

CLINICAL REPORT

Fusidic Acid-resistant *Staphylococcus aureus* in Impetigo Contagiosa and Secondarily Infected Atopic Dermatitis

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Fusidic acid-resistant *Staphylococcus aureus* (FRSA) has been identified as a causative agent in outbreaks of impetigo and its emergence has been associated with increased use of topical fusidic acid. The frequency of FRSA in atopic dermatitis (AD) has been less extensively investigated. The aim of this study was to investigate the bacterial spectrum and frequency of FRSA in patients with impetigo or secondarily infected AD. A prospective study in our clinic in 2004 to 2008 included 38 patients with impetigo and 37 with secondarily infected AD. *S. aureus* was the predominant finding in all groups (bullous impetigo 92% (12/13), impetigo 76% (19/25) and secondarily infected AD 89% (33/37)). Seventy-five percent of *S. aureus* were fusidic acid resistant in bullous impetigo, 32% in impetigo and 6.1% in secondarily infected AD (bullous impetigo vs. AD $p < 0.0001$, impetigo vs. AD $p < 0.05$). We then performed a retrospective patient record review including all patients with impetigo or secondarily infected AD seen at the clinic during the first and last year of the prospective study. In the first year 33% (19/58) of the *S. aureus* isolates were fusidic acid-resistant in impetigo and 12% (5/43) in secondarily infected AD ($p < 0.05$). In the last year corresponding values were 24% (6/25) for impetigo and 2.2% (1/45) for AD ($p < 0.01$). In summary, the prospective study and the patient record review both showed higher FRSA levels in impetigo than in AD. FRSA levels were persistently low in AD. Continued restrictive use of topical fusidic acid is advised to limit an increase in FRSA levels in dermatology patients. **Key words:** fusidic acid; *Staphylococcus aureus*; impetigo; atopic dermatitis.

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Skin and soft tissue infections (SSTIs) are common conditions managed by dermatologists, general practitioners and other medical professionals, both in outpatient care and in hospitals. Impetigo contagiosa (in the following referred to as impetigo) and secondarily infected atopic dermatitis (AD) are two SSTIs often caused by *S. aureus*. One treatment strategy for these infections has

been the use of a topical preparation of fusidic acid, a narrow spectrum anti-staphylococcal antibiotic. Fusidic acid is also used in systemic treatment of conditions such as osteomyelitis and joint graft infections and can sometimes be a useful treatment option for methicillin-resistant *S. aureus* (MRSA) infection. *In vitro* exposure to fusidic acid selects for resistance in *S. aureus*, which is why fusidic acid is usually not administered as a single antimicrobial agent in systemic treatment (1). In contrast, topical preparations of fusidic acid have often been prescribed as single therapy. Despite this there were few clinical reports on staphylococcal resistance to fusidic acid in dermatology from its introduction in the 1960s and in the three decades that followed (2).

In the last 10 years, a fusidic acid-resistant clone of *S. aureus* (FRSA) associated with impetigo has emerged. The first reports of this shift in the resistance pattern of *S. aureus* came from Sweden and Norway in 2002 after widespread outbreaks of impetigo (3, 4). In 2003, due to the reports of FRSA, the Swedish Medical Products Agency recommended avoidance of topical fusidic acid in the treatment of impetigo (5–7). Instead, cleansing of crusts with water and a mild soap and, when necessary, oral antibiotics, was advised.

Later studies have established the presence of the same FRSA clone in the UK, Ireland and France (8–10). This particular FRSA has been carefully characterized and termed the epidemic European fusidic acid-resistant impetigo clone (EEFIC) (11). The EEFIC chromosome carries the fusidic acid-resistance determinant *fusB* (12, 13). The *fusB* gene encodes a protein that binds to elongation factor G (EF-G), a key player in staphylococcal protein synthesis. Fusidic acid targets EF-G and inhibits translation from RNA to protein. The *fusB* protein induces resistance through binding to EF-G, thereby protecting it from fusidic acid and maintaining protein synthesis and viability of the bacteria (14). In addition to fusidic acid, the EEFIC is resistant to penicillin and, in some cases, erythromycin (11).

