Methicillin-resistant *Staphylococcus aureus*: epidemiology and antimicrobial susceptibility experiences from the University Hospital ‘Luigi Vanvitelli’ of Naples

D. Pignataro^a, F. Foglia^{b*}, M. T. Della Rocca^a, C. Melardo^a, B. Santella^a, V. Folliero^b, S. Shinde^b, P. C. Pafundi^{id c}, F. C. Sasso^c, M. R. Iovene^a, M. Galdiero^b, G. Boccia^d, G. Franci^d, E. Finamore^{a*} and M. Galdiero^{a,b}

^aSection of Microbiology and Virology, University Hospital “Luigi Vanvitelli” of Naples, Naples, Italy; ^bDepartment of Experimental Medicine, University of Campania “Luigi Vanvitelli”, Naples, Italy; ^cDepartment of Advanced Medical and Surgical Sciences, University of Campania “Luigi Vanvitelli”, Naples, Italy; ^dDepartment of Medicine, Surgery and Dentistry “Scuola Medica Salernitana”, University of Salerno, Baronissi (SA), Italy

ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the important pathogens worldwide showing resistance to several widely used antibiotics. This has made the treatment of MRSA infections harder, especially due to their prevalence in the hospital setting. We evaluated the antibiotic susceptibility patterns of healthcare-associated MRSA infections with a focus on Vancomycin Intermediate *S. aureus* (VISA) and macrolide-licosamide-streptogramin B (MLS_B) phenotypes. A total of 417 *Staphylococcus aureus* (*S. aureus*) cases were isolated between January 2017 and December 2018, through several clinical specimens collected from the University Hospital ‘Luigi Vanvitelli’ of Naples. We identified bacterial strains using Matrix-Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF) and antimicrobial susceptibility using Phoenix BD (Becton Dickinson, NJ, USA). Out of the total 417 *S. aureus* cases, 140 were MRSA (33.6%) and of these, 50% were soft tissue infections. All MRSA and Methicillin sensitive *S. aureus* MSSA isolates were susceptible to linezolid and daptomycin. Two MRSA cases exhibited intermediate resistance to vancomycin and were of constitutive MLS_B phenotype. Among the MRSA strains, 11.4% were constitutive and 43.6% were inducible MLS_B phenotypes and 8.6% were macrolide-streptogramin B phenotype. This study characterized the epidemiological status, antibiotic resistance patterns, and current prevalent phenotypes of healthcare-associated MRSA. This knowledge can aid clinicians in improving the antimicrobial stewardship program by adapting appropriate guidelines for the proper use of MRSA antibacterial agents.

Keywords

Methicillin-resistant *Staphylococcus aureus*; antibiotic susceptibility patterns; healthcare infections; MLS_B phenotypes; vancomycin

Introduction

In recent years, there has been a progressive increase in antimicrobial resistance in gram-negative and gram-positive pathogens, especially in the hospital environment [1]. Specifically, the acronym ‘ESKAPE’ categorizes infections caused by six bacterial species (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp.*), known for their ability to ‘escape’ from antibiotics’ biocide action [2]. The infections sustained by these bacteria place a significant burden on healthcare systems and have important global economic costs due to the resource usage required to fight the increasingly difficult infections [3]. The infections caused by *S. aureus* are generally suppurative, affecting most organs and apparatus and are extremely variable by location and gravity [4].

The introduction of penicillin in the early 1940s revolutionized the treatment of *S. aureus* infections,

but the massive use of this antibiotic, within a few years, favored the diffusion of resistant strains in the hospital environment and also in the larger community [5,6]. The need to find new substances that survive the problem of rampant resistance has encouraged the production of synthetic molecules like methicillin. Despite the initial success, the first methicillin-resistant *S. aureus* strain (MRSA) was isolated a few years after its introduction [7]. Subsequently, MRSA strains became a worldwide problem with a resulting endemicity in hospitals and healthcare facilities defined as ‘hospital’ or ‘healthcare-associated’ MRSA (HA-MRSA) [8]. The spread of HA-MRSA clones is associated with typical risk factors related to the hospital environment: combined and extended antibiotic therapies, medical devices, comorbidity profiles and lacking hospital hygiene measures [9]. HA-MRSA strains are resistant to penicillinase-resistant penicillins, all beta-lactams, and wide antibiotic classes. A new generation of cephalosporins have been recently developed, such as ceftarolin. Potential

CONTACT Emiliana Finamore ✉ emiliana.fnamore@unicampania.it 📧 Section of Microbiology and Virology, University Hospital “Luigi Vanvitelli” of Naples, Naples, Italy

*Pignataro D. and Foglia F. share the first authorship.

