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INVESTIGATIVE REPORT

A Retrospective Analysis of Skin Bacterial Colonisation, Susceptibility and Resistance in Atopic Dermatitis and Impetigo Patients

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Atopic dermatitis (AD) and impetigo are skin conditions where bacterial colonisation and infection, especially with *Staphylococcus aureus* play an important role. We compared skin bacterial population, resistance patterns and choice of antimicrobial agents in patients diagnosed with AD and impetigo during 2005 and 2011 in our department. Number of positive cultures in the AD group were 40 and 53 in 2005 and 2011, with *S. aureus* found in 97.5% and 100%, respectively. Differences in resistance were marginal. In impetigo, *S. aureus* was found in all 70 patients in impetigo patients in 2005 and all 40 patients in 2011. Antibiotic resistance to specifically fusidic acid was more common in 2005 (22.8%) versus 2011 (5%) ($p=0.078$). The most commonly used oral antimicrobial was cefadroxil (in 57.5% and 52.8% of AD and 58.6% and 35% of impetigo patients in 2005 and 2011, respectively). Our observations confirm the high prevalence of *S. aureus* in both diseases and, interestingly, show a declining resistance trend in impetigo. *Key words: antibiotic resistance; atopic dermatitis; cefadroxil; fusidic acid; impetigo; Staphylococcus aureus.*

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Atopic dermatitis (AD) is a chronic relapsing inflammatory disorder of the skin that affects up to 20% of children worldwide (1). Impetigo, on the other hand, is a bacterial skin infection that primarily affects children (2). Overlap in terms of microbial swab results' pattern, and emergence of resistant bacterial strains occur however (3). The role of bacteria in both diseases and particularly *Staphylococcus aureus*, which can be isolated from up to 90% of atopic skin lesions, has been well established and thoroughly studied over the last decades (4). Accordingly, management of AD has been developed to include measures that help reduce *S. aureus* colonisation on the skin including oral antibiotics, antibacterial soaps and various combinations of antibiotics and steroids (5). Unfortunately, successive generations of resistant staphylococci have emerged since Kirby (6) first published the discovery of penicillinase-producing staphylococci in the 1940's. In the following years, various strains have been found to develop resistance against more antibiotics including methicillin, fusidic acid and erythromycin (7, 8). While the role of antibiotics targeting staphylococci in impetigo is well established, antibiotic treatment of *S. aureus* in AD has been the focus of debate in recent years. On the one hand, a systematic review could not find a significant difference in outcome of antibiotic treated AD in comparison with placebo (9). On the other hand, the fact that AD patients can develop exacerbations related to overgrowth of *S. aureus* could rationalise the initiation of local or oral antibiotic therapy (4, 5, 10).

The aim of this study was therefore to evaluate the significance of primarily *S. aureus* in AD and impetigo and detect if there were any changes in the colonisation pattern by comparing microbial swab results in 2005 and 2011. Our aim was also to detect if there was a notable change in our treatment measures and if that had resulted in any alteration of bacterial resistance.

MATERIAL AND METHODS

A comparative retrospective study was performed in patients with AD and impetigo with positive skin swab results during 2005 and 2011. The data was retrieved from patients' medical records with the above-mentioned diagnoses which were either admitted to our wards at Sahlgrenska University Hospital or attended our dermatology outpatient clinics. The 2 groups were then compared in terms of age, sex, bacterial culture results, resistance, choice of antimicrobial agent and whether the chosen treatment was changed after the bacterial culture results. Missing data from our registry were collected afterwards with the help of the microbiology lab records.

