# Decolonization of *Staphylococcus aureus* in patients with atopic dermatitis: a reason for increasing resistance to antibiotics?

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## Abstract

**Introduction:** Exacerbation of atopic dermatitis can be associated with bacterial infection. The skin of patients is colonized with *Staphylococcus aureus* in 90% of cases. An attempt has been made to demonstrate that eradication significantly reduces the severity of the disease. Studies indicate the efficacy of topical antibiotics, topical corticosteroids and calcineurin inhibitors. Due to increasing resistance to drugs and the defective antimicrobial peptide profile, decolonization is virtually impossible.

**Aim:** To determine the prevalence of *S. aureus* colonization among patients with atopic dermatitis and to assess antimicrobial susceptibility of isolated strains to antibiotics, especially fusidic acid and mupirocin.

**Material and methods:** One hundred patients with atopic dermatitis and 50 healthy subjects were microbiologically assessed for the carriage of *S. aureus*. Antimicrobial susceptibility tests were performed using the broth-microdilution method for antibiotics: ampicillin, ciprofloxacin, daptomycin, erythromycin, fusidic acid, linezolid, lincomycin, mupirocin, tetracycline and vancomycin.

**Results:** *Staphylococcus aureus* strains were isolated from the majority of our patients, either from the skin (71%) or the anterior nares (67%). In the present study, 10% of isolations represented methicillin-resistant *S. aureus* (MRSA). Antibiotics exhibited diverse activities against clinical isolates of *S. aureus*. Among those tested, the highest rates of resistance were shown for ampicillin – 58.5%, lincomycin – 37.5% and erythromycin – 31.0%. Enhanced resistance levels were expressed to mupirocin (17.5%) and fusidic acid (15.5%).

**Conclusions:** According to the increasing rate of resistance and quick recolonization after discontinuation of the treatment, chronic use of topical antibiotics is not recommended and should be limited to exacerbation of atopic dermatitis with clinical signs of bacterial infection.

**Key words:** *Staphylococcus aureus*, atopic dermatitis, mupirocin, fusidic acid.

## Introduction

Atopic dermatitis (AD) is a chronic, pruritic skin disease mainly affecting children, which follows a remitting and relapsing course. It occurs in 10% to 20% of children and 1 to 3% of adults [1]. Patients with AD have a unique predisposition to be colonized or infected by a number of microbial organisms, mostly *Staphylococcus aureus* and *Herpes simplex*. Studies have shown that between 80% and 100% of patients with AD present nasal or skin colonization by *S. aureus*, while the prevalence is 5% to 30% in healthy individuals [2]. A correlation between the severity of the eczema and colonization with *S. aureus* has been demonstrated, and it has been determined that bacterial colonization is an important factor aggravating skin lesions [3]. The pathogens concentration (cfu/cm$^2$) on the skin of AD patients is significantly higher than that of healthy population [4]. Suppressed levels of ceramides, free lipoid acids, superficial polar lipids, skin natural antimicrobial peptides (LL-37, β-defensin), fibronectin receptors exposure of adhesin-binding cell wall of *S. aureus*, and destruction of the skin barrier by substances excreted by these germs are responsible for skin colonization in AD [5]. Worldwide

studies suggest that the prevalence of methicillin-resistant *S. aureus* (MRSA) in the population with AD varies from 0 to 30.8% [6–8]. In the USA, where Community Acquired-MRSA (CA-MRSA) is now the most common pathogen cultured from patients with skin and soft-tissue infections in emergency departments, the colonization rate of AD patients is as high as 18.3% [9]. There are no prevalence data for MRSA colonization among AD patients in Poland.

## Aim

The aim of this study was to determine the prevalence of MRSA and *S. aureus* colonization in this group of patients, and to evaluate the antibiotic resistance of the isolated strains.