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antimicrobial agents are represented by daptomycin, linezolid, trimethoprim/sulfamethoxazole and vancomycin [10]. Unfortunately, in the last years, vancomycin-resistant strains have spread. These strains were isolated for the first time in 1997 [11] and studies have shown the spread of similar strains across different countries [12]. MRSA strains can also exhibit resistance to the macrolide-licosamide-streptogramin B (MLS_B) antibiotic class, generally used for soft tissue and skin infections treatments [10]. Phenotypically, MLS_B resistance is expressed in three forms and is detected by routine susceptibility testing. Constitutive phenotype strains (cMLS_B) are resistant to both erythromycin (macrolide) and clindamycin (lincosamide). Inducible strains (iMLS_B) are resistant to erythromycin and falsely showed susceptibility to clindamycin [13]. The treatment with clindamycin in patients with iMLS_B resistance induces the development of cMLS_B resistant strains, consequently leading to therapeutic failure. So, it is pertinent to identify MLS_B resistance prior to choosing the best therapy for infected patients. Fragmentary data about MRSA strain prevalence and MLS_B phenotype characteristics had been collected in our hospital. The study aim was to determine resistance rates and antibiotic susceptibility patterns of MRSA strains isolated from several clinical specimens from patients affected with health-care-associated MRSA from the University Hospital 'Luigi Vanvitelli' of Naples. We also evaluated the incidence of vancomycin susceptibility profile in our hospital to limit the increase of MRSA strains with vancomycin intermediate (VISA) or complete (VRSA) resistance.

Materials and methods

Bacterial isolates

In this study, a total of 417 *S. aureus* isolates were collected from human samples across different anatomical districts. The clinical specimens such wounds, purulent exudates, ulcer swabs, sputum, skin swabs, urine, vaginal and rectal swabs, blood and indwelling medical devices (i.e. central line tips, peripheral intravenous catheters), were collected from hospitalized patients from University Hospital 'Luigi Vanvitelli' of Naples from January 2017 to December 2018.

Isolation and identification of *S. aureus*

The samples were inoculated into Mannitol Salt Agar medium and incubated at 35°C for overnight. Colonies growth was observed and identified using matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS), performed on an AutoFlex® II TOF/TOF mass spectrometer (Bruker Daltonics, Bremen, Germany) with

Flexcontrol™ software 3.0 (Bruker Daltonics, Bremen, Germany) for automatic acquisition of mass spectra. For the identification of MRSA, all strains were screened for methicillin resistance using oxacillin (1 µg) and ceftioxin (30 µg) disk diffusion method (Kirby-Bauer) on Muller-Hinton agar (MHE) plates [14]. Isolates were considered resistant when the diameter of inhibition for oxacillin was < 26 mm, and for ceftioxin was < 22 mm, according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines, valid at the time of the interpretation [15]. Samples were tested in duplicate. All isolates were identified as resistant to oxacillin and ceftioxin using disk diffusion test. The MLS_B phenotypes were detected by Kirby-Bauer routine antibiotic susceptibility testing and automatized system. MRSA isolates that have shown resistance to both erythromycin and clindamycin, were considered cMLS_B phenotype. Instead, iMLS_B phenotype showed the presence of a D-shape inhibition clindamycin disk and the absence of erythromycin inhibition zone. The strains resistant to erythromycin and susceptibility to clindamycin were classified as MS_B phenotype, according to EUCAST guidelines [16]. The minimum inhibitory concentration of vancomycin was detected using the E-test method (AB bioMérieux) [17]. MRSA isolates were interpreted resistance or susceptibility according to the EUCAST breakpoints [17].

Antibiotic-resistant pattern

The *S. aureus* isolates were subjected to automatized antimicrobial susceptibility testing Phoenix BD (Becton Dickinson, NJ, USA). In short, the identification broth (ID) was inoculated with pure bacterial colonies and adjusted to the McFarland (McF) of 0.5, using a Phoenix (Becton Dickinson, NJ, USA). A 25 µL volume of standardized ID broth suspension was added to the Phoenix broth (Becton Dickinson, NJ, USA), which was previously integrated with a drop of Phoenix indicator (Becton Dickinson, NJ, USA). Indicator and broth were loaded into the Phoenix panels, sealed, registered, and deposited in the Phoenix device. The results were explained using the Epicenter software version 7.22A (Becton Dickinson, NJ, USA) after 16 h of incubation [18].