The study was initiated by a thorough electronic search of all patient visits during 2005 and 2011 with the code L20 (AD). The diagnostic codes were derived from the Swedish version of the International Classification of Diseases, tenth revision "ICD-10" and it was assigned by the designated dermatologist during each visit. Thereafter, visits including nurses' visits for ultraviolet therapy, dressing application and visits where no bacterial culture was taken were excluded. Afterwards, only patients whose AD rash had been swabbed for culture from lesional skin were chosen and analysed given that the culture result was positive. Skin swabs were not taken as a routine but merely on the suspicion of a secondary infection. Patient records from 2005 and 2011 were then compared in terms of age, sex, bacterial culture result, resistance and the choice of antimicrobial agent at the first visit and whether that treatment was changed after the culture result. The same process was applied in impetigo patients (L010) and secondary infected dermatoses

(L011) in 2005 and 2011. Similarly, results from both years were compared with regards to the above-mentioned categories. In general, there was no overlap between impetigo and AD groups.

All data were analysed with R version 3.0.3 (The R Foundation for Statistical Computing Vienna, Austria). Fisher's exact test was used to test for differences between proportions. All tests were then 2-tailed and $p > 0.05$ was considered statistically significant.

RESULTS

The demographic data of the studied AD and impetigo groups are shown in Table I.

Bacterial cultures and susceptibility testing

Different types of bacterial colonisation in AD patients in 2005 and 2011 are illustrated in Table II. There is an evident dominance of positive *S. aureus* swabs in both years. Strep. A, B, C, and G were less commonly found in variable frequencies. Within the 2005 positively cultured group, resistant clones were generally noticed in 10.3% (4/40) of the patients, amongst whom 2.5% (1/40) developed resistance against clindamycin, 2.5% (1/40) against penicillin V and 5% (2/40) against fusidic acid.

In the 2011 AD group, there was one case in which growth of *S. aureus* was accompanied by *Candida albicans*. Almost every susceptibility testing done on *S. aureus* revealed penicillinase-producing strains, while resistance was noticed in 11.3% (6/53) of that group with only 3.7% (2/53) resistant to fusidic acid, 5.7% (3/53) to clindamycin and 1.9% (1/53) to penicillin V.

A similar picture was seen in impetigo. In the 2005 group, *S. aureus* was found in all of the swabs (Table II). All *S. aureus* strains but one were penicillinase-producing. Resistant strains comprised 34.3% (24/70) while specific resistance to fusidic acid, clindamycin, penicillin V, doxycycline and tobramycin was appreciated in 22.8% (16/70), 7.1% (5/70) 2.8% (2/70), 1.4% (1/70) and 1.4% (1/70), respectively.

In impetigo patients in 2011, 17.5% (7/40) had resistant *S. aureus*, i.e fewer than in 2005 ($p = 0.078$). In the 2011 group, one case of methicillin-resistant *S. aureus* (MRSA) was found, in addition to, clindamycin and fusidic acid resistant *S. aureus* in 10% (4/40) and 5% (2/40) of the patients, respectively.

Table I. *Demographic data of the final groups included in this study*

	AD 2005 $n = 40$	AD 2011 $n = 53$	Impetigo 2005 $n = 70$	Impetigo 2011 $n = 40$
Male, *n*	22	26	20	19
Female, *n*	18	27	50	21
Age mean (SD)	22.5 (18.2)	26.7 (17.7)	28 (22.1)	35.2 (27.6)
Median (range)	18.2 (0.6; 70.4)	17.7 (1.7; 65.3)	22.1 (0.2; 84.8)	27.6 (0; 90.5)

Table II. *Number and percentage of patients with positive bacterial strains in each disease group*

Bacteria	AD 2005 *n* (%)	AD 2011 *n* (%)	Impetigo 2005 *n* (%)	Impetigo 2011 *n* (%)
S. aureus	39 (97)	53 (100)	70 (100)	40 (100)
Strep. A[a]	4 (10)	6 (11.3)	3 (4.3)	2 (5)
Strep. B	5 (12.5)	5 (9.4)	4 (5.7)	2 (5)
Strep. C	0 (0)	1 (1.9)	1 (1.4)	1 (2.5)
Strep. G	2 (5)	5 (9.4)	2 (2.9)	0 (0)

[a]Strep. A: group A streptococcus.

