

Short Report

Antimicrobial susceptibility of skin-colonizing *S. aureus* strains in children with atopic dermatitis

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Children with atopic dermatitis (AD) are prone to recurrent cutaneous and occasional systemic infections caused by *Staphylococcus aureus*. Antibiotic therapy represents an important component of the overall management of AD, especially during exacerbations of disease. Erythromycin is still widely used as a first-line antibiotic for this indication. We studied 115 consecutive children (mean age: 2.7 yr, range: 0.2–15) with moderate to severe AD (mean SCORAD: 43.2, range: 16–77) presenting to our outpatient department. *Staphylococcus aureus* was isolated from 100 of 115 (87%). Antimicrobial susceptibility testing revealed resistance against erythromycin in 18 and against roxithromycin in 19%, respectively. Six percentage of the strains were resistant or only intermediately susceptible to fusidic acid, 13% to amoxicillin and 1% to clindamycin. All strains isolated were susceptible to oxacillin, amoxicillin/clavulanic acid, cefadroxil and cefuroxim. The high rate of primary resistance to macrolides should be born in mind when starting antibiotic therapy in children with AD. Since Gram-positive cocci represent the only relevant microbial agents in AD, first generation cephalosporins such as cefadroxil, whose antimicrobial spectrum is basically restricted to Gram-positive bacteria, would appear to be the ideal first-line antibiotics for the treatment of bacterial superinfections.

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The skin of patients with atopic dermatitis (AD) is persistently colonized with staphylococci: 90–95% of children with AD (as opposed to 15–25% of healthy controls) harbour *Staphylococcus aureus* on their skin surface (1, 2). Colonization is not restricted to eczematous lesions, but staphylococci tend to spread to unaffected sites as well – a process referred to as ‘self-contamination’ (3). *Staphylococcus aureus* colonization density per square centimetre is 100- to 1000-fold higher in AD than in healthy carriers, and it is correlated with disease severity (1, 4). Individual strains of staphylococci tend to persist for a long time in AD (2). Dryness and scaliness of the skin surface facilitate their adhesion, and excoriations promote the development of subcutaneous infections (5).

Recurrent staphylococcal infections are very common among AD patients (6). In addition to cutaneous infections (folliculitis, panaritium, abscess formation etc.), serious systemic infections such as osteomyelitis (7), endocarditis (8) and septicaemia (9) have repeatedly been reported and traced to cutaneous *S. aureus* strains. Furthermore, staphylococci can be spread from the skin surface of AD patients to newborns or other persons susceptible to invasive *S. aureus* infections (10). Staphylococcal colonization is therefore relevant both for the AD patient and susceptible contact persons. For the management of widespread cutaneous infections associated with exacerbations of AD, systemic antibiotic therapy is mandatory. We therefore assessed antimicrobial susceptibility of *S. aureus* strains

isolated from children with AD presenting to our outpatient department.

Material and methods

Skin swabs were taken from 115 consecutive children presenting with AD to the University of Hamburg, Department of Dermatology, Division of Paediatric Dermatology. Swabs were taken from affected areas only. Children who had received topical or systemic antibiotic therapy for any reason within the preceding 4 wk were excluded from the study. The children had a mean age of $2.71 \pm \text{yr}$ (range: 0.2–15). Diagnosis of AD was established according to the criteria delineated by Hanifin and Rajka (11). Severity of AD was assessed using the SCORAD score (12). The mean SCORAD score was 43.2 ± 14.4 (range: 16–77), representing moderate to severe AD.

