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The Need to Develop New Antimicrobial Molecules, as Revealed by *in vitro* Assessment of Drug Resistance in Staphylococcal Skin Infections Treated with Autologous Bacterial Vaccine

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Abstract: *Staphylococcus spp. is a facultative pathogen, which can be found in the commensal microbiota of humans, most often in moist skinfolds and mucous membranes. This microorganism has the ability to cause various infections, in almost every organ of the body, with an increased frequency in the skin and soft tissues, being involved in pathologies like acne, folliculitis, furunculosis, hidradenitis suppurativa, cellulitis, abscesses, but also in secondary infections in diseases with an altered cutaneous barrier. The prolonged evolution of these diseases and severe outcome can be influenced by various factors, most importantly being the antimicrobial resistance. We have evaluated the antimicrobial susceptibility profiles, according to the Comité de l' Antibiogramme de la Société Française de Microbiologie recommendations, for strains of Staphylococcus spp. isolated from acne or different types of skin and soft tissue infections in patients recommended to receive autologous bacterial vaccine. Most frequent identified species was Staphylococcus epidermidis, followed by Staphylococcus aureus. The antimicrobial resistance was higher for antibiotics usually used in the treatment of skin and soft tissue infections, with interesting differences of the resistance profile for the strains isolated from patients before receiving autologous bacterial vaccine compared with the ones from individuals already treated. Another important finding was represented by the differences in the resistance profile according to the age group of the patients. The results of this study underline the importance of antimicrobial resistance surveillance in finding new molecules and alternative therapies, the necessity of a personalized approach in medical acts and of a continuous connection between clinic and laboratory research.*

Keywords*: Staphylococcus spp., antimicrobial resistance, autovaccine, antibiotics development*

1. Introduction

Staphylococcus spp., a Gram-positive genus, is widely involved in human infections, having the potential of affecting almost every organ of the body [1,2]. Skin and soft tissues represent the most frequent infection site [2,3]. *S. aureus* is a facultative pathogen, found in the commensal microbiota of almost 50% humans [2,4]. Colonization spots are mainly represented by moist skinfolds and mucous membranes, such as the gastrointestinal, vaginal, and rectal mucosae, nasal portage being the most frequent, seen in approximately 30% of the population [1,4]. There are studies that prove a link between *S. aureus* colonization and skin and soft tissue infections (SSTIs), therefore decolonization should be aimed in order to achieve long-term cure [5].

Staphylococcal SSTIs represent an important public health problem, since they are mostly involved in frequent diseases of the pilo-sebaceous unit such as folliculitis, furunculosis, acne, hidradenitis suppurativa, but also in abscesses, wounds, cellulitis and secondary skin infections in diseases with an

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altered cutaneous barrier (Example: atopic dermatitis, eczema, vesicular-bullous disorders and many others) [6–8].

In the treatment of infections one of the main roles is played by chemistry [9]. One of the first effective treatment for a bacterial infection is the result of multiple studies, but as well thanks to the chemical synthesis of aniline [9]. In the last century of fight against infections, chemical synthesis of new drugs was one of the most important assets [9].

The developed antimicrobial molecules target different components of the bacterial cell or processes, the most important ones being presented in Table 1.

Table 1. Chemical formula and mechanism of action for the most frequently used antibiotics

Antibiotic [10]	**Chemical formula** [11]	**Mechanism of action** [12]
Penicillins	$C_{16}H_{18}N_2O_4S$	Inhibit cell wall synthesis
Cephalosporins	$C_{15}H_{21}N_3O_7S$	
Carbapenem	C6H7NO	
Glycopeptides	$C_{36}H_{64}N_8O_{17}$	
Fosfomycin	$C_3H_7O_4P$	
Aminoglycosides	$C_{38}H_{64}N_8O_{14}$	Inhibitors of protein synthesis
Macrolides	$C_{33}H_{45}ClN_2O_{10}$	
Lincosamides	$C_9H_{20}NO_5S^+$	
Streptogramin B	$C_{45}H_{54}N_8O_{10}$	
Tetracyclines	$C_{22}H_{24}N_2O_8$	
Chloramphenicol	$C_{11}H_{12}Cl_2N_2O_5$	
Fusidic acid	$C_{31}H_{48}O_6$	
Linezolid	$C_{16}H_{20}FN_3O_4$	
Tedizolid	$C_{17}H_{15}FN_6O_3$	
Mupirocin	$C_{26}H_{44}O_9$	
Nitrofurantoin	$C_8H_6N_4O_5$	
Rifampicin	$C_{43}H_{58}N_4O_{12}$	
Trimethoprim	$C_{14}H_{18}N_4O_3$	Folic acid metabolism inhibitors
Trimethoprim-sulfamethoxazole	$C_{24}H_{29}N_7O_6S$	
Fluoroquinolone	C_9H_6FNO	Inhibitors of DNA replication
Daptomycin	$C_{72}H_{101}N_{17}O_{26}$	Interacts with bacterial membrane stability