While fusidic acid-resistance is an established problem in impetigo there are fewer reports on FRSA in AD. The resistance pattern of *S. aureus* in patients with AD is of special interest since the skin of these patients is colonized with *S. aureus* in up to 90% of cases (15). In published reports the frequency of FRSA is highly variable. In 2002 Sule et al. (16) tested 62 patients with

AD from an outpatient clinic in Cambridge and found FRSA in 50%. Peeters (17) reported increasing rates of FRSA in patients with AD referred to their dermatology inpatient department in Utrecht, The Netherlands, ranging from 9.7% in 1995 to 23.4% in 2001. In 2004 Hoeger (18) described a group of 115 children presenting with AD in the Division of Paediatric Dermatology, University of Hamburg. Six percent of the *S. aureus* strains were fusidic acid-resistant. Recently, Niebuhr et al. (19), Hannover, Germany, investigated antimicrobial resistance in 102 children and adults with AD and *S. aureus*-positive skin swabs. They found FRSA in 25% of cases (19).

Because of the relatively few studies on FRSA in AD we wanted to compare FRSA frequencies in impetigo and secondarily infected AD in our clinical setting at the Department of Dermatology and Venereology, Sahlgrenska University Hospital, Gothenburg, Sweden.

METHODS

Prospective study 2004 to 2008

The study was performed at the Department of Dermatology and Venereology at Sahlgrenska University Hospital, Gothenburg, Sweden, from June 2004 to May 2008. The study was approved by the regional ethics committee in Gothenburg.

For a first visit to the Department of Dermatology patients need a referral, which is usually issued by a general practitioner at a primary healthcare facility. The Department of Dermatology has clinics in three hospitals in the greater Gothenburg area. The largest clinic is situated at Sahlgrenska Hospital. Patients who presented to the authors at this clinic with either impetigo or secondarily infected AD were asked to participate. Patients were not selected to be seen by the authors. In addition to examination of skin lesions, a swab sample for bacterial culture was taken from a clinically infected skin lesion in each patient. Bacterial cultures were sent to the Department of Clinical Bacteriology, Sahlgrenska University Hospital, according to standard procedure. Fusidic acid is included in the routine susceptibility testing for all *S. aureus* isolates and is carried out with the disc diffusion method. Isolates were characterized as FRSA or fusidic acid-sensitive *S. aureus* (FSSA), but genotype (EFFIC or not) was not determined. The diagnosis (impetigo, bullous impetigo or secondarily infected AD) was based on clinical evaluation before the result of the bacterial culture was available.

Seventy-five patients, 38 presenting with impetigo (13 of whom had bullous impetigo) and 37 with secondarily infected AD agreed to participate in the study. The age range in the impetigo group was 1–49 years, with a mean of 18 years and a median of 17 years. The age range in the bullous impetigo group was 2–30 years, with a mean of 18 years and a median of 18 years. The age range in the secondarily infected AD group was 6 months to 62 years, with a mean of 30 years and a median of 29 years.

Patient record review

The patient record review covered all clinics belonging to the Department of Dermatology and was carried out in 2009. The review was approved by the regional ethics committee in Gothenburg. One or several diagnostic codes from the Swedish version of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), are assigned to every patient visit by the dermatologist who was consulted. All

patient records are computerized. A search for all patients given the diagnostic codes for “impetigo”, “secondarily infected dermatoses”, “prurigo Besnier”, “otherwise specified AD” or “AD unspecified” in the time periods June 2004 to May 2005 (first year of the prospective study) and June 2007 to May 2008 (last year of the prospective study) was made. This rendered a total of 2353 patient records (1184 from June 2004 to May 2005 and 1169 from June 2007 to May 2008) that were reviewed. A total of 283 records described dermatoses other than impetigo or AD or lacked a definitive diagnosis and were excluded. All records describing ongoing impetigo or secondarily infected AD together with the securing of a bacterial culture from afflicted skin were selected for further analysis. These records also included those of the patients who were included in the first and last year of the prospective study. The results of the bacterial cultures including antibiotic resistance patterns for *S. aureus* were collected from the register at the Department of Clinical Bacteriology.

In June 2004 to May 2005 there were 101 patients with impetigo and a bacterial culture from clinically infected skin was taken in 66 of those patients. The age range in the impetigo group ($n=66$) was 9 days to 81 years, with a mean of 26 years and a median of 23 years. There were 966 patients with AD, of whom 450 patients presented with a flare-up and 144 of those patients received oral antibiotics. A bacterial culture was taken in 55 of the patients receiving antibiotics. There were no bacterial cultures from the patients with flare-ups who were treated without oral antibiotics. The age range in the secondarily infected AD group ($n=55$) was 7 months to 86 years, with a mean of 25 years and a median of 21 years.