Statistical analysis

Statistical analysis was conducted using the IBM SPSS software (version 22.0; IBM SPSS Inc., New York, USA). Rates of MRSA and methicillin-sensitive *S. aureus* (SA) infections were presented as numbers and percentages. Chi-square test was used to evaluate the relation between the two groups of categorical variables. A *P* value of ≤ 0.050 was considered statistically significant.

Table 1. Healthcare-associated methicillin-resistant *Staphylococcus aureus* and methicillin-sensitive *Staphylococcus aureus* in different type of samples (N = 417). MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-sensitive *Staphylococcus aureus*. *Determined using Chi-squared test, statistically significant at $P \leq 0.005$.

Type of infections	MRSA (n = 140)	MSSA (n = 277)	P value*
Respiratory	36 (25.7)	89 (32.1)	0.259
Blood and medical device	23 (16.4)	19 (6.9)	0.005*
Soft tissue	70 (50)	144 (52)	0.756
Skin Other	5 (3.6)	14 (5.1)	0.622
	6 (4.3)	11 (3.9)	1.000

Results

During the study period, 417 non-repetitive *S. aureus* strains were isolated from hospitalized patients of University Hospital 'Luigi Vanvitelli' of Naples. All the cultures obtained refer to infection diagnosed within 48 hours of admission or in an outpatient with extended health-care. Among these, 33.6% were found to be positive for methicillin-resistant *S. aureus*. No statistically significant differences were observed between male (233) and female patients (184). The prevalence of MRSA in each group was 42.2% (59) for female and 57.8% (81) for male, respectively. Instead, the rate of infections with MRSA strains was higher in patients aged 31–60 (42.1%) and 61–90 (43.6%) years old compared with those under 31 (14.3%) years old but not statistically significant ($p = 0.437$). Among all MRSA cases, 51.3 % were collected from soft tissue infections like ulcers, burn wounds and abscess. (Table 1) MRSA was significantly more frequent in the

bloodstream and in medical devices-associated bacteremia ($p = 0.005$) whereas MSSA was frequently isolated in respiratory and soft tissue infections. All isolates (MRSA and MSSA) were susceptible to linezolid and daptomycin treatments, whereas more MRSA isolates were resistant to ciprofloxacin (77.1%), clindamycin (61.4%) and erythromycin (65%). MRSA isolates were significantly more resistant ($p < 0.005$) than MSSA isolates to ciprofloxacin, clindamycin, erythromycin, rifampicin and tetracycline. The antibiotic resistance patterns of the MRSA and MSSA isolates are shown in (Table 2). Out of the MRSA strains, 138 (98.6%) were susceptible to vancomycin and teicoplanin whereas two (1.4%) showed intermediate resistance to VISA. The strains with intermediate resistance to VISA were isolated from two patients with an infected wound and an abscess. Moreover, both isolates were also of the cMLS_B phenotype. Finally, of a total of 140 MRSA isolates, 63.57% showed MLS_B resistance. Of these, as shown in Table 3, 43.6% were iMLS_B phenotype.

Discussion

The continuous increase in multi-drug resistant *S. aureus* infections poses critical problems and negatively affects on clinical antibiotic treatment. MRSA strains are often resistant not only to β -lactam antibiotics, but also to antimicrobial agents commonly used in hospital empirical therapies such as aminoglycosides, quinolones, and macrolides [19]. In this scenario, constant monitoring of MRSA susceptibility patterns is

Table 2. Antibiotic resistance patterns of healthcare-associated methicillin-resistant *Staphylococcus aureus* and methicillin-sensitive *Staphylococcus aureus* isolates (N = 417). MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-sensitive *Staphylococcus aureus*. *Determined using Chi-squared test, statistically significant at $P \leq 0.005$.

Antibiotic	Resistant MRSA isolates (n = 140)	Resistant MSSA isolates (n = 277)	p value*
Ceftaroline	59 (42.1)	-	n.a.
Ciprofloxacin	108 (77.1)	39 (14.1)	< 0.005*
Daptomycin	-	-	n.a.
Clindamycin	86 (61.4)	81 (29.2)	< 0.005*
Erythromycin	91 (65)	90 (32.5)	< 0.005*
Gentamicin	52 (37.1)	87 (31.4)	0.272
Linezolid	-	-	-
Penicillin	139 (99.3)	209 (75.5)	< 0.005*
Rifampicin	38 (27.1)	7 (2.5)	< 0.005*
Trimethoprim/sulfamethoxazole	22 (15.7)	39 (14.1)	0.662
Tetracycline	32 (22.9)	11 (4)	< 0.005*
Teicoplanin	2 (1.4)	-	n.a.

