fusidic acid group found the cosmetic acceptability of their treatment good ($p<0.0001$). Fusidic acid was also superior in bacteriological efficacy, eradicating *S. aureus* in 92.3% of patients, whereas clioquinol eradicated *S. aureus* in only 55.2% of patients ($p=0.004$).

New fusidic acid 2%/betamethasone valerate 0.1% lipid cream. It is important to relieve the dryness of eczematous skin, and the use of corticosteroid cream without emollients and moisturizers may lead to further problems with dryness and subsequent itching in some patients. A new formulation of fusidic acid and betamethasone in a lipid cream has recently been developed to provide an alternative treatment for patients with infected eczema in whom the existing combination cream does not provide an adequate moisturizing effect. The efficacy of this new lipid cream was compared with that of fusidic acid/betamethasone cream in a double-blind, randomized controlled study (24). In this study, 630 patients aged 6 years or older with infected atopic eczema received treatment with fusidic acid/betamethasone lipid cream, fusidic acid/betamethasone cream, or the lipid cream vehicle. At the end of 2 weeks' treatment, total severity scores were reduced by 82.9% in the lipid cream group, 82.7% in the cream group, and 33.0% in

the vehicle group. Successful bacteriological response was seen in 89.7%, 89.6% and 25.0% of patients, respectively, and adverse events of pruritus or a burning sensation in 2.6%, 1.6% and 13.6%, respectively.

The new fusidic acid/betamethasone lipid cream has thus been shown to be as effective and well tolerated as fusidic acid/betamethasone cream. It provides patients and doctors with an alternative, so that patients' individual needs and preferences for emollient treatment can be better met.

Efficacy of fusidic acid/steroid combination products: Comment

The unifying theme of all these comparative studies was the efficacy of the fusidic acid/corticosteroid preparations. These were as effective as or more effective than the comparator preparations in terms of clinical efficacy, antibacterial activity and cosmetic acceptability.

DEVELOPMENT OF RESISTANCE

A major concern in using topical antibiotics is the emergence of antibiotic drug resistance. This is of particular importance with an antibiotic such as fusidic acid, which has a major medical role against methicillin-resistant staphylococci. Since the launch of topical fusidic acid, resistance levels to this antibiotic have remained low (25). Resistance to fusidic acid has been reported in closed environments, such as hospital wards, where the risk of cross-infection is high (26). Increased levels of resistance have also been reported in dermatology departments where fusidic acid/corticosteroid use has been high (27). It is possible that the way these preparations were used was responsible, as a retrospective review of 8 previously conducted clinical trials using fusidic acid/betamethasone to treat infected or potentially infected eczema showed that the emergence of fusidic acid-resistant strains was observed in only 2.8% of patients given fusidic acid-containing cream, compared with 2.5% given the comparator cream (28). These authors concluded that fusidic acid/betamethasone, when given for short periods, leads to little selective pressure for the development of resistance to fusidic acid. Furthermore, in the recent prospective study of the new fusidic acid/betamethasone lipid cream, selection of *S. aureus* isolates resistant to fusidic acid was seen in 2.3% of the patients who applied fusidic acid, and 1.9% of those given the vehicle only, which again suggests that short-term use of fusidic acid/betamethasone does not increase resistance (24).

This conclusion has been supported by two studies looking at the emergence of drug resistance to fusidic acid in patients with eczema treated for short, 2-week periods with topical preparations containing fusidic