In June 2007 to May 2008 there were 53 patients with impetigo and a bacterial culture was taken in 33 of those patients. The age range in the impetigo group ($n=33$) was 1–90 years, with a mean of 31 years and a median of 21 years. There were 950 patients with AD, of whom 545 patients presented with a flare-up and 124 of those patients received oral antibiotics. A bacterial culture was taken in 55 of the patients receiving oral antibiotics. The age range in the secondarily infected AD group ($n=55$) was 1–90 years, with a mean of 29 years and a median of 24 years.

Statistics

The statistical test used to compare frequencies of FRSA between groups was Fisher's exact test. The significance level was $p < 0.05$.

RESULTS

Prospective study 2004 to 2008

Impetigo. Thirty-eight patients presenting with clinical signs of impetigo agreed to participate in the study. Thirteen of these patients had intact blisters or identifiable recently ruptured blisters and were therefore given the diagnosis bullous impetigo. The remaining 25 patients were given the diagnosis impetigo.

S. aureus was the main bacterial finding in 17 cultures (68%) from patients with impetigo (Table I). MRSA was found in one patient (4.0%) in the impetigo group, a 6-year old boy who had not been hospitalized and who had not travelled outside Sweden. One patient (4.0%) presented with *S. aureus* and haemolytic group A streptococci. Coagulase-negative staphylococci and *Bacillus cereus* were other infrequent findings in cultures.

Table I. Prospective study 2004 to 2008. Frequency and distribution of bacteria in impetigo and bullous impetigo. For each bacteria/group of bacteria the number of patients is presented

	Impetigo (n = 25)	Bullous impetigo (n = 13)
<i>S. aureus</i>	17 (68%)	11 (85%)
Methicillin-resistant <i>S. aureus</i> (MRSA)	1 (4.0%)	–
<i>S. aureus</i> + Group A streptococci	1 (4.0%)	1 (7.6%)
Coagulase negative staphylococci	2 (8.0%)	–
<i>Bacillus cereus</i>	1 (4.0%)	–
Normal skin flora	1 (4.0%)	–
Negative culture	2 (8.0%)	1 (7.6%)

Bullous impetigo. *S. aureus* was found in 11 cultures (85%) from patients with bullous impetigo. One patient (7.6%) presented with *S. aureus* and haemolytic group A streptococci. One patient (7.6%) had a negative culture.

Secondarily infected AD. Thirty-seven patients with clinical signs of secondarily infected AD were included in the study. *S. aureus* was the main finding in 28 patients (76%) (Table II). In addition, MRSA was found in one patient (2.7%), a 20-year-old man who had spent the last 6 months abroad and had visited outpatient clinics in Thailand and rural areas in Vietnam due to an infected insect bite of the foot. Three patients (8.1%) presented with *S. aureus* and haemolytic group A streptococci and one patient (2.7%) with *S. aureus* and β -haemolytic group C streptococci.

Fusidic acid-resistant *S. aureus* (FRSA). Resistance to fusidic acid was tested in all but one of the *S. aureus* isolates found during the course of this study. In the impetigo group a total of 19 patients had *S. aureus* (17 patients with *S. aureus*, one patient with MRSA and one patient with *S. aureus* in combination with haemolytic group A streptococci). Six of these patients (32%) had FRSA (Fig. 1). The MRSA was sensitive to fusidic acid.

In the bullous impetigo group 12 patients with *S. aureus* were found (11 patients with *S. aureus* and one patient with *S. aureus* in combination with haemolytic group A streptococci). Nine of these patients (75%) had FRSA.

In the secondarily infected AD group a total of 33 patients with *S. aureus* were found (28 patients with *S. aureus*, one patient with MRSA, three patients with *S. aureus* in combination with haemolytic group A strep-

Table II. Prospective study 2004 to 2008. Frequency and distribution of bacteria in secondarily infected atopic dermatitis (AD). For each bacteria/group of bacteria the number of patients is presented

	Secondarily infected AD (n = 37)
<i>S. aureus</i>	28 (76%)
Methicillin-resistant <i>S. aureus</i> (MRSA)	1 (2.7%)
<i>S. aureus</i> + Group A streptococci	3 (8.1%)
<i>S. aureus</i> + Group C streptococci	1 (2.7%)
Coagulase negative staphylococci	2 (5.4%)
Negative culture	2 (5.4%)