## Material and methods

### Patients and bacterial isolates

Patients were enrolled in our study during their visits in the Outpatient Clinic and during hospitalization in the Department of Dermatology, Venereology and Allergology in Gdańsk (Medical University in Gdansk, 28 beds) from August 2014 to August 2015. There was no selection of patients by sex or by localization and severity of lesions. Atopic dermatitis was diagnosed following the criteria of Hanifin and Rajka, which include among others pruritus, typical morphology and distribution of eczematous lesions, chronicity of the disease and personal or family history of atopy [10]. The study was approved by the local Research Ethics Board (approval number NKBBN/242-477/2014). Voluntary informed consent in writing was obtained from all participants. The exclusion criteria included chronic dermatological condition with a compromised skin barrier (e.g. psoriasis), diagnosis of any other chronic condition that increases the risk of MRSA colonization, oral or intravenous antibiotic treatment in the previous 4 weeks, treatment with topical antibiotics in the past 2 weeks, treatment with systemic corticosteroids or immunosuppressive drugs in the past 4 weeks, history of hospitalization, surgery, dialysis or residence in a long-term facility in the past year, indwelling catheter or a percutaneous device at the time of enrollment. Skin and nasal swabs (Bionovo, sterile swabs with medium Amies) collected from 100 patients with AD and 50 controls were used to detect the presence of *S. aureus*. The control group consisted of patients without personal or family history of skin or allergic diseases who visited the Dermatological Outpatient Clinic for the dermatoscopy evaluation of moles.

### Identification of *S. aureus* and MRSA strains

Preliminary identification and detection of SA and MRSA strains was conducted on the ChromID MRSA/ChromID *S. aureus* biplate (bioMérieux) for simultaneous detection of *S. aureus* and methicillin-resistant *S. aureus* (MRSA).

### Antimicrobial agents

Antimicrobial susceptibility tests were performed in case of positive SA and MRSA strains isolated. The antibiotics tested included ampicillin (Carl Roth GmbH), ciprofloxacin (Fluka), daptomycin (Sigma-Aldrich), erythromycin (Sigma-Aldrich), fusidic acid (Sigma-Aldrich), linezolid (Sigma-Aldrich), lincomycin (Sigma-Aldrich), mupirocin (Sigma-Aldrich), tetracycline (Sigma-Aldrich) and vancomycin (Sigma-Aldrich).

### Antimicrobial activity

Minimal inhibitory concentration (MIC) was determined manually by the broth microdilution method in Mueller Hinton broth according to the Clinical and Laboratory Standards Institute (CLSI) recommendations [11]. Assays for daptomycin were performed in a medium supplemented with $Ca^{2+}$ (50 mg/l). Polypropylene 96-well plates with bacteria at initial inoculums of $0.5 \times 10^5$ CFU/ml exposed to tested compounds were incubated for 18 h at 37°C. Minimal inhibitory concentration was taken as the lowest concentration of the compound at which a visible growth of bacteria was not observed. According to CLSI and EUCAST (European Committee on Antimicrobial Susceptibility Testing) recommendations, the experiments were performed in triplicate. Research was conducted in the laboratory of the Department of Inorganic Chemistry, Medical University in Gdansk. The bacterial isolates were categorized into the resistant or susceptible ones using interpretative criteria provided by CLSI [11].

## Results

### Patients and bacterial isolates

A total of 200 specimens were collected from 100 patients during the study. Atopic dermatitis patients consisted of 55% of males and 45% of females, age: 1 to 63 years, median: 22.3 ±15.6 years. *Staphylococcus aureus* was reported in 75 (75%) of 100 skin swabs and 73 of 100 nasal swabs (73%). Six (6%) of 100 nasal swabs and 5 (5%) of 100 skin swabs were positive for MRSA. A total of 100 specimens were collected from 50 healthy subjects in the control group. Seven (14%) of 50 nasal swabs and 2 (4%) of 50 skin swabs were positive for *S. aureus*. MRSA colonization was not reported in the control group. Clinical characteristics are shown in Table 1.