acid. The first was a case-controlled study to assess the effect of short-term use of fusidic acid/betamethasone cream in clinically infected eczema on the emergence of fusidic acid-resistant strains of *S. aureus* (FusR *S. aureus*) (29). Forty-six patients were randomized to receive either the fusidic acid/betamethasone cream or topical 2% mupirocin ointment plus betamethasone cream used twice daily for 2 weeks. Both groups showed a similar significant improvement in clinical severity of the eczema at the end of the study. Microbiologically, no patients developed fusidic acid resistance during the study. Baseline samples from the site of worst eczema showed FusR *S. aureus* in 26% of patients, with no significant difference between treatment groups. After 2 weeks, there was a reduction in prevalence and population density of *S. aureus* (sensitive and resistant) at the worst eczema site ($p < 0.0001$), but no significant change in the prevalence of carriage or population density of FusR *S. aureus*, although there was a downward trend in both groups. The prevalence of carriage of either *S. aureus* (sensitive and resistant) or FusR *S. aureus* in the nares did not change between baseline and 2 weeks. The authors concluded that the use of topical fusidic acid containing preparations for a 2-week period does not promote resistance to fusidic acid in the skin or nares.

The second study was an open study to examine the efficacy in atopic eczema of cyclical therapy, alternating fusidic acid/hydrocortisone cream or 1% hydrocortisone cream each for 2 weeks in children, and fusidic acid/betamethasone cream or betamethasone 0.1% cream in adults, and to determine the occurrence of fusidic acid drug resistance using this regime (Chu AC, poster presentation at American Academy of Dermatology Meeting, 2001). Of 24 patients recruited into the study, 18 were children and 6 adults. Prior to starting the study, all patients had been using a topical corticosteroid and emollient, and one patient had been using fusidic acid/hydrocortisone cream for 8 months. Seventeen patients were poorly controlled, with frequent exacerbations of their eczema often requiring a course of systemic antibiotics. Swabs of lesional skin grew *S. aureus* in 22 patients: 21 were sensitive to fusidic acid and one (the child using long-term fusidic acid/hydrocortisone) was resistant to fusidic acid. Patients responded well to cyclical therapy, with most patients being well controlled. The mother of one patient, an 8-year-old boy, kept a detailed diary before and after treatment. In the 12 months prior to the study he had required 2 hospital admissions and 4 courses of oral antibiotics for infected atopic eczema. Following the start of the trial, no further oral antibiotics were required (Fig. 2).

Patients were reviewed every month for at least 2 months (3 patients were reviewed for 12 months) and swabs were taken at each visit. As shown in Table III, the prevalence of carriage of *S. aureus* decreased over time, and no new cases of FusR *S. aureus* were observed. This

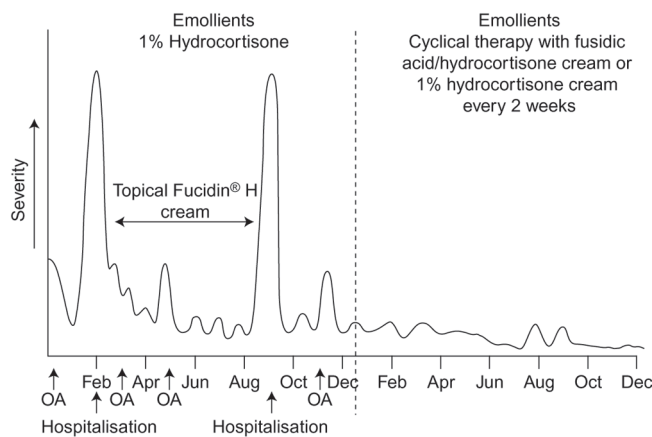


Fig. 2. Eczema diary kept by the mother of an 8-year-old child. The curve shows severity as assessed by the mother. The child received fusidic acid together with hydrocortisone cream for several months in the first year, but suffered a severe exacerbation when this was discontinued. After initiation of cyclical therapy with fusidic acid/hydrocortisone cream or 1% hydrocortisone cream every 2 weeks, severity decreased markedly, and there were no further flare-ups requiring oral antibiotics or hospitalization. OA: oral antibiotics.

study demonstrates that, even with prolonged treatment of up to one year, as long as the fusidic acid preparation is only used for 2 weeks each month, control of eczema is good and there is no selective pressure on *S. aureus* to develop fusidic acid resistance.

