Antibiotic Susceptibility of *Staphylococcus Aureus* Isolated from Skin Lesions in Children. A Retrospective Analysis from a Tertiary Care Italian Pediatric Hospital

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Research

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Abstract

Background: knowledge on antibiotic susceptibility of *S.aureus* strains isolated from skin lesions in pediatric Italian patients is limited.

Methods: retrospective analysis of antibiotic susceptibility of *S.aureus* strains isolated from skin infections observed from January 2013 to June 2019 at the IRCCS Istituto Giannina Gaslini, Genoa – Italy

Results: a total of 1833 strains were analyzed. Methicillin resistance was more frequent in cultures from outpatients than from inpatients (18% vs. 14%, $p=0.04$) as well as resistance to cotrimoxazole (8% vs. 4.1%, $p<0.001$) Resistance to ampicillin was 99% in both groups, while to clindamycin it was 11% and 14%, respectively. Among topical antibiotics fusidic acid showed the better resistance profile (3%).

Conclusions: the proportion of antibiotic resistance in *S.aureus* skin infections in Italian children is not negligible. This could represent a problem, especially for orally administered drugs.

Background

Staphylococcus aureus is the most common cause of skin infections with an increasing prevalence of antibiotic resistance and consequent restriction of treatment options.¹

To our knowledge, data about resistance profile of *S. aureus* in skin lesions in children are overall poor, mostly in Italy.

We evaluated antibiotic susceptibility of *S. aureus* isolated from cutaneous lesions in patients followed up at a tertiary care Italian pediatric hospital.

Materials And Methods

The IRCCS Istituto Giannina Gaslini - Genoa is a tertiary care children's hospital in Northern Italy serving as local pediatric hospital for the Genoa area but representing also a referral hospital nationwide and for many foreign countries.

All *S. aureus* strains isolated from skin lesions in patients < 18 years from January 2013 to June 2019 were extracted from the Laboratory of Microbiology database. In case of multiple isolations of the same strain in a single patient only the first isolate was considered. Subsequently data were anonymized, according to Gaslini Institute data protection policy based on European Union Data Protection Rules. The need for informed consent was waived given the retrospective nature of the study and the anonymization of the data.

S. aureus identification was confirmed by MALDI-TOF technology (Vitek MS, BioMerieux, France), according to the manufacturer's instructions. For each strain the susceptibility to the following antibiotics (Vitek MS, BioMerieux, France) was recorded: ampicillin, methicillin, ciprofloxacin, clindamycin, cotrimoxazole, fusidic acid, mupirocin, gentamicin. These last 3 drugs were included since in Italy they have topical formulations and are frequently sold as out of the counter drugs. The interpretation of the results was based on The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint criteria.²

Since the study was based on a laboratory database no information was available on demographic and clinical data, but only ward of admission was available, that was used to classify patients as outpatients if sampled in

Emergency Department, Dermatology Unit and Infectious Diseases Unit, considering the hospital protocols for hospital admission. Patients from all other wards were considered inpatients.

Statistical analysis

Data were reported as proportions with 95% Confidence Interval (95%CI). Differences among proportions were evaluated by chi-square test with Yates correction or Fisher's exact test, when appropriate. A P value < 0.05 was considered as statistically significant. Analysis was performed by means of the web platform Social Science Statistics. <https://www.socscistatistics.com/>

Results

During the study period a total of 1833 *S.aureus* strains were extracted, 430 (23.4%) classified as from out-patients. Table 1 reports on antibiotic susceptibility among isolated strains, stratified as from outpatients or inpatients. The proportion of methicillin-resistant *S.aureus* (MRSA) was significantly higher in outpatients (18% vs. 14%, $p = 0.04$). Ampicillin resistance was 99% in both subsets and also resistance to clindamycin and ciprofloxacin was similar in the 2 groups. On the contrary, resistance to cotrimoxazole was significantly higher in outpatients ($p < 0.001$, chi-square test).

Table 1
Proportions of resistance in 1833 *S.aureus* strain isolated from skin lesions.

	Outpatients n = 430			Inpatients n = 1403			Total n = 1833		
	Tested (n)	Resistant strains (n)	Not tested (n)	Tested (n)	Resistant strains (n)	Not tested (n)	Tested (n)	Resistant strains (n)	Not tested (n)
Methicillin	420	77 (18, 95%CI 15–22)	10 (2.3, 95%CI 1–4)	1382	198 (14, 95%CI 12–16)	21 (1.5, 95%CI 1–2)	1802	275 (15, 95%CI 13–17)	31 (1.7, 95%CI 1–2)
Ampicillin	191	189 (99, 95%CI 98–100)	239 (56, 95%CI 51–60)	697	692 (99, 95%CI 98–100)	706 (50, 95%CI 48–53)	888	881 (99, 95%CI 99–100)	945 (52, 95%CI 50–54)
Clindamycin	413	45 (11, 95%CI 8–14)	17 (3.9, 95%CI 2–6)	1331	187 (14, 95%CI 12–16)	72 (5, 95%CI 4–6)	1744	532 (30, 95%CI 28–32)	89 (4.9, 95%CI 4–6)
Cotrimoxazole	427	35 (8, 95%CI 6–11)	3 (0.7, 95%CI 0–1)	1401	58 (4.1, 95%CI 3–5)	2 (0.1, 95%CI 0–0)	1828	93 (5, 95%CI 4–6)	5 (0.3 95%CI 0–1)
Ciprofloxacin	387	23 (6, 95%CI 4–8)	43 (10, 95%CI 7–13)	1228	92 (7, 95%CI 6–9)	175 (12, 95%CI 11–14)	1615	115 (7, 95%CI 6–8)	218 (12, 95%CI 11–13)
Gentamicin	427	39 (9, 95%CI 6–12)	3 (0.7, 95%CI 0–1)	1398	166 (12, 95%CI 10–14)	5 (0.5, 95%CI 0–1)	1825	205 (11, 95%CI 10–12)	8 (0.4, 95%CI 0–1)
Fusidic acid	281	10 (3.6, 95%CI 1–6)	149 (35, 95%CI 30–39)	874	28 (3.2, 95%CI 2–4)	529 (38, 95%CI 35–40)	1155	38 (3.3, 95%CI 2–4)	678 (37, 95%CI 35–39)
Mupirocin	130	2 (1.5, 95%CI -1-4)	300 (70, 95%CI 65–74)	425	27 (6, 95%CI 4–9)	978 (70, 95%CI 67–72)	555	29 (5, 95%CI 3–7)	1278 (70, 95%CI 68–72)
Numbers in parenthesis are percentages with 95% Confidence Interval.									