The cell wall of bacteria are mainly composed of peptidoglycan chains, which extend from sugars and cross-link through the D-alanyl-alanine portion with other chains in the presence of penicillin binding protein [12]. Glycopeptides bind to D-alanyl-alanine and prevent its interaction with penicillin binding protein [12]. β-lactam ring of antibiotics mimics D-alanyl-alanine portion, but after the interaction with penicillin binding protein the synthesis of peptidoglycan is interrupted, which leads to the lysis of bacterium [12].

Another mechanism of action is represented by the inhibition of protein synthesis, some antimicrobials, like aminoglycosides and tetracyclines, target the 30S subunit of the ribosome, while others, like chloramphenicol, macrolides and oxazolidinones, act on the 50S ribosome subunit [12].

Other mechanisms include the inhibition of DNA replication, like in the case of fluoroquinolones, or folic acid metabolism, by sulfonamides and trimethoprim [12] (Figure 1).

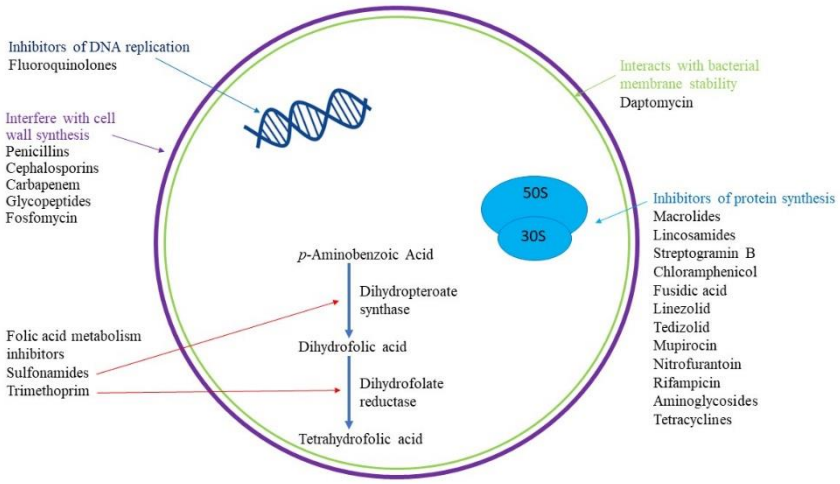

Figure 1. Mechanisms of action for the most frequently used antibiotics in staphylococcal infections

Antibiotic resistance may affect patient prognosis. It is problematic in health care settings where microorganisms are frequently multi-drug resistant and consequently more difficult to treat, but also, more recently, in community acquired infections [1,7,8,13].

S. aureus is one of the most frequent microorganisms involved in nosocomial infections, which poses extensive antimicrobial resistance, increasing mortality rate in hospitalized patients [14,15]. Treatment options for SSTIs are becoming more limited, as antimicrobial resistance widens [1,16,17]. Newer antibiotics (dalbavancin, oritavancin, tedizolid, and delafloxacin) have been included in the Infectious Diseases Society of America's guidelines from 2014 [18]. Trimethoprim-sulfamethoxazole, tetracyclines, and linezolid could be the treatment of choice against *S. aureus* strains, the last two having similar mechanism of action [7]. Normally, during ribonucleic acid (RNA) translation the amino acids are transferred from an aminoacyl–transfer RNA complex held in the P site of the ribosomal complex to the ones located in the A site, which contributes to the movement of the aminoacyl–transfer RNA complex in site E, and consequently exiting of the ribosome (Figure 2 A) [12,19,20]. Linezolid binds to nucleic acid residues in the peptidyl transferase from site A of the ribosome and prevents the amino acid transfer from aminoacyl groups on transfer RNA located in the P site to the one from the site A, and interrupts the protein elongation (Figure 2 B) [12,17,19–21].