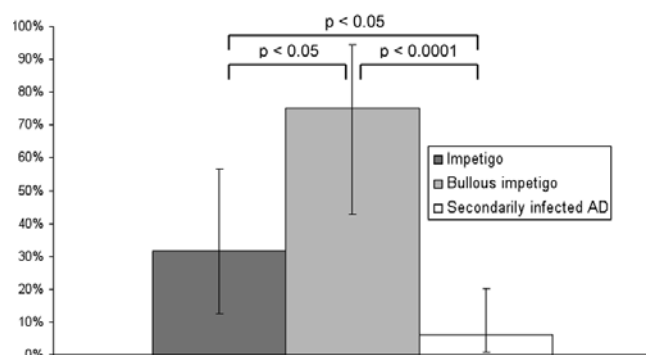


Fig. 1. Prospective study 2004 to 2008. Frequency (%) of fusidic acid-resistance in *S. aureus* (FRSA) isolates from patients with impetigo, bullous impetigo or secondarily infected atopic dermatitis (AD). Frequency of FRSA was compared between groups with Fisher's exact test. Values are presented with a 95% confidence interval. Significance level was $p < 0.05$.

tococci and one patient with *S. aureus* in combination with β -haemolytic group C streptococci). Two of these patients (6.1%) had FRSA. The MRSA was sensitive to fusidic acid. In one case resistance to fusidic acid was not tested (reason unknown).

There were statistically significant differences in the frequency of FRSA between groups. FRSA were more frequent in impetigo and bullous impetigo than in secondarily infected AD ($p < 0.05$ and $p < 0.0001$, respectively). Furthermore, FRSA were found more often in bullous impetigo than in impetigo ($p < 0.05$).

Patient record review

In the time period from June 2004 to May 2005 bacterial cultures were taken in 66 patients with impetigo and in 55 patients with secondarily infected AD. *S. aureus* was found in 88% (58/66) of patients with impetigo and in 78% (43/55) of patients with secondarily infected AD. The result from the bacterial cultures is summarized in Tables III and IV. In impetigo 33% (19/58) of the *S. aureus* isolates were fusidic acid-resistant, but in secondarily infected AD the corresponding value was only 12% (5/43) ($p < 0.05$) (Fig. 2).

In the time period from June 2007 to May 2008 bacterial cultures were taken in 33 patients with impetigo and in 55 patients with secondarily infected AD. The result from the bacterial cultures is summarized in Tables III and IV. *S. aureus* was found in 76% (25/33) of patients with impetigo and in 84% (46/55) of patients with secondarily infected AD. In impetigo 24% (6/25) of the *S. aureus* isolates were fusidic acid-resistant and the corresponding value for secondarily infected AD was 2.2% (1/45) ($p < 0.01$) (Fig. 2). In one *S. aureus* isolate from a patient with secondarily infected AD (patient included in the prospective study) fusidic acid-resistance was not determined.

There was no statistically significant change in the frequencies of FRSA in impetigo or secondarily in-

Table III. Patient record review. Frequency and distribution of bacteria in impetigo. For each bacteria/group of bacteria the number of patients is presented

	Impetigo	
	June 2004 to May 2005 (n = 66)	June 2007 to May 2008 (n = 33)
<i>S. aureus</i>	45 (68%)	21 (64%)
Methicillin-resistant <i>S. aureus</i> (MRSA)	—	1 (3.0%)
<i>S. aureus</i> + Group A streptococci	2 (3.0%)	—
<i>S. aureus</i> + Group B streptococci	5 (7.6%)	2 (6.1%)
<i>S. aureus</i> + Group G streptococci	—	1 (3.0%)
<i>S. aureus</i> + other bacteria	6 (9.1%)	—
Coagulase negative staphylococci	2 (3.0%)	2 (6.1%)
Group A streptococci	1 (1.5%)	1 (3.0%)
<i>Bacillus cereus</i>	1 (1.5%)	—
Other bacteria	—	2 (6.1%)
Negative culture	4 (6.1%)	3 (9.1%)

infected AD when the two time periods were compared ($p=0.60$ for impetigo and $p=0.11$ for secondarily infected AD).