### Antibiotic sensitivity pattern of *S. aureus*

The antibiotics used in this study exhibited diverse activities against clinical isolates of *S. aureus*. The vancomycin MIC value was the lowest among the tested antibiotics and varied between 0.125 and 8 µg/ml. Minimal inhibitory concentration 90 (the minimal inhibitory con-

centration for 90% of isolates) was the lowest for vancomycin and ciprofloxacin. The highest MIC 90 was noted for erythromycin, lincomycin, mupirocin and tetracycline among patients with AD. Similar results were obtained for the control group (Table 2). Among the conventional antibiotics tested, the highest rates of resistance were shown for ampicillin – 58.5%, daptomycin – 54.7%, lincomycin – 37.5% and erythromycin – 31.0%. The following percentage of resistant strains were noted to mupirocin – 17.5%, tetracycline – 15.5%, and ciprofloxacin – 13.0%. In the control group, strains resistant to ampicillin – 4%, daptomycin – 4%, erythromycin – 2%, fusidic acid – 1%, lincomycin – 3%, and tetracycline – 1% were noticed. One hundred percent of strains in the control group were sensitive to ciprofloxacin, linezolid, mupirocin and vancomycin. The antimicrobial resistance patterns (%) of *S. aureus* in patients with atopic dermatitis and control group are shown in Figure 1. For the following antibiotics: ciprofloxacin, erythromycin, lincomycin, and tetracycline, the percentage of resistant strains was significantly higher in the MRSA group as compared to MSSA (Figure 2).

**Table 1.** Clinical characteristics of patients with atopic dermatitis and the control group

| Parameter | Patients | Control | *P*-value |
|---|---|---|---|
| Total no.: | 100 | 50 | 0.0001[b] |
| Children | 38 | 2 | |
| Adults | 62 | 48 | |
| Age [years] | 22.3 ±15.6 | 35.1 ±13.4 | 0.0001[a] |
| Gender (%): | | | |
| Female | 45 | 50 | |
| Male | 55 | 50 | |
| Presence of SA (%): | | | 0.0001[b] |
| On the skin | 75 | 4 | |
| Anterior nares | 73 | 14 | |
| Presence of MRSA (%): | 11 | 0 | |
| CA-MRSA | 54.5 | 0 | |
| HA-MRSA | 45.5 | 0 | |

*[a]U Mann-Whitney test, [b]χ² test.*

## Discussion

### Epidemiology of *S. aureus* and MRSA strains in AD

Methicillin-resistant *S. aureus* is a major pathogen in many infectious diseases. In 1961, the first methicillin-resistant strains were reported. In 1980, MRSA strains became an endemic problem at different proportions at hospitals in several countries. Commonly, infections caused by MRSA were limited to hospitals (Hospital Acquired-MRSA, HA-MRSA). Community-acquired infections (Community Acquired-MRSA, CA-MRSA) have been increasingly recorded since the last decade. The first report on CA-MRSA infection in a patient without any contact with the hospital environment was recorded in 1980 in the United States. Worldwide studies suggest that the prevalence of MRSA in the population with AD is divergent. For example, in the study carried by Hoeger in 2004 on pediatric outpatient population with AD, the MRSA strains were not identified [12]. However, in New

**Table 2.** Minimal inhibitory concentration (MIC) values of *Staphylococcus aureus* strains isolated from atopic dermatitis (AD) patients and control group

| Agents | MIC [μg/ml] | | | | | | *P*-value |
|---|---|---|---|---|---|---|---|
| | Patients with AD | | | Control group | | | |
| | Range | MIC 50 | MIC 90 | Range | MIC 50 | MIC 90 | |
| Ampicillin | 0.125–32.0 | 2.0 | 16.0 | 0.25–32.0 | 16.0 | 32.0 | 0.125584 |
| Ciprofloxacin | 0.125–>512.0 | 0.5 | 2.0 | 0.125–1.0 | 0.25 | 1.0 | 0.2214 |
| Daptomycin | 0.125–4.0 | 2.0 | 4.0 | 1.0–2.0 | 2.0 | 2.0 | 0.6965 |
| Erythromycin | 0.125–>512.0 | 0.5 | > 512.0 | 0.125–>512.0 | 1.0 | > 512.0 | 0.7188 |
| Fusidic acid | 0.0–32.0 | 0.125 | 8.0 | 0.125–16.0 | 1.0 | 16.0 | 0.0242 |
| Linezolid | 0.25–32.0 | 1.0 | 4.0 | 1.0–4.0 | 2.0 | 4.0 | 0.125059 |
| Lincomycin | 0.25–>512.0 | 1.0 | 64.0 | 0.25–>512.0 | 0.5 | > 512.0 | 0.25239 |
| Mupirocin | 0.125–>512.0 | 0.5 | > 512.0 | 0.125–32.0 | 0.25 | 32.0 | 0.25257 |
| Tetracycline | 0.125–64.0 | 0.5 | 32.0 | 0.125–32.0 | 0.5 | 32.0 | 0.8630 |
| Vancomycin | 0.125–8.0 | 0.5 | 2.0 | 0.25–1.0 | 1.0 | 1.0 | 0.8069 |