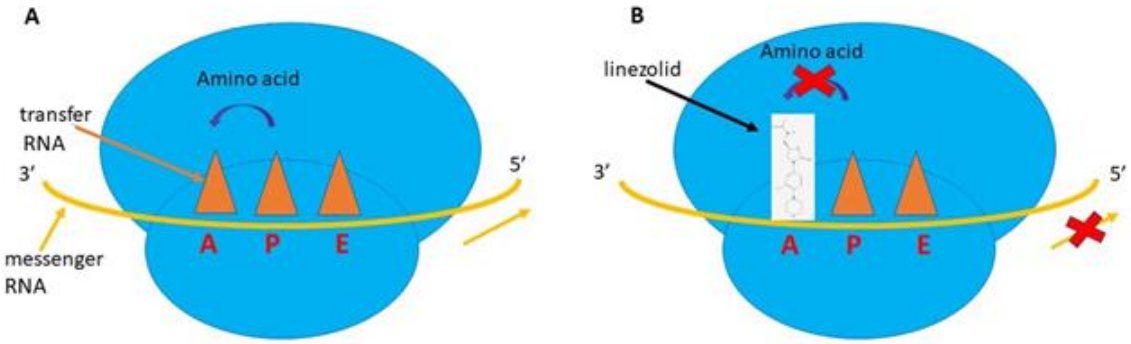

Figure 2. Protein translation process in bacteria ribosome in normal conditions (A) and in the presence of linezolid (B)

Cutibacterium acnes is the main organism associated with the pathogenesis of acne vulgaris, while purulent skin lesions are frequently colonized with staphylococci [22,23]. Patients are usually treated for long periods with systemic tetracyclines and/ or topical antimicrobials (including antibiotics such

as clindamycin, erythromycin) for long periods of time [22,23]. The development of antimicrobial resistance is controversial in this case [24,25]. Recently, the American Association of Dermatology recommended the reduced use of antibiotics in acne vulgaris in order to diminish the risk of antimicrobial resistance [26].

While folliculitis may clinically resemble acne (follicular pustules), in this case *S. aureus* is undoubtedly the most commonly incriminated microorganism [27]. If *S. aureus* infection affects deeper the pilo-sebaceous unit, it is possible to develop furunculosis [6]. The recovery from recurrent furunculosis can usually be achieved if *S. aureus* carriage is eradicated [28].

One of the most widespread staphylococcal SSTI is represented by skin abscess, which can evolve with dissemination and sepsis [29,30]. Incision and drainage are the golden standard, usually sufficient for mild cases. Antimicrobial therapy can also be added, but severe cases with bacteremia or sepsis require strong antibacterial agents such as linezolid or glycopeptides (vancomycin, telavancin) [30].

The role of *Staphylococcus* spp. in the pathogenesis of hidradenitis suppurativa is still controversial, as it is not yet determined if inflammation follows colonization or the other way around [31,32]. Antibiotic treatment may help improve hidradenitis suppurativa lesions, but relapse of the disease is common after treatment interruption [29]. However coagulase negative staphylococci, *S. lugdunensis* in particular, were associated with biofilm chronic infections and the aggravation of hidradenitis suppurativa [33,34]. Wound infections can be polymicrobial, but *Staphylococcus* spp. in general and *S. aureus* in particular are the major pathogens [15].

In the context of emerging multi-drug resistance, the need for research in chemistry field in order to develop new antimicrobial drugs and the necessity to find alternative therapies, such as autovaccines in chronic SSTIs become stringent [35–37]. Autovaccines or autologous bacterial vaccines are used to treat recurrent or persistent staphylococcal infections, including chronic furunculosis and wound infections, for over a century [35,36,38]. They consist of suspensions of surface antigens, virulence factors, and other bacterial proteins obtained from the particular staphylococcal strain causing the patients' persistent infection [35]. This offers them the great advantage of being highly specific compared to conventional antibiotic therapy [36].

The recommendation of alternative therapies in patients with chronic SSTIs is usually made after the repeated failures of standard therapy. Consequently, this may represent a high-risk group of patients, as carriers of strains with increased antibacterial resistance, both associated with a higher epidemiological risk.

Since there is very limited data regarding the antimicrobial resistance rates of bacteria strains isolated from patients receiving autovaccines for the therapy of SSTIs, our study aims to explore the antimicrobial resistance profiles of staphylococcal strains.

2. Materials and methods

We have evaluated the antimicrobial susceptibility pattern for strains of *Staphylococcus* spp. isolated between January 2018 and January 2019 from acne or different types of skin and soft tissue infections in patients which have received the recommendation to follow treatment with autologous bacterial vaccine. We included strains isolated from patients older than 18 years old, which had in the medical history at least one failed treatment for their condition. The strains were in 88.89% of the cases from persons not treated before with autologous bacterial vaccine, and almost all the patients reported prior treatment with antibiotics before sampling. The taxonomy of the strains was confirmed using MALDI-TOF MS. The antimicrobial susceptibility pattern was assessed by the disc diffusion method according to the Comité de l' Antibiogramme de la Société Française de Microbiologie (CASFM) 2019 recommendations [10].