CONCLUSION

Eczema of all types frequently becomes infected with *S. aureus*, and infection may exacerbate the eczema, making it less responsive to topical corticosteroids. The short-term use of a fusidic acid corticosteroid combination preparation effectively controls infection without risk of drug resistance developing. In the author's clinic, all patients referred with eczema are treated with daily baths, emollients, moisturizers and cyclical 2-week treatments with a fusidic acid/corticosteroid preparation of suitable strength alternating with corticosteroid alone. Where xerosis is a particular problem, the new formulation of fusidic acid/betamethasone in a lipid cream would be indicated.

Table III. Culture results for 24 patients with atopic eczema treated with cyclical therapy, alternating fusidic acid/hydrocortisone cream or 1% hydrocortisone cream every 2 weeks in children ($n = 18$), and fusidic acid/betamethasone cream or betamethasone 0.1% cream in adults ($n = 6$)

Time point	Patients with fusidic acid sensitive <i>S. aureus</i> n (%)	Patients with fusidic acid resistant <i>S. aureus</i> n (%)
Recruitment ($n = 24$)	21 (88)	1 (4.1)
2 months ($n = 24$)	17 (71)	0
6 months ($n = 16$)	9 (57)	0
9 months ($n = 7$)	4 (56)	0
12 months ($n = 3$)	1 (33)	0

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DISCUSSION

Q: Would you use fusidic acid for all patients with acute atopic eczema, or are there certain criteria, e.g. impetiginization? Even patients with no visible impetiginization could still be heavily colonized with *S. aureus*.

Chu: This is a good question. We do not get the results of swabs back for several days so we have to go with our clinical instinct. My clinical instinct is that if there are signs such as exacerbation of the eczema, erythema, or broken skin, then infection is present. These patients invariably do very well on fusidic acid/steroid combinations. Furthermore, there is no risk in using these combinations: as we have heard, development of resistance is very low, fusidic acid is not allergenic, and it is well tolerated. Therefore, in this scenario I always use a fusidic acid/steroid combination, for up to 2 weeks at a time. Fusidic acid should not be used continuously for more than 2 weeks.

Q: Could you comment on the use of silver in undergarments to decrease bacterial burden?

Chu: Silver has a good antibacterial effect, but I did not include it in this presentation because it is not available in combination with a steroid. It is useful in situations where secondary infection is a concern, such as second-degree burns, and it is now a component in many of the preparations used for leg ulcers.

Q: How do you treat patients with atopic eczema who have methicillin-resistant *S. aureus* (MRSA)?

Chu: MRSA creates problems as the patients have to be isolated and seen in a separate room. We very rarely see MRSA in our atopic eczema outpatients – very occasionally it is seen in patients who have been admitted to hospital. If this occurs, Hammersmith Hospital has special eradication procedures that have to be followed, including the use of mupirocin and systemic antibiotics.

Q: Can fusidic acid be used in such cases?

Chu: I am bound by hospital policy, and at Hammersmith the policy is to use mupirocin.

Q: How do you treat resistant atopic eczema of the eyelids?

Chu: Atopic eczema frequently occurs on the face among both children and adults. The eyelids are very sensitive and often become infected. In these cases, I see no problem in using the fusidic acid/hydrocortisone combination for short-term treatment. If the problem persists, as the skin is so thin I would use a topical immunomodulatory, such as pimecrolimus. This can be used in combination with cyclical fusidic acid cream (2 weeks on and 2 weeks off) to keep infection under control.

Q: With long-term use of steroids, do you see problems such as tachyphylaxis?

Chu: I have not encountered any tachyphylaxis. I always give my patients diaries: in any one month, they use fusidic acid/steroid combination therapy for the first 2 weeks, and steroids only for the next 2 weeks. If the eczema is under control they can stop using steroids – thus they do have intermittent breaks. When the infection is brought under control, the skin condition and dryness often improve markedly. Because the “vicious cycle”, described by Dr Leung, has been interrupted, it is much easier to achieve good results using only emollients, and the patients seem more responsive to steroids when they do use them.