Staphylococcal strains were isolated on blood agar plates (Columbia blood agar; BioMérieux, Nürtingen, Germany) and tested for coagulase activity with a coagulase slide test (Slidex Staph Plus; BioMérieux). Individual colonies were suspended in sterile sodium chloride (0.9%) suspension. Antimicrobial susceptibility was assessed with the agar disc-diffusion method following standard procedures (13). The following antibiotic discs were used: amoxicillin (25 µg), amoxicillin/clavulanate (20/10 µg), oxacillin (1 µg), cefuroxim (30 µg), erythromycin (15 µg), clindamycin (2 µg), fusidic acid (10 µg) (all discs from BioMérieux), cefadroxil (30 µg) and roxithromycin (15 µg) (discs from Becton Dickinson, Heidelberg, Germany). Bacterial suspensions were plated onto Müller-Hinton agar (BioMérieux) and cultured over night at 37°C. Sensitivity, intermediate sensitivity, and resistance were determined by the zone of complete growth inhibition around each disk according to reference standards (Table 1). Strains were stored on nutrient soy broth agar (Oxoid, Wesel, Germany).

Results

One hundred strains of *S. aureus* were isolated from 115 patients (87% positive). Results of antimicrobial susceptibility testing are summarized in Fig. 1. Among the antibiotics tested, macrolides showed the highest rates of resistance (erythromycin 18%, roxithromycin 19%, with another 3% of the strains only intermediately sensitive). Not unexpectedly, given the comparatively high prevalence of penicillinase-producing staphylococci, 13% of the strains were resistant to amoxicillin, but none of the strains was

Table 1. Antimicrobial susceptibility of 100 *Staphylococcus aureus* strains and reference values for the disc-diffusion method

	Amoxicillin*			Amoxicillin/ clavulanic acid†			Oxacillin†			Cefadroxil*			Cefuroxim†			Clindamycin†			Erythromycin‡			Roxithromycin†			Fusidic acid§		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Inhibition (mm)	≥21	15–20	≤14	≥20	0	≤19	≥13	11–12	≤11	≥18	13–17	≤12	≥23	15–22	≤14	≥21	15–20	≤14	≥21	17–20	≤16	≥21	16–20	≤15	≥22	16–21	≤15
Distribution of susceptibility (%)	87	13	0	100	0	0	100	0	0	100	0	0	100	0	0	99	1	0	82	0	18	78	3	19	94	3	3

S, susceptible; I, intermediately susceptible; R, resistant.

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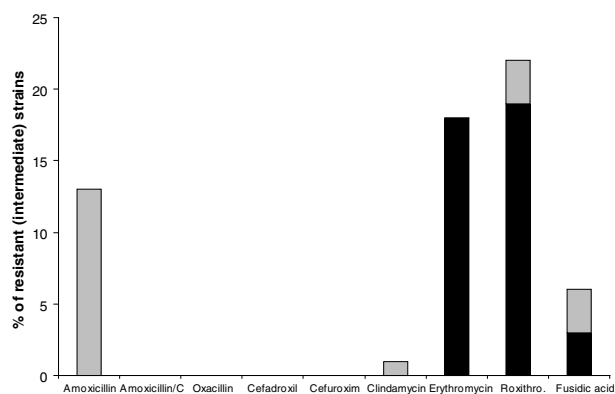


Fig. 1. Skin colonizing *Staphylococcus aureus* in children with atopic dermatitis: antimicrobial resistance patterns. Strains (n = 100) isolated from 115 children. Bright bars = intermediate susceptibility, dark bars = resistance.

resistant against the combination of amoxicillin plus the penicillinase-inhibitor clavulanic acid. Similarly, we observed no resistance against oxacillin, cefadroxil and cefuroxim and clindamycin; only one of the strains was merely intermediately susceptible to the latter.

Discussion

Our study confirms previous findings of a high prevalence of *S. aureus* skin colonization in children with AD (1, 2). We found a high rate of primary macrolide resistance among colonizing *S. aureus* strains which were however fully susceptible to penicillase-stable β -lactame antibiotics, cefadroxil and clindamycin.

In spite of growing concern about rising resistance rates, erythromycin is still one of the mainstays of therapy for this indication (4, 14, 15). Recent reports from worldwide antimicrobial surveillance programmes indicated that between 49 (USA, 16), 38 (Europe, 17) and 24% (Asia, 18) of all *S. aureus* strains are now resistant to erythromycin. In a German study published in 1998 (19), 26% of *S. aureus* strains isolated in dermatological patients were erythromycin-resistant. Higher rates of resistance in these studies when compared with ours is probably attributable to the fact that all of these studies included (mainly or exclusively) hospitalized patients, where rates of antimicrobial resistance are notoriously higher owing to increased 'selection pressure'. Data for children with AD were not available so far.