3.Results and discussions

We evaluated the antimicrobial resistance profile for 290 strains of *Staphylococcus* spp. The median age of the patients was 29 years old. The identified species were *Staphylococcus epidermidis*

(44.13%), *Staphylococcus aureus* (34.18%), *Staphylococcus lugdunensis* (7.93%), *Staphylococcus capitis* (6.89%), *Staphylococcus haemolyticus* (3.1%), *Staphylococcus hominis* (1.72%), *Staphylococcus warneri* (1.03%), *Staphylococcus intermedius* (0.34%), *Staphylococcus simulans* (0.34%) and *Staphylococcus pasteuri* (0.34%) (Figure 3).

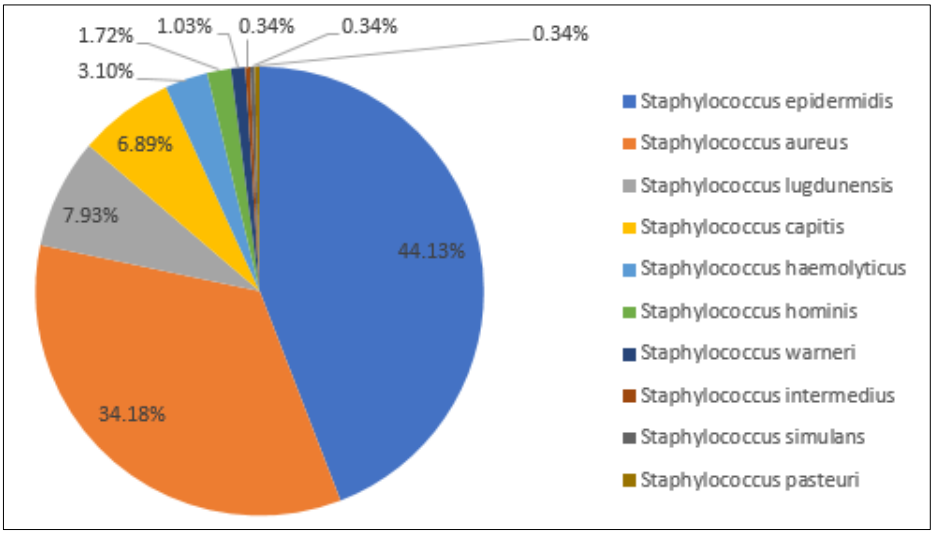

Figure 3. Identified species of *Staphylococcus* spp.

The predominance of the sources from which the strains were isolated varied with the age groups. If in the younger groups, the majority of cases were represented by acne, in the other ones the predominance was shifted towards other pathologies with purulent secretions, for example a great part of the cases of infected wounds were identified in the group of patients older than 65 years old. All the patients presenting with infected wounds in this study reported them as a consequence of various small surgical interventions. Moreover, *S. aureus* identified from folliculitis was more often in persons aged between 26 and 45 years old, while the strains from hidradenitis were frequently isolated in people aged between 36 and 55 years-old (Table 2).

Table 2. Source of isolation according to the age group

Age groups / Pathologies	<26 years	26-35 years	36-45 years	46-55 years	56-65 years	>65 years
Acne	56.06%	22.80%	2.77%	5.55%	6.66%	18.18%
Purulent secretion	24.24%	43.85%	50%	55.6%	53.36%	45.46%
Folliculitis	1.51%	3.5%	2.77%	0	0	0
Furunculosis	9.09%	5.31%	11.11%	11.1%	6.66%	9.09%
Osteomyelitis	1.51%	0	0	5.55%	6.66%	0
Hidradenitis suppurativa	1.51%	3.5%	8.33%	11.1%	0	0
Pustules	3.06%	17.54%	19.44%	5.55%	13.33%	0
Infected wounds	1.51%	0	0	5.55%	0	27.27%
Nasal swab	1.51%	3.5%	5.58%	0	13.33%	0

22.64% of the analyzed strains were resistant to cefoxitin, being classified as methicillin resistant *Staphylococcus* strains. An increased percent of the tested strains was resistant to antibiotics usually used in dermatologic infections. For example, an important part of the strains was resistant to erythromycin (resistant strains – 60.69%), tetracycline (46.90% resistant strains), clindamycin (29.66% resistant strains), and fusidic acid (21.79% of the strains were resistant). The reduced susceptibility was observed in individuals who have not received autologous bacterial vaccine, as well as in the ones already treated (Figure 4).