DISCUSSION

In this study we investigated the spectrum of bacteria and frequency of fusidic acid-resistance among *S. aureus* isolates in patients with impetigo, bullous impetigo and secondarily infected AD. We performed a prospective study in 2004 to 2008 in one of the clinics of the Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden. Patients with impetigo or secondarily infected AD seen by the authors in a clinic with many urgent referrals were asked to participate. This approach yielded a series of patients who were not strictly consecutive, since time does not always allow for inclusion of patients in a study. To investigate the possibility of a selection bias we performed a retrospective patient record review including

Table IV. Patient record review. Frequency and distribution of bacteria in secondarily infected atopic dermatitis (AD). For each bacteria/group of bacteria the number of patients is presented

	Secondarily infected AD	
	June 2004 to May 2005 (n = 55)	June 2007 to May 2008 (n = 55)
<i>S. aureus</i>	30 (55%)	22 (40%)
Methicillin-resistant <i>S. aureus</i>	1 (1.8%)	1 (1.8%)
<i>S. aureus</i> + Group A streptococci	3 (5.5%)	6 (11%)
<i>S. aureus</i> + Group B streptococci	2 (3.6%)	8 (15%)
<i>S. aureus</i> + Group C streptococci	2 (3.6%)	1 (1.8%)
<i>S. aureus</i> + Group G streptococci	2 (3.6%)	5 (9.1%)
<i>S. aureus</i> + Group A & G streptococci	—	1 (1.8%)
<i>S. aureus</i> + other bacteria	3 (5.5%)	2 (3.6%)
Group G streptococci	—	1 (1.8%)
Coagulase negative staphylococci	5 (9.1%)	2 (3.6%)
Other bacteria	3 (5.5%)	3 (5.5%)
Negative culture	4 (7.3%)	3 (5.5%)

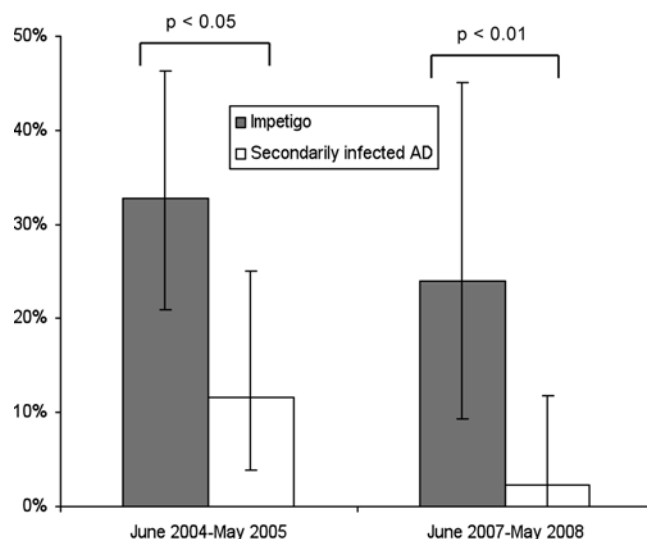


Fig. 2. Patient record review. Frequency (%) of fusidic acid-resistance in *S. aureus* (FRSA) isolates from patients with impetigo or secondarily infected atopic dermatitis (AD) in the retrospective patient record review (June 2004 to May 2005 and June 2007 to May 2008). Frequency of FRSA was compared between groups with Fisher's exact test. Values are presented with a 95% confidence interval. Significance level was $p < 0.05$.

all bacterial cultures taken from the skin of patients with ongoing impetigo or secondarily infected AD during the first and last year of the prospective study. Patient records from all clinics of the Department of Dermatology were included in this review. Unlike the prospective study, the patient record review did not allow for a differentiation of bullous and non-bullous impetigo since we could not be sure that all dermatologists at the clinic documented the exact appearance of lesions. The prospective study and the patient record review gave a similar result regarding age-distribution of patients, bacterial spectrum and frequency of fusidic acid-resistance in *S. aureus* isolates.

S. aureus was the predominating bacteria in impetigo and secondarily infected AD (76–92%) in both the prospective study and the patient record review. The frequency of FRSA was consistently higher in impetigo than in AD. In the prospective study, where the impetigo group was subdivided, 75% of *S. aureus* isolates found in bullous impetigo were fusidic acid-resistant.

In Sweden both impetigo and AD are treated by general practitioners as well as by dermatologists. It is reasonable to assume that patients with more severe symptoms are referred to a dermatologist and this is important to consider when evaluating the data presented here. A similar study in a primary healthcare setting might have rendered another result.

This small study shows a low frequency of FRSA among *S. aureus* isolates in patients with secondarily infected AD (2.2–12%) and, encouragingly, it remained low during the study. Hopefully, this reflects the situation at large in Sweden. Some indication of this comes from the antimicrobial resistance-surveillance

database ResNet, which is based on routine susceptibility testing in laboratories from all Swedish counties (20). ResNet offers continuous monitoring of FRSA levels throughout the country (based on data from 100 consecutive strains of *S. aureus* sent in by all county laboratories once yearly). The data provided by ResNet represent a sample of all cultures positive for *S. aureus* and are not restricted to dermatology patients. In the years 2004 to 2008 the rates of FRSA have averaged 5.9% in Sweden and 6.8% in the Gothenburg region, which is of the same magnitude as in our patients with secondarily infected AD.