High rates of erythromycin resistance are particularly relevant to skin and soft tissue infections in children: not only are Gram-positive infections in children more common than in adults (18); erythromycin is frequently prescribed

for paediatric respiratory tract infections, and primary resistance to erythromycin is thus nearly twice as common in *S. aureus* strains isolated from children than those isolated from adults (18).

Topical therapy of bacterial skin infections offers potential advantages over systemic therapy such as absence of systemic side-effects and reduced cost. However, recurrence rates are more than twice as high in topically treated impetigo (20). Furthermore, topical therapy promotes the development of resistant strains. Resistance rates against fusidic acid are directly proportional to the amount of ointment sold; they have increased in some counties from 0 to 25% over the past years (21). We attribute the comparatively low rate of 6% intermediately sensitive or resistant *S. aureus* strains to the fact that fusidic acid is not (yet) used extensively in our study population; high levels of resistance (up to 78% of inpatients with AD) were recently reported from the UK (22). Fusidic acid, when given orally, is used as a second-line antibiotic against severe staphylococcal infections; increasing topical use of this agent would thus severely restrict its effectiveness in these situations. Finally, the possibility of severe post-streptococcal diseases such as glomerulonephritis following streptococcal impetigo should warrant oral therapy as the standard treatment of impetigo (23).

In view of the increasing incidence of streptococcal skin infections among children in general (18) – and in children with AD in particular (18) – oral antimicrobial agents with a predominant activity against these Gram-positive bacteria are required. Oxacillin and flucloxacillin are frequently recommended in textbooks as first-line therapy for children with AD and bacterial infections (15). Although highly active against *S. aureus*, they have only limited activity against streptococci and can thus not be recommended for safe coverage of both microorganism (24). Furthermore, increasing rates of methicillin-resistant *S. aureus* MRSA were observed during flucloxacillin therapy (23). Antibiotics, which fulfill the criteria cited above and that, are licensed for children are amoxicillin/clavulanate, clindamycin and first (or second) generation cephalosporins such as cefadroxil or cefuroxim, respectively. In our study, no strain was resistant against any of these agents (only one strain revealed intermediate sensitivity against clindamycin). In recent antimicrobial susceptibility surveys, only 3% of *S. aureus* strains (and none of the β -haemolytic streptococci) were resistant against amoxicillin/clavulanate (17, 18), but up to 16% of *S. aureus* and 10% of *S. pyogenes* were resistant to clindamycin (16); again, it has to be

pointed out that these studies involved hospitalized patients. Only limited data are available for first and second generation cephalosporines. No resistance against cephalaxine was observed in 190 cases of skin infections caused by *S. aureus* and in 47 such infections caused by *S. pyogenes* (18); resistance of *S. aureus* against cefazoline was observed in 16% (16).

Amoxicillin/clavulanate covers Gram-positive as well as many Gram-negative strains; clindamycin is active against a variety of anaerobic bacteria (24). Gastrointestinal side-effects are therefore frequently associated with the use of both antibiotics. However, broad coverage is not required in case of AD, since *S. aureus* and *S. pyogenes* are the only bacterial microorganism causing skin and soft tissue infections or contributing to exacerbations of AD (1, 2, 9, 15).

First generation cephalosporins such as cefadroxil are therefore particularly suitable for the treatment of flare-ups of AD associated with bacterial infections. Their antimicrobial spectrum is restricted to Gram-positive bacteria (including most penicillinase-producing *S. aureus* strains) and a limited number of Gram-negative strains such as *Haemophilus influenzae* (24). Therefore, and also because of its good intestinal absorption, the rate of gastrointestinal side-effects is much lower than with amoxicillin. Finally, their long serum half-life allows for once or twice daily therapy (as opposed to three to four applications with amoxicillin).

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