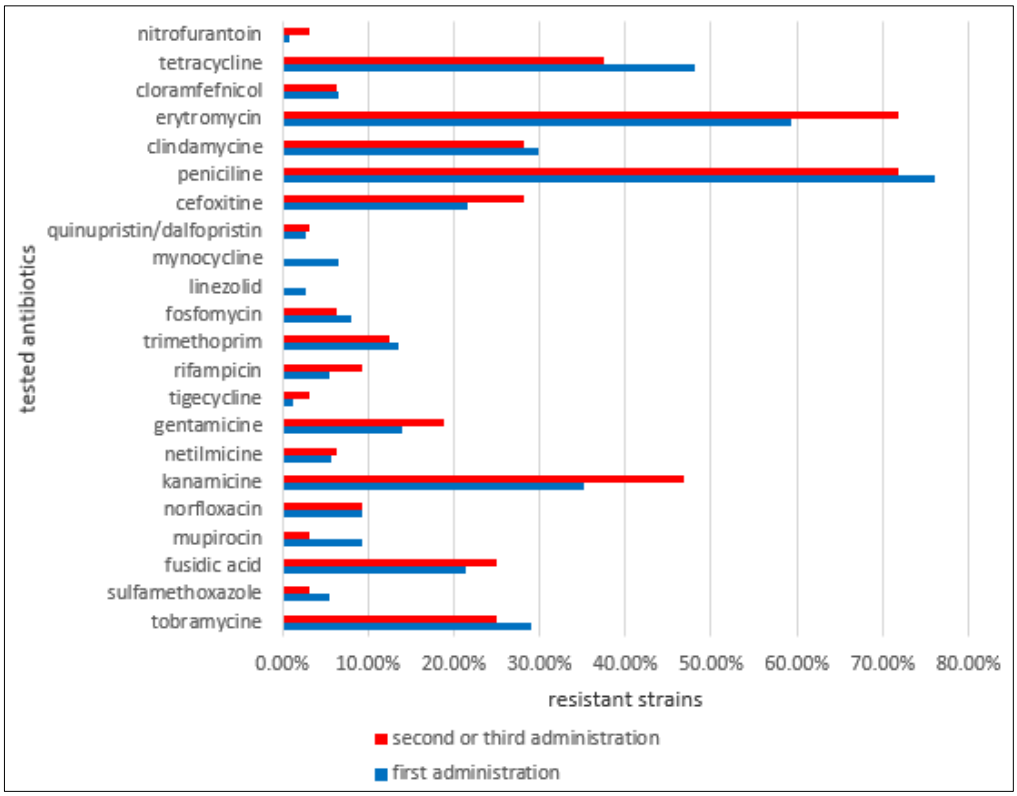

Figure 4. Distribution of resistant strains according to the series of autovaccines received

Fosfomycin resistance was more frequently observed in *S. warneri* (66.66%), *S. capitis* (73.33%) and *S. aureus* (93.81%). Regarding tobramycin, most often the resistance was observed in *S. hominis* and *S. haemolyticus*, while for norfloxacin and tigecycline a high percentage of resistant strains was observed. *S. capitis* had an increased resistance for mupirocin and linezolid, while *S. aureus* had a low susceptibility to nitrofurantoin, minocycline and quinupristin-dalfopristin (Figure 5).