*MIC 50 – MIC for 50% of isolates. MIC 90 – MIC for 90% of isolates. Significant differences between groups determined with U Mann-Whitney test.*
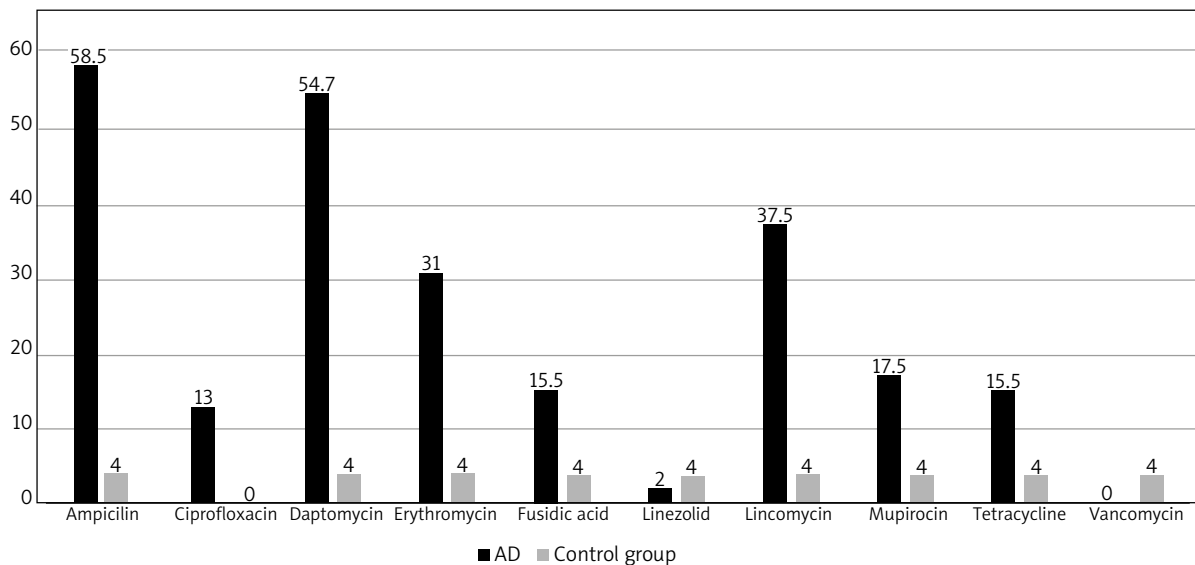
**Figure 1.** Antimicrobial resistance patterns (%) of *S. aureus* in patients with atopic dermatitis and the control group
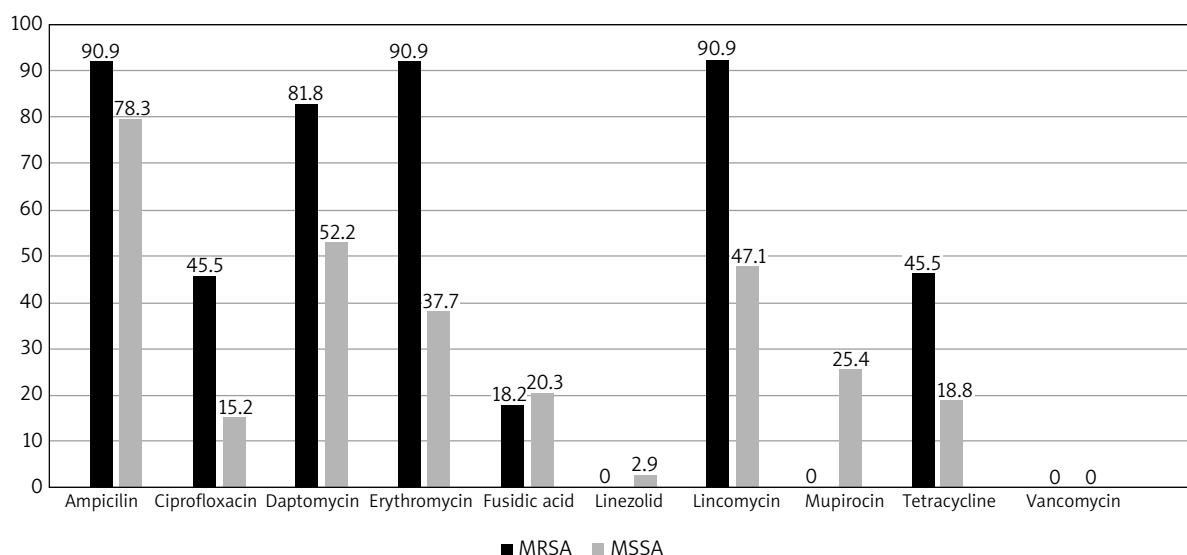