Treatment choice prior to and after culture results

Oral cefadroxil and flucloxacillin and topical betamethasone valerate with clioquinol (Betnovat® with chinoform) cream were the most commonly chosen antimicrobial agents in all groups. Further statistical data are demonstrated in Table III.

In the 2011 AD group, oral antibiotic treatment was occasionally initiated after the sensitivity testing results. That occurred twice with flucloxacillin, once with clindamycin and once with erythromycin.

In the 2005 impetigo patients, fusidic acid was notably prescribed to no more than one patient. Results of bacterial culture led to prescription of cefadroxil to two patients who had initially received flucloxacillin or penicillin V.

A wider spectrum of antimicrobial treatments was used against impetigo in 2011. In one patient, Altargo® was substituted by flucloxacillin following the culture result. Otherwise, the bacterial laboratory results did not affect treatment decisions.

DISCUSSION

AD and impetigo are 2 conditions in which *S. aureus* plays a significant role. The dominantly high prevalence of *S. aureus* in atopic patients is thought to be due to the strong affinity of their inflamed skin to this bacterium which is supported by the reduction of *S. aureus* counts on treatment with anti-inflammatory topical corticosteroids or tacrolimus (11). In addition, *S. aureus* superantigens are believed to be the key stimulant to the inflammatory process in AD (12).

Impetigo, on the other hand, presents in both a bullous form and, more commonly, non-bullous form. *S. aureus* is dominantly found in the former while the latter might also present growth of *S. pyogenes*. The mechanism by which bullae form is thought to be related to *S. aureus*-produced exfoliative toxins against desmoglein-1, which results in a cleavage within the granular layer of the epidermis (13).

In both AD and impetigo, presence of *S. aureus* in culture results was universal

Table III. *Number and percentage of prescribed oral antibiotics and antimicrobial treatment*

Drug	AD 2005 *n* (%)	AD 2011 *n* (%)	Impetigo 2005 *n* (%)	Impetigo 2011 *n* (%)
Oral antibiotics				
Cefadroxil	23 (57.5)	28 (52.8)	41 (58.6)	14 (35)
Cefelaxin	0 (0)	0 (0)	1 (1.4)	0 (0)
Cefotaxim IV	0 (0)	0 (0)	0 (0)	1 (2.5)
Clindamycin	6 (15)	5 (9.4)	5 (7.1)	3 (7.5)
Cloxacillin	0 (0)	0 (0)	0 (0)	1 (2.5)
Doxycycline	0 (0)	0 (0)	1 (1.4)	0 (0)
Erythromycin	1 (2.5)	1 (1.9)	2 (2.9)	0 (0)
Flucloxacillin	7 (17.5)	11 (20.8)	15 (21.4)	12 (30)
Penicillin-V	0 (0)	0 (0)	2 (2.9)	1 (2.5)
Non-oral	3 (7.5)	8 (15.1)	3 (4.3)	8 (20)
Altargo®	0 (0)	0 (0)	0 (0)	7 (17.5)
Antimicrobial treatment				
Betnovat® with chinoform	14 (35)	21 (39.7)	0 (0)	15 (37.5)
Fusidic acid	1 (2.5)	0 (0)	1 (1.4)	1 (2.5)
Kenacutan®	12 (30)	0 (0)	0 (0)	0 (0)
Microcid®	0 (0)	0 (0)	2 (2.9)	0 (0)
Non-topical	13 (32.5)	32 (60.3)	67 (95.7)	17 (42.5)

AD: atopic dermatitis; Altargo®: retapamulin; Betnovat® with chinoform: betamethasone valerate with clioquinol; Kenacutan®: triamcinolone acetonide with halquinol; Microcid®: hydrogen peroxide.

throughout 2005 and 2011 with no significant statistical differences between both years. *S. aureus* was in most cases penicillinase-producing in accordance with previous studies (2, 9). In both years, *streptococci* were less common and often concomitant with *S. aureus,* with mainly Group A and B in AD and impetigo (see Table II). Historically, Group A (*Streptococcus pyogenes*) used to be the most common cause of impetigo in the 20th century before the notable expansion of *S. aureus* (13).