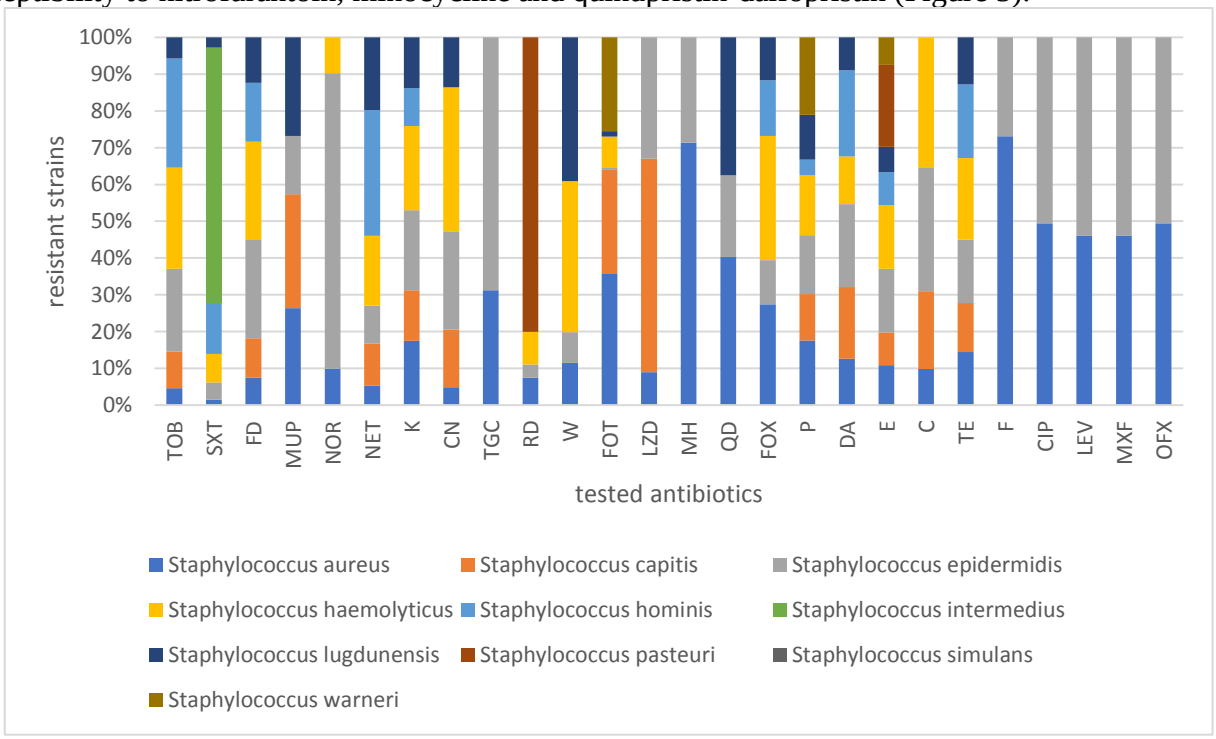

Figure 5. Antimicrobial resistance according to the identified specie

Interestingly, different antimicrobial resistance patterns for strains isolated in various age groups were observed. For example, for tobramycin, if in the 56-65 years old age group 15% of the strains were resistant, in the 26-35 years old age group the resistance percentage was more than double (32.43%). In addition, for fusidic acid, there was an impressive higher number of resistant strains for the people aged between 46-55 years, especially compared with the 56-65 years age group (5%). In the 36-45 years age group 2.27% of the strains were resistant to trimethoprim, while in the other groups the percentages were much higher. The strains isolated from persons older than 56 years had approximately 10 times more resistant strains to trimethoprim (20%).

Interestingly, in strains isolated from people aged 36-45 years, we noticed a decreased resistance for erythromycin (13.64%) and clindamycin (45.45%), compared with the resistance of erythromycin in the ones younger than 26 years old (38.46%) and of clindamycin (80%) in individuals older than 65 years. For penicillin resistance we noticed a spike in the group of 46-55 years old (Figure 6).