**Figure 2.** Antimicrobial resistance patterns (%) of *S. aureus* in patients with atopic dermatitis among MRSA and MSSA strains

Zealand, 2% of *S. aureus* isolates from pediatric AD cases were MRSA [13]. In addition, Niebuhr *et al.* found MRSA in 3% of *S. aureus* isolates in patients with AD [14]. Up to 30% of *S. aureus* isolates from AD cases were reported to be MRSA in a Taiwanese study population in 2011 [15]. It was also reported that *S. aureus* colonies on the skin of patients with AD easily changed from being methicillin sensitive to being methicillin resistant when antibacterial agents were administered over a long period of time [16]. *Staphylococcus aureus* strains were isolated from the majority of our patients, either from

the skin (75%) or the anterior nares (73%). There are no prevalence data for MRSA colonization among AD patients in Poland. In the present study of the 100 nasal swabs, 6 (6%) and 5 of 100 skin swabs (5%) were positive for MRSA (54.5% CA-MRSA, 45.5% HA-MRSA). The definition of CA-MRSA was coined by the Center for Disease Control and Prevention (CDC) in 2000. It refers to MRSA infection in a person who has none of the following established risk factors: isolation of MRSA more than 48 h after hospital admission; history of hospitalization, surgery, dialysis or residence in a long-term care facility

within one year of the MRSA culture date; the presence of an indwelling catheter or a percutaneous device at the time of culture; or previous isolation of MRSA [17]. More recently, the emergence of MRSA clone colonizing farm animals (livestock-associated (LA)-MRSA) have been reported in Europe [18]. LA-MRSA possesses the same virulence potential as *S. aureus* from humans and is associated with the same manifold clinical pictures. LA-MRSA represents about 13% of MRSA-linked severe skin and soft tissue infections [19]. It can enter hospitals either *via* patients who suffer from infections caused by these bacteria or *via* patients with nasal colonization. Finally, it can lead to nosocomial infections such as surgical site infections, infections after joint arthroplasty, ventilator associated pneumonia, or septicemia [20]. Usually LA-MRSA is resistant to β-lactams, macrolides, lincosamides, streptogramins, and tetracyclines. It is susceptible to glycopeptides, daptomycin, tigecycline, rifampicin, fusidic acid, fosfomycin, and linezolid.