In contrast to the data presented in this study, some authors have reported much higher levels of FRSA in AD in other European countries (16, 17, 19). One reason for the current low levels of FRSA in Sweden might be the recommendation which was issued by the Swedish Medical Products Agency in 2003, which states that topical fusidic acid should not be used in the treatment of impetigo. We have followed this recommendation since it was introduced. Although we did not see a rise in FRSA-levels in impetigo or secondarily infected AD during this study, we did not detect a decline either. This could be due to the small number of patients in the study, but it could also be speculated that community FRSA levels have reached a plateau. However, a marked drop in sales of topical fusidic acid preparations has been paralleled with a decrease in the frequency of FRSA in SSTIs (not specified) in primary healthcare in Sweden. This was described in a study in eight Swedish counties, showing that a sales peak for topical fusidic acid was reached in 2001, followed by a peak in FRSA-levels in 2002 (as reported from ten different laboratories). In the two years that followed, topical fusidic acid sales and FRSA levels declined (21). In contrast, persisting high levels of FRSA in dermatology patients, despite a drop in the use of topical fusidic acid, was reported from the UK (22). During the same time period (2001 to 2004) levels of FRSA increased in non-dermatology outpatients and hospital patients. This was attributed to an attained reservoir of FRSA in the community and it was speculated that the effect of restricted use of topical fusidic acid may first be seen after a lag period.

Other authors have studied the relationship between prescription and use of topical fusidic acid and prevalence of FRSA (16, 22–25). Sule et al. (16) questioned 62 dermatology outpatients with AD and *S. aureus* about their use of topical fusidic acid in the preceding 6 months. Recent exposure to topical fusidic acid was correlated with the presence of FRSA. Subgroups were small, but the study indicated that prolonged or intermittent use was associated with increased carriage of FRSA. Ravenscroft (23) documented an association between high levels of prescription of topical fusidic acid and an increase in FRSA in Harrogate, North Yorkshire,

UK. In a later publication by the same author there was no indication that short-term (2 weeks) use of a topical fusidic acid/corticosteroid combination in patients with AD increased FRSA (24).

Although it could be argued that the decrease in FRSA observed in primary healthcare in Sweden is part of the normal dynamic of an epidemic, it seems wise to continue to use topical fusidic acid with caution. We believe that investigating antibiotic resistance in *S. aureus* isolates from dermatology patients is of great importance. Firstly, with the well-documented high level of *S. aureus* colonization on atopic skin it would be unfortunate to see a rise in FRSA levels in patients with AD, since they could serve as a community reservoir. In that context it is important to note that the patients with AD in this study presented with signs of secondary infection. Thus, the data does not reflect colonization in a random sample of patients with AD but rather the flora of lesions in patients with flare-ups. There is, however, no logical reason to assume that patients with AD without flare-ups would have higher levels of FRSA. Secondly, surveillance of both MRSA and FRSA in dermatology patients is vital because of the rapid spread of community-associated MRSA (CA-MRSA). CA-MRSA strains were first discovered in the San Francisco region in the mid-1990s and typically cause necrotic skin lesions. CA-MRSA exhibit other resistance patterns than hospital-acquired MRSA, and some CA-MRSA strains (as well as some MRSA strains) are sensitive to fusidic acid (26). Therefore, systemic treatment with fusidic acid, in combination with other antibiotics, could be of potential use in MRSA eradication (27). To waste this possibility would be unwise, as reviewed by Howden & Grayson (1).

In conclusion, we report high levels of FRSA in both bullous and non-bullous impetigo, whereas FRSA-levels were persistently low in secondarily infected AD. We suggest that topical use of fusidic acid should be avoided in order to prevent an increase in FRSA levels in the community. FRSA has been shown to have increased resistance to other antibiotics. Furthermore, fusidic acid is used systemically for the treatment of severe infections, such as osteomyelitis, joint graft infections and even MRSA eradication. Indiscriminate use of topical fusidic acid could potentially make the drug worthless in a near future. Repeated investigations of this kind in the same clinical setting is of value to monitor any changes in resistance patterns that restrictive use of fusidic acid can induce.

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The authors declare no conflict of interest.

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