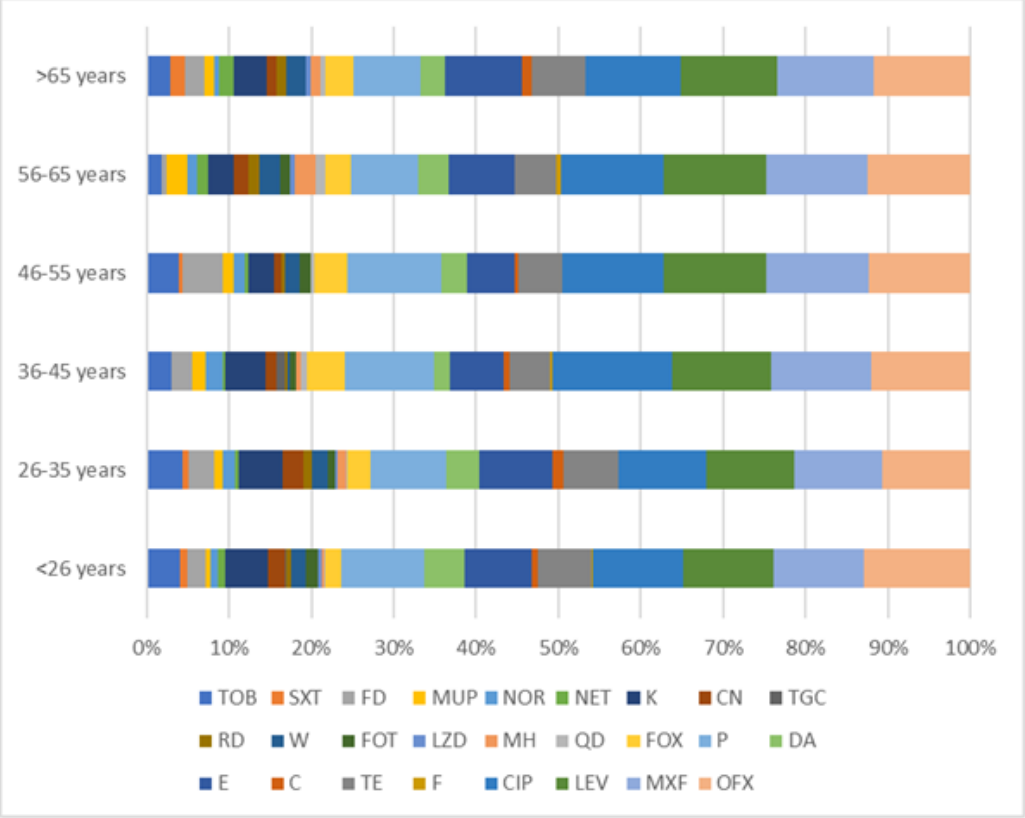

Figure 6. Distribution of antimicrobial resistance according to the age group

Skin abscess is one of the most frequent form of manifestation of *S. aureus* SSTI and in selected cases the infection can spread to deeper anatomical structures potentially causing damage to any part of the body, via bloodstream and septic dissemination [29,30]. Abscess formation is triggered by entry of the pathogen inside the body, either through an infected hair follicle (folliculitis) or through a breach in the skin, such as a wound [39]. Uncomplicated abscesses are routinely treated by incision and drainage alone, but antibiotics such as tetracyclines, trimethoprim/sulfamethoxazole and clindamycin can also be added to the therapy [30]. Linezolid and glycopeptides are used in severe, hospital-acquired infections [8,30,40].

Folliculitis can sometimes be hard to differentiate from acne, as it can also present with inflammatory lesions in the form of papules, pustules and nodules (in case of deep folliculitis) [27]. The major pathogen involved is *S. aureus*, which colonizes hair follicles usually from humid areas of the body [27,28]. As is the case for acne, tetracyclines and clindamycin/ rifampicin association are routinely used as course of treatment, but recent studies have proven the clinical efficacy of fusidic

acid, with reduced resistance [30]. Contrary to these recommendations, almost a quarter of the strains included in our study were resistant to fusidic acid.

When the infection of the hair follicle spreads to the underlying subcutis, a boil or furuncle develops, which is a specific type of abscess [6,28,41]. In the vast majority of the cases, community-acquired MRSA is the etiologic agent [6,41]. In case of carbuncle formation (clustering of furuncles), extending infection with cellulitis or systemic response, antibiotic therapy should be initiated [6,28]. Recurrent furunculosis can be treated by *S. aureus* decolonization with specific sensitive antibiotics, since there appears to be a link between the disease and nasal and skin carriage of this microorganism [6,41].

In the case of hidradenitis suppurativa, germs, including *S. aureus* and coagulase-negative staphylococci such as *S epidermidis* were found to be associated with the inflammatory aspects seen in this disease, but the relationship between them is not fully understood yet [31,32]. Bacterial colonization may lead to inflammation but also inflammatory lesions can become secondary infected [42]. Generally, antimicrobial agents such as tetracyclines or the association of rifampicin with clindamycin may temporary ameliorate hidradenitis suppurativa clinical manifestations, but rate of recurrence is high after antibiotic discontinuation [43]. However, a study conducted in France by Guet-Revillet *et al*. proved that the combination of rifampicin with moxifloxaxcin and metronidazole can fully cure hidradenitis suppurativa lesions [44].

Staphylococcus spp. can infect virtually all types of wounds, from burns, ulcers and surgical wounds to traumatic ones [15]. *S. aureus* is among the most commonly isolated pathogens from wounds, usually acquired from the hospital and therefore multi-drug resistant, more difficult to treat and with a higher mortality rate, but other *Staphylococcus* strains are also incriminated [15]. The emergence of MRSA poses a challenge to the antimicrobial therapy because of its resistance to beta-lactams, therefore more potent antibiotics like linezolid and vancomycin represent the central components of treatment [14,45].