Table 3. Distribution of macrolide-licosamide-streptogramin B phenotype in patients with methicillin-resistant *Staphylococcus aureus* infections (N=140). MLS_B=macrolide- licosamide-streptogramin B; cMLS_B=constitutive MLS_B; iMLS_B=inducible MLS_B; MS_B=macrolide-streptogramin B.* The remaining 51 isolates have only MRSA phenotype and were sensitive to erythromycin and clindamycin. MRSA = methicillin-resistant *Staphylococcus aureus*.

Type of phenotype	cMLS _B phenotype	iMLS _B phenotype	MS _B Phenotype	MRSA
n (%)	16 (11.4)	61(43.6)	12 (8.6)	51 (36.4)

crucial for the proper clinical administration of patients to study the diffusion and distribution of MRSA strains in the hospital and the community. The present study analyzed MRSA healthcare-associated infections among patients admitted to our hospital. Among the (*S. aureus* strains 33,6%) were MRSA. No significant differences were observed between male and female patients, in agreement with other studies [20]. More than 50 % of the MRSA strains were resistant to ciprofloxacin, erythromycin, clindamycin and demonstrated a significant increase in the resistance to tetracycline and rifampicin compared with that of MSSA. The prevalence of HA-MRSA infections has shown a considerable geographical variation [21,22]. Compared with our study, a higher rate of healthcare-associated MRSA infections was reported in Turkey (71.5%) [23], Bangladesh (53.1%) [24], Japan (52%) [25], USA (54%) [26] and western Nepal (43.6%) [27], whereas India (8%) reported lower rates [28]. In contrast, the prevalence of MRSA strains reported in our study is higher than that of Germany (9.1%), France (12.9%), Austria (5.9 %) and other European countries, according to European Network for Surveillance of Antimicrobial Resistance (ENSA) [29]. The increasing prevalence of MLS_B antibiotic resistance among *S. aureus* has alerted scientists worldwide. Routine antibiotic sensitivity tests can identify the cMLS_B phenotype but iMLS_B and MSB are detected only if the erythromycin and clindamycin discs are placed next to each other. Hence, in the presence of iMLS_B phenotype, treatment with clindamycin can induce therapeutic failure [30]. We reported that 43.6% of the MRSA strains had the iMLS_B phenotype and the phenotype rates differences between the MRSA and MSSA isolates showed that MRSA isolated had a higher percentage of MLS_B phenotypes [31]. This regional change in the observed bacterial susceptibility patterns are likely related to the varied use of antimicrobials by clinicians. We reported the phenotype rates differences between the MRSA and MSSA isolates and showed that MRSA isolated had a higher percentage of MLS_B phenotypes. These results suggested that the D-test method can be used to reveal and confirm the iMLS_B resistance phenotype in HA-MRSA. Other therapeutic options in the case of severe MRSA infections was represented by vancomycin, the last line of defense in positive cocci infection. However, its increasing use and patient's prolonged hospitalization has favored the development of MRSA strains with intermediate (VISA) or complete (VRSA) resistance to vancomycin [32]. In our hospital, we did not isolate VRSA strains but identified two VISA cases (1.4%) among the MRSA isolates contrasting data from other countries [33]. All MRSA isolates were susceptible to linezolid, one of the therapies used to treat severe infections. These encouraging data suggested that the importance of an epidemiology update regarding HA-MRSA infections could

prevent the increase of VISA strains and therapeutic failure.

In conclusion, the epidemiology of HA-MRSA is essential as it guides infection control and prevention policies, guidelines and related activities or prevention of HA-MRSA and other hospital-related infections. In our study the comparison between MRSA and MSSA strains showed a significant resistance for ciprofloxacin, tetracycline and rifampicin antibiotic and also rates of *S. aureus* phenotype type. Data did not report any VISA strains. These results underline the necessity to carefully check the single Minimum Inhibitory Concentration (MIC) of Vancomycin above all in the treatment of serious MRSA infections. In case of resistance to other drugs, susceptibility methods should also be tested before use in the treatment of serious MRSA infections. Our studies confirmed that the hospital-related factors such as overcrowding, hand hygiene practices, and the existence of antimicrobial stewardship program are important determinants of HA-MRSA. Defining the epidemiology situation about one of the major healthcare-acquired infections encourages clinicians to improve the antimicrobial stewardship guidelines on MRSA patient treatment to mitigate further increase of resistant strains and prevent the development of new ones.

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Disclosure statement

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ORCID

P. C. Pafundi <http://orcid.org/0000-0002-0310-3529>

Data availability statement

The data that support the findings of this study are available from the corresponding author, E.F., upon reasonable request.

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