A majority of patients had bacteria that were sensitive to the recommended antibiotics. Of significance, some of our patients were previously enrolled in another study (14) also discussing development of fusidic acid resistant *S. aureus* in Sweden. The relatively low resistance frequency is thought to result from the proportionally small number of patients included in that study as well as from the prudent use of topical fusidic acid in Sweden. Interestingly, fusidic acid resistance in our impetigo patients was as high as 22.8% in 2005, before it dropped to 5% in 2011. This drop, which could be attributed to the fact that fusidic acid was more generously used in the past (15), led to significantly reduced total number of resistant *S. aureus* in our impetigo 2011 group in comparison to 2005. Irrespective of these results, prescribing of the aforementioned cream was markedly not preferred by our doctors in those studied groups.

In contrast to fusidic acid results, clindamycin resistance was rarely noted in AD and impetigo patients in both years.

While methicillin-resistant *S. aureus* (MRSA) continues to be a major problem worldwide, Sweden has always been known to have a low MRSA prevalence (16). MRSA was, accordingly, found only once in both groups in 2005 and 2011. Pencillinase-resistant penicillin and cefadroxil have been recommended as first line therapy for infected dermatoses. In fact, flucloxacillin and cefadroxil have been specifically proved to be effective in AD and impetigo (10, 17). Accordingly, the antibiotic of choice at the first visit did not deviate from those aforementioned antibiotics. Indeed, the choice of using local or topical therapy should be mainly influenced by the severity of impetigo or AD although, in some reports, resistance to local therapy can be as high as 50% of the cases (18). In our study, triamcinolone acetonide with halquinol (Kenacutan®) was used by a significant number of patients in 2005 either as a sole agent or in combination with oral antibiotics. Kenacutan® was, however, never mentioned in 2011 since it had been withdrawn from the Swedish market in 2007. Halquinol is known to have a good antibacterial effect especially against *S. aureus*. However, it has been linked to cause irritant , allergic and photoallergic dermatitis (19, 20). On the other hand, betamethasone valerate with clioquinol (Betnovat® with chinoform) continued to be used in 2011 as often as in 2005. The synergistic anti-inflammatory and anti-microbial effect makes the previously mentioned cream often preferable for secondarily infected dermatoses (21). In spite of earlier reports of medium efficacy of clioquinol against AD, an *in vitro* study in our clinic showed that betamethasone valerate with clioquinol had high efficacy against all microbes with no significant resistance (22, 23). Retapamulin (Altargo®), which was used by many impetigo patients in our study, had a good clinical success rate compared to placebo in the treatment of impetigo with good tolerance in a recent double-blind study with patients recruited from 5 countries (24). It was, however, seldom used in our study as a sole agent. Lastly, hydrogen peroxide cream (Microcid®), which was used by only a few patients, is nevertheless considered to be an effective topical alternative to retapamulin in mild impetigo (25).

The health care system in Sweden commences with primary health care physicians who manage patients, preliminarily, before referring complicated cases to secondary and tertiary care hospitals. This in turn might have led to some selection-bias. In addition, our study is most likely limited by its retrospective nature.

In conclusion, our observations support existing knowledge with regard to the predominant bacteria in AD and impetigo. The high level of resistance of *S. aureus* against fusidic acid would be an argument against its routine use especially in impetigo. Alternatively, flucloxacillin and cefadroxil continue to be effective against *S. aureus* and streptococci depending on the clinical picture. These results should, hopefully, help doctors in our locality to anticipate bacterial swab results in infected AD and

impetigo patients and thus implement the appropriate anti-microbial therapy without delay.

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