Usually, *Cutibacterium acnes* is the causative agent for acne vulgaris, but *S. epidermidis* and *S. aureus* also proved to be involved in the pathogenesis of the disease [25]. *Staphylococcus* species are present in higher concentration in inflammatory acne lesions, such as papules and pustules and in cases that are more serious, like generalized infections [23].

In the treatment of infections various molecules have been developed, but there is an increased number of mechanisms through which the bacteria manage to avoid their effects [12]. For example, the bacterial cells have the ability to prevent the accumulation of antibiotics by decreasing the uptake or increasing the efflux [12]. The decrease in uptake can be observed especially for small hydrophilic molecules, like β-lactams or fluoroquinolones, which can cross the outer membrane only through porins and any change in the porin structure or number can influence the antimicrobial susceptibility [12]. Regarding the increased efflux of molecules, almost all classes of antibiotics are susceptible to the action of efflux pumps [12]. Other resistance mechanisms include modification of the target or antibiotic inactivation [12].

Antimicrobial resistance is an increasing concern, as more and more *Staphylococcus* strains are becoming resistant to tetracyclines, antimicrobial agents commonly used for the treatment of acne [22,25]. In our study, almost half of the strains were resistant to tetracycline. However, a study from Pennsylvania showed the exact opposite, that patients who received a long-term tetracycline course of antibiotics were less prone to be colonized with *S. aureus*, without increasing antimicrobial resistance [24]. A study conducted in Iran showed that rifampicin had the highest sensitivity of all the antibiotics used to treat acne vulgaris, with the statement that it should not be used as monotherapy, as it can easily induce resistance [25,46]. Conclusion sustained also by the American Association of Dermatology, which does not recommend using topical antibiotics as monotherapy, and in regard to systemic antibiotics they should be used only in moderate to severe acne resistant to topical therapies and in combination with a topical retinoid and benzoyl peroxide [26]. For *S. aureus* SSTIs the most

effective antibiotics were linezolid followed by trimethoprim sulfamethoxazole and tetracyclines [7]. For clindamycin the susceptibility was of 86% [7].

In our study almost a quarter (22.41%) of the strains were cefoxitine resistant, results similar with the ones reported by other studies, 27% in a hospital in Hawai'i, 27.3% in a dermatologic setting, 29.7% in six dermatology centres from five states [7]. Compared with results reported 25 years ago, when the methicillin resistant strains were identified in 13.5% of the cases, the increasing tendency can be firmly underlined [47].

Although some studies reported a high susceptibility to linezolid, in some cases reaching 100% of the tested strains [7], in our samples we detected a 2.41% rate of resistance. Comparing the resistance patterns for rifampicin and nitrofurantoin of other studies were all the strains were susceptible [7], in the present collection of strains the resistance was of 5.86% for rifampicin and 1.03% for nitrofurantoin.

In general, older persons have a higher susceptibility to infections compared to younger adults, especially infections like pneumonia, SSTIs, urinary tract infections, infective endocarditis, bacterial meningitis and others [48]. Other studies reported SSTIs being more frequent identified in younger patients rather than in older ones [48], while in our data we found an increased number of old adults with wound infections.

Alexander Fleming highlighted the importance of chemistry research in designing and modifying molecules to develop new drugs or to enhance the properties of the existing ones [9,49–51]. After decades, in the context of antimicrobial resistance this is more necessary than ever [9]. Surveillance of antimicrobial resistance being a great asset in identifying the mechanisms and studying the molecular basis in order to develop new drugs [9].

4. Conclusions

Most frequently identified staphylococcal specie was represented by *S. epidermidis.* Antimicrobial resistance assessment of the strains showed similar results with the ones reported in literature, for example cefoxitin, and in consequence the proportion of methicillin resistant strains. Concerning other drugs, like linezolid, rifampicin or trimethoprim sulfamethoxazole, for which some studies reported no resistant strains, we detected resistant strains, finding which underlines the importance of antimicrobial resistance surveillance and in some cases the necessity of developing local guidelines according to the results.

We noticed differences in the antimicrobial resistance profile of the strains regarding the group age of the patients and the previous administration of the autologous bacterial vaccine.

The accelerated rhythm of antimicrobial resistance development may lead to a shortage of efficient antibiotic drugs, reducing the ability to treat various infections. The fight against resistance to antimicrobial drugs is an ongoing process which constantly needs input from the surveillance systems, the laboratory research and the clinical outcome, in order to synthesis new molecules.

Considering the high variability of bacterial characteristics involved in infections and the different host response among individuals a more personalized approach is required. One possibility could be represented by autologous bacterial vaccine, a product used in different veterinary illnesses and in human medicine regains attention.

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