As for drugs with topical formulations, resistance to gentamycin and fusidic acid was similar in in- and outpatients, while for inpatients resistance to mupirocin was significantly higher ($p = 0.0309$, chi-square test), even if many strains were not tested for mupirocin susceptibility (70% in both groups).

Discussion

In this study we describe the profile of antimicrobial susceptibility of *S. aureus* strains isolated from cutaneous lesions in a pediatric tertiary care center in Italy. To our knowledge, no other Italian data on this topic are available.

The first observation we can drive is that even if the prevalence of MRSA we observed was lower than in other pediatric studies from other countries^{3,4,5}, the proportion this pathogen on skin lesions was significantly higher in outpatients compared with inpatients. However, since 95%CI of the proportions are imbricated it is probable that this difference is not clinically relevant but represents only a statistical effect.⁶

Since no other pediatric Italian data are available we can not make any national comparison, but it must be noted that European data (including also adults) report a MRSA prevalence of 15.1%, with a North (0%) to South (29%) increasing gradient⁷, that is consistent with our observations.

A recent Italian consensus on the treatment of skin infections in pediatrics⁸ indicated clindamycin for first line treatment in communities where proportions of MRSA is $> 10\%$ if clindamycin resistance is $< 10\%$. Considering our epidemiology clindamycin (11% in out- and 14% in inpatients resistant strains) did not meet these criteria and could not represent a possible choice for empirical therapy before susceptibility tests availability. We do not know if this observation can be generalized to other Italian regions, but this observation should represent a warning. In spite of the significantly higher proportion of strains resistant to cotrimoxazole in outpatients (8% vs. 4.1%), as already described⁹, in our study resistance to cotrimoxazole was lower than the 10% threshold proposed for other drugs to be used for first line therapy of skin lesions⁸ and therefore it could represent an acceptable first choice, pending susceptibility tests. The generally lower proportion of resistant strains in inpatients could seem a paradox. However, IGG has a strict policy of antibiotics use and effective patients' isolation procedure in presence of resistant strains¹⁰ that could at least partially explain this observation.

The use of topical antibiotics has been associated with selection of resistant strains.¹¹ In our study data on resistance to mupirocin could be poorly reliable because of the high proportion (70%) of untested strains; Fusidic acid showed a very low proportion of resistance (about 3% of resistance) but also in this case near 1/3 of strains were not tested. Finally, topical gentamycin is a highly used over the counter topical antibiotic in Italy, and indeed the resistance is not negligible (9–12%). Our data suggest that fusidic acid is the better topical choice⁸, at least in our epidemiological condition.

The main limitation of this study is the lack of clinical data, due to fact that it is derived from a laboratory database. Despite this, it gives information about an important item such as antimicrobial resistance in pediatric staphylococcal skin infections in a geographic area and clinical field where epidemiological data are lacking.

Conclusions

S. aureus strains isolated from skin infections in Italian children shows a high proportion of resistance, especially in outpatients (18%), is high also for clindamycin (11%), while is not negligible for cotrimoxazole (8%). This could represent a problem for initial antibacterial therapy in the outpatient setting pending cultures results. As an apparent

paradox, resistance proportions are lower in cultures from inpatients. This could be due to a strict control of antibiotic administration and adherence to isolation procedures, that represent cornerstones to reduce the spread of antibiotic resistant bacteria within hospitals.

Declarations

Ethics approval and consent to participate: Not applicable since retrospective analysis of anonymous laboratory data

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

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Authors' contribution

Marilea Lezzi	Data collection and analysis, 1 st paper draft, final version approval
Roberto Bandettini	Study design, data collection, final version approval
Elisabetta Ugolotti	Data collection, final version approval
Carolina Saffioti	Data and results analysis and comments, final version approval
Alessio Mesini	Data and results analysis and comments, final version approval
Carlotta Pastorino	Data and results analysis and comments, final version approval
Francesca Manunza	Data and results analysis and comments, final version approval
Marta Ferretti	Data and results analysis and comments, final version approval
Giacomo Brisca	Data and results analysis and comments, final version approval
Elio Castagnola	Study design, data and results analysis and comments, paper review, final version approval

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