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RESEARCH ARTICLE

COMPARISON OF ANTIBIOTIC SENSITIVITY OF MRSA WITH MSSA AMONG *STAPHYLOCOCCUS AUREUS* ISOLATES FROM PATIENTS IN THE 48 MILITARY HOSPITAL IN SANA'A CITY, YEMEN

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Abstract

Background and objectives: A number of infectious disorders can be opportunistically brought on by *Staphylococcus aureus* (*S. aureus*), which colonizes human skin and mucous membranes. Methicillin (MRSA) resistance is a frequent occurrence, as are resistances to a number of clinically useful antibiotics. Though MRSA affects healthcare systems and society all throughout the world, it is most severe in underdeveloped countries. The Clinical and Laboratory Standards Institute (CLSI) advises that cumulative antibiotic data for *S. aureus* be analyzed and reported on an annual basis to help clinicians choose the best preliminary empirical antimicrobial therapy. The most recent report from our center on this subject, however, was more than 7 years ago.
Subjects and methods: Well-proven *S. aureus* data were gathered from inpatient and outpatient clinical samples at the 48th Military Hospital, Sana'a, Yemen, from January 1, 2022, through December 2022, using a retrospective cross-sectional design. Using Kirby-Bauer disk diffusion, antimicrobial susceptibility testing (AST) was carried out. Calculations were made on the rate of antibiotic resistance between MRSA and MSSA as well as the correlation between MRSA.
Results: Among the 265 unique isolates, the overall prevalence of MRSA was 37.4%. Inpatients had a greater risk factor for MRSA with an OR of 2.7 (p<0.001). A risk factor was also found with the catheter sample, and devices with an OR=3.7 (p=0.003). Methicillin resistance was predictive of resistance to most antibiotics. Zero resistance rate to linezolid, and vancomycin was observed for the MRSA and MSSA strains. The prevalence of multidrug resistant (MDR) isolates was 60.4%. Significantly higher in MRSA (68.7%) versus 55.4% for MSSA.
Conclusion: This study's MRSA prevalence was higher than that of earlier research from the same hospital; it is a progressive issue and much below the desired rates. Additionally, there was notable resistance to erythromycin, imipenem, and clindamycin. Vancomycin and linezolid are currently the top two options for the empiric treatment of MRSA. In order to stop the emergence of MDR species, it is suggested against giving newer antibacterial medications while the older ones are still effective.
Keywords: Antibiotic patterns; multidrug resistant (MDR); MRSA, MSSA, *S. aureus*, Sana'a, Yemen.

INTRODUCTION

One of the most prevalent colonizers and a source of several illnesses is *S. aureus*[1]. It was found that *S. aureus* was the second leading pathogen of antimicrobial resistance-related deaths in 2019[2]. It is known that *S. aureus* isolates became resistant to penicillin within one to two years of its introduction, methicillin less than a year after its use[3], and vancomycin after about 40 years[4] since its introduction into clinical use. Even while one of them may appear to be effective *in vitro*, clinical resistance against all other

antibiotics in the same class usually results from the mechanism of resistance, which alters the target of the antibiotic[5]. *Staphylococcus* bacteria make penicillinase, a specific form of *beta-lactamase* that cleaves the -lactam ring of the penicillin molecule and renders the antibiotic useless. Methicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin, and flucloxacillin are examples of antibiotics with the ability to withstand degradation by *staphylococcal* penicillinase[6]. At the same time, multidrug resistance (MDR) may coexist against different classes through different mechanisms as well. Methicillin resistance in *Staphylococcus aureus* (MRSA) itself can be seen as another definition of multidrug resistance[7]. It is associated with several epidemiological features[8] and may indicate increased resistance against other agents (e.g., clindamycin)[9]. Of course, the use of antibiotics creates selective pressure for MRSA and other resistant isolates, but in developing nations, improper use of antibiotics for common diseases may also contribute to increased resistance. Meanwhile, the high frequency of MRSA in developed countries may be the result of improper use or over-the-counter antibiotics.

Although given to treat a specific disease in a specific patient, antibiotics, unlike other drugs, have effects that extend to much more than just the patient. This is true even when prescribed and used correctly. In addition, they frequently contaminate meat and poultry intended for human consumption that are domestically produced or imported, and serve as direct causes of disease or colonization in humans[10]. In the current era, due to the recent development and clinical approval of new, powerful antibiotics as new potent antibiotics, using anti-staphylococcal agents sparingly, trying older agents with a narrow/targeted spectrum at the first lines by an appropriate dose and duration, hesitating to prescribe antibiotics in cases where there is no evidence-proven indication, and, if the circumstances allow, waiting for the antibiogram results are all important strategies to follow. Additionally, due to the quick establishment of resistance mutations, rifampin (RIF) or fluoroquino-lones (FQ) monotherapy of *S. aureus* infections should be avoided[11]. Another promising finding is the "seesaw effect," which shows increased beta-lactam activity when antibiotics targeting glyco- and/or lipo-peptides are less effective[12].