### Antibiotic resistance

The higher rate of MRSA in the AD population may reflect higher overall prevalence rates and different management strategies, such as antibiotic use. Therefore, they should be used only when clinical signs of infection are presented, rather than to decolonize. Several studies concerning the effect of antimicrobial treatment on the *S. aureus* colonization and the severity of inflammation gave conflicting results. In open or double-blind placebo-controlled trials, topical or systemic antibiotics were able to reduce colonization density and led to a partial improvement of skin lesions [21–23]. In addition, some authors reported that topical steroids in combination with antibiotic treatment can cause elimination of *S. aureus* from the skin in some patients with AD [24]. On the other hand, treatment with oral antibiotics did not lead to a significant improvement of AD in two double-blind placebo-controlled studies [25, 26]. There are reports suggesting that treatment with antibiotics can temporarily reduce bacterial colonization and improve AD severity. However, these benefits last no longer than 3 months [27]. Antibacterials effective against *S. aureus* include azithromycin, cefuroxime axetil, clarithromycin and erythromycin, while MRSA eradication by clindamycin, fusidic acid, trimethoprim-sulfamethoxazole and intranasal mupirocin can be effective [28]. In our study, a high resistance rate to conventional antibiotics was noticed. Thirty-one percent of isolated strains were resistant to erythromycin and 15.5% to tetracycline. Our results are comparable with those of Kędzierska and Hoeger [12, 29]. In those studies, the resistance rate to erythromycin was 14% and 18%, respectively. The increasing resistance to macrolides may suggest that erythromycin should no longer be applied in this case. In the present study, strains resistant to fusidic acid (FA) and mupirocin were also noticed.

### Fusidic acid

Fusidic acid is an antibiotic that has been used in clinical practice in Europe since the 1960s in the treatment of skin and soft tissue infections, including infected atopic dermatitis. Fusidic acid has a high *in vitro* activity against *S. aureus, S. epidermidis*, some *Corynebacterium* and Gram-positive anaerobes such as *Clostridium*. Fusidic acid-resistant *S. aureus* (FRSA) has been reported in many countries, with the prevalence ranging from 0.3% to 52.5% [30, 31]. Accordingly, in the present study, 15.5% of strains resistant to fusidic acid were noted. *Staphylococcus aureus* resistance to FA is known to be already higher in dermatology patients compared with other disciplines and may result in treatment failure. Heng *et al.* reported FA resistance among *S. aureus* strains to be 11.3% among dermatology inpatients, which was higher than in patients of all disciplines (6%) [32]. This higher rate of resistance is consistent with the findings by Shah and Mohanraj in the UK, with reported resistance rates of 50% among dermatology outpatients, 9% among primary care non-dermatology patients, and 10% among hospital inpatients [33, 34]. Katopodis *et al.* reported extremely high rates of FA resistance (88.9%) among children in Greece with CA-MRSA infections and acknowledged widespread use of FA in the community [35]. In contrast, in China where topical FA has been available only since 2003, Liu *et al.* detected no FA resistance in children with CA-MRSA infection [36]. Two major fusidic acid resistance mechanisms have been reported in *S. aureus* namely, the alteration of the drug target site which is due to mutations in fusA (encoding elongation factor G − EF-G) or rplF (FusE, encoding ribosome protein L6) [37] and the protection of the drug target site by FusB family proteins, including fusB, fusC and fusD [38]. Inappropriate use of topical antibiotics leading to resistance may threaten the efficacy of systemic antibiotics for the treatment of serious *S. aureus* infections such as osteomyelitis and severe surgical wound infections. Therefore, the topical use of FA for empirical treatment and decolonization of *S. aureus* should be restricted. Limiting the use of FA to less than two weeks for mild and localized secondary infection in atopic eczema has been recommended by the national guidelines [39].