For patients for whom there are no yet available microbiological test results to target treatment, the analysis and presentation of cumulative antibiogram reports should occur at least once per year, according to the Clinical and Laboratory Standards Institute (CLSI) M39[13]. The focus of the current investigation is the fact that it has been more than 8 years since the 48 Military Hospital in Sana'a, Yemen had reported *S. aureus.*

SUBJECTS AND METHODS

At the 48 Military hospital, a tertiary referral care facility in Sana'a, Yemen, this cross-sectional retrospective study was carried out. Clinical samples of various specimen types were collected from hospitalized in-patients and patients attending the outer clinic of the hospital from 1st January 2022 to December 2022. Sample types were considered as follows; wound secretions, blood, respiratory secretion and sputum, abscess, tissue, bone and intra-articular fluid, urine, pleural, peritoneal, and pericardial fluids; catheters and devices and others. Medical records were used to gather information about *S. aureus* isolates. The first isolate was examined for each patient during a one-year period, regardless of the body site from which the sample was taken or the antimicrobial susceptibility pattern, in accordance with CLSI M39 criteria[14]. Furthermore, isolates with missing data were disregarded.

***S. aureus* identification:** In this study, we used phenotypic approaches to identify *S. aureus* isolates and assess their antibiotic susceptibility (AST). To accomplish this, each specimen was examined using a variety of identification techniques, such as Gram-stained smear light microscopy, observation of colony morphology and growth patterns on different media, such as deoxyribonuclease agar and mannitol salt agar, and manual biochemical reactions, such as catalase and coagulase tests.

Antibiotic sensitivity: The modified Kirby-Bauer disc diffusion method was used to assess the antibiotic sensitivity of bacterial isolates on Mueller-Hinton agar. The inhibitory zone diameter was interpreted in accordance with the 2017 Clinical Laboratory Standards Institute guidance[15].

Detection of MRSA: Cefoxitin disc diffusion was used to detect MRSA strains as recommended by CLSI to detect methicillin resistance[15,16]. Cefoxitin can be utilized to screen diverse MRSA populations since it is a more effective inducer of mec-A gene expression than oxacillin or methicillin.

MDR determination: MDR was defined as no susceptibility to $\geq$ 1 agent in $\geq$ 3 antimicrobial categories. *Beta-lactamse* was excluded as an antimicrobial category in order to evaluate frequencies of MDR between isolates of MSSA and MRSA. The antibiotic susceptibility (or resistance) pattern in this study identifies the antibiotics to which an isolate is also susceptible (or resistant).

Statistical analysis: Data analysis was done using the Epi Info statistical program, version 6 (CDC, Atlanta, USA). The association of MRSA with baseline characteristics of clinical samples received for *S. aureus* were determine by calculating *OR*, 95% *CI*, X^2 and *p* value. Different antibiotic resistance patterns and their frequency were calculated and difference rate and significance of resistant to different antibiotics were calculated. The significance of the observed difference between groups was assessed using the *Chi* squared test with a threshold *p*-value of 0.05.

RESULTS

The results of the study are illustrated in three tables. Table 1 shows the association of MRSA with baseline characteristics of clinical specimens received of *S. aureus* at the 48th Military Hospital in Sana'a City for the year 2022. There was an association between

MRSA and the inpatient group where the risk factor associated with contracting inpatient MRSA equals 2.7, *CI*=1.6 -4.4 , *p*<0.0001. Also, MRSA was associated with abscess, tissue, bone and intra-articular fluid samples with the risk factor associated with MRSA being 1.9, *p*=0.05. There was an association of MRSA with catheters, devices samples where the risk factor associated with MRSA was 3.7, *p*=0.003. There was no association with other factors. MRSA isolates were resistant against erythromycin (ERY), clindamycin (CLI), ciprofloxacin (CIP), and levofloxacin (LVX) by >80%. All MSSA isolates had resistance rates <50% against each of the tested antibiotics. When reporting the most common antibiotic styles in Table 2, we included nitrofurantoin (NIT) even though it is mainly used for urinary tract infections. Overall, the MDR was 60.4% and was significantly different (*p*-value 0.03) between the MRSA (68.7%) and MSSA (55.4%) isolates with 13.3% difference; and beta-lactams were omitted from the definition of drug resistance (Table 3).

Table 1: Association of MRSA with baseline characteristics of clinical samples received for *S. aureus* (n=265).