### Mupirocin

Mupirocin (pseudomonic acid A) is approved in ointment formulation in the United States for the topical treatment of impetigo and secondary wound infection caused by *S. aureus* and *S. pyogenes*. In addition, a nasal formulation is approved by the United States Food and Drug Administration (FDA) for use in eradicating nasal carriage of *S. aureus* in adult patients and health care personnel, as part of a comprehensive infection control program to reduce the risk of infection among patients

at high risk of MRSA. Mupirocin is also increasingly used outside the hospital context because of the growing incidence of CA-MRSA and because, to date, mupirocin resistance levels have been lower than those of hospital-acquired MRSA [40]. Nevertheless, the increasing resistance to this agent has been reported and three categories of susceptibility for *S. aureus* were described. These categories are: mupirocin susceptibility with MICs below 1 μg/ml, a low-level mupirocin resistance with MICs from 8 to 64 μg/ml, and a high-level mupirocin resistance with MICs over 512 μg/ml [41]. In the present study, the low-level mupirocin resistance was noted in 9.46% and high-level one in 16.89% of the isolated strains. Most isolates that demonstrate high-level mupirocin resistance have acquired plasmid-mediated mupA, which encodes a novel isoleucyl RNA synthetase [42]. Isolates with low-level mupirocin resistance usually have acquired base changes in the native isoleucyl RNA synthetase gene, ileS [40]. Controlling MRSA transmission and infections is important in healthcare facilities, and decolonization is often recommended to achieve this goal (strength of evidence, IB–II) [43]. However, many reports emphasize the need to exercise caution when using this strategy, because carriage of MRSA with low-level mupirocin resistance is strongly associated with persistent colonization after eradication therapy [44]. If the clinical use of mupirocin increases, an increase in the prevalence of mupirocin resistance is likely to follow.

### Antiseptic agents

Antiseptic agents represent an alternative to topical antibiotics in patients with AD, which are not generally recommended in the treatment of AD. An exception to the above antimicrobial agents is the use of bleach baths with intranasal topical mupirocin. According to Huang *et al.*, chronic use of dilute bleach baths with intermittent intranasal application of mupirocin ointment decreased the clinical severity of AD in patients with clinical signs of secondary bacterial infections [45]. Except for bleach baths with intranasal mupirocin, no topical antistaphylococcal treatment has been shown to be clinically helpful in patients with AD, and is not routinely used [46]. Antiseptics have been found to be better tolerated and less likely to induce bacterial resistance as compared to antibiotics. The main advantages of antiseptics over antibiotics are that they have low potential of inducing bacterial resistance, rarely cause delayed-type hypersensitivities or allergic reactions and come in a variety of preparations to suit individual needs [47]. Besides bleach baths, other antiseptics (triclosan, potassium permanganate, chlorhexidine gluconate and polyhexanide) are also available as an alternative, but at higher cost and without any randomized controlled trials published to date [48].

## Conclusions

There are no prevalence data for MRSA colonization among AD patients in Poland. The aim of this study was to determine the prevalence of MRSA and *S. aureus* colonization in this group of patients, and to evaluate the antibiotic resistance of the isolated strains, especially fusidic acid and mupirocin, which are widely used for decolonization of *S. aureus*. In the present study, 10% of isolations represented methicillin-resistant *S. aureus*. Among the tested antibiotics, 17.5% of strains were resistant to mupirocin and 15.5% to FA. The authors suggest that topical fusidic acid and mupirocin should be used to treat acute skin infections only for a short period of time. Furthermore, topical therapy of bacterial skin infections promotes the development of resistant strains. We hope that the cautious use of these topical antimicrobials will reverse the trend of increasing resistance observed among healthy subjects with colonization of *S. aureus*. The current popular practice of using diluted bleach baths once or twice weekly to reduce cutaneous staphylococcal colonization may also in the future alter the prevalence of MRSA and *S. aureus* in AD patients. However, there are many limitations to these studies, which therefore warrant further investigation on the impact of antiseptic use in AD. The approach of adding antiseptic agents to emollients and body washes is a convenient measure of introducing an additional agent into the AD management regimen. Finally, this study clearly emphasizes that susceptibility tests of clinical *S. aureus* isolates to antimicrobial drugs should be regularly performed before initiating therapy. Moreover, due to the increased risk of bacterial resistance that may occur as a result of the habit of using antibiotics in AD too often, it is important to monitor the rate of resistance to oral or topical antistaphylococcal drugs.

## Conflict of interest

The authors declare no conflict of interest.

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