Type of specimens	MSSA n=166 N (%)	MRSA N=99 N (%)	*OR*	*CI*	X^2	*P*
Sex						
Male n=147	98 (66.7)	49 (33.3)	0.68	0.4-1.1	2.2	0.13
Female n=118	68 (57.6)	50 (42.4)	1.4	0.8-2.4	2.2	0.13
Hospitalized						
Yes n= 123	62 (50.4)	61 (49.6)	2.7	1.6-4.4	14.6	<0.001
No n=142	104 (73.2)	38 (26.8)	0.37	0.2-0.6	14.6	<0.001
Blood n=23	13 (56.5)	10 (43.5)	1.3	0.59-3.1	0.4	0.52
Wound secretions n=45	30 (66.7)	15 (33.3)	0.8	0.4-1.5	0.37	0.54
Respiratory secretions and sputum n=41	24 (58.5)	16 (41.5)	1.1	0.7-2.2	0.14	0.7
Abscess, tissue, bone, intra-articular fluid n=44	22 (50)	22 (50)	1.9	1.01-3.5	3.6	0.05
Urine n=25	17 (68)	8 (2)	0.77	0.3-1.8	0.33	0.56
Pleural, peritoneal, and pericardial fluids n=39	29 (74.4)	10 (25.6)	0.53	0.24-1.1	2.6	0.1
Catheters and devices =21	14 (66.7)	7 (33.3)	3.7	1.4-9.6	8.3	0.003
Others n=27	16 (59.3)	11 (40.7)	1.2	0.5-2.6	0.14	0.7

Table 2: Antibiotic Resistance rate for MSSA comparing with MRSA isolated from clinical specimens.

Antibiotics	Total *S. aureus* n=265 N (R %)	MSSA n=166 N (R %)	MRSA n=99 N (R %)	% Difference	*p*
Trimethoprim/sulfamethoxazole	98 (37)	34 (20.5)	64 (64.6)	43.5	<0.0001
Clindamycin	149 (56.2)	57 (34.3)	92 (93)	58.7	<0.0001
Erythromycin	156 (58.9)	75 (45.2)	81 (81.8)	36.6	<0.0001
Chloramphenicol	65 (24.5)	40 (24.1)	25 (25.3)	1.2	0.8
Tetracycline	122 (46)	55 (33.1)	67 (67.7)	34.6	0.0007
Gentamicin	65 (24.5)	5 (3.01)	60 (61)	57.9	<0.0001
Rifampin	45 (17)	3 (1.8)	42 (42.4)	40.6	<0.0001
Cefoxitin	99 (37.4)	0 (0.0)	99 (100)	100	<0.0001
Ciprofloxacin	123 (46.4)	34 (20.5)	89 (89.9)	69.4	<0.0001
Doxycycline	100 (37.7)	53 (31.9)	47 (47.5)	15.6	0.01
Levofloxacin	116 (43.8)	45 (27.1)	71 (71.7)	44.6	<0.0001
Imipenem	102 (38.5)	3 (1.8)	99 (100)	98.2	<0.0001
Moxifloxacine	65 (24.5)	8 (4.8)	57 (57.6)	52.8	<0.0001
Nitrofurantoin	10 (3.8)	0 (0.0)	10 (10.1)	10.1	<0.0001
Vancomycin;	0 (0)	0 (0.0)	0 (0.0)	0	-
Linezolid	0 (0)	0 (0.0)	0 (0.0)	0	-

DISCUSSION

The goal of this investigation was to identify the cumulative antibiotics pattern (Table 2) for *S. aureus* isolates in the 48th Military Hospital in order to be included in antibiotic stewardship programs, as advised by CLSI M39[13]. After analyzing 265 *S. aureus* isolates from clinical samples, the overall prevalence of MRSA isolates was 37.4%. Over 80% resistance rates against Erythromycin, Clindamycin, Ciprofloxacin and imipenem were seen among MRSA isolates which is of concern because Clindamycin and imipenem are two of the most commonly prescribed antibiotics empirically. No resistance was discovered with linezolid (LZD), and vancomycin (VAN). Although this was the case, in hospital settings, MRSA remained a rare occurrence until the 1990s, at which point its prevalence in hospitals surged and it is now endemic[17]. Now, MRSA infecting humans and causing a number of infections, including skin and soft tissue infection (SSTI),

pneumonia, and sepsis, it can also infect animals, causing livestock-associated MRSA (LA-MRSA) sickness[18]. In the current study, the prevalence of MRSA was lower than previous reports by Al-Safani *et al*., in the same center[6] (19%), Khalili *et al*.,[19] and Mehrez *et al*.,[20] in Iran, as well as less than that reported in Yemen by Al-Akwa *et al*.,[21] (23.5%). Alyahawi *et al*., (17.6%)[22] but similar to that recently reported by Qodrati *et al*.,[23] in Iran (37.5%). When a comparison of isolates causing invasive infection from 29 European countries in 2018 is made, the current result will be placed after Cyprus, Romania and Portugal, in fourth place and these countries are among the countries with the most prevalence of MRSA. Additionally, the general rate in Europe is 19.3% in the same report[24]. In the present study, the overall prevalence of MDR isolates was 60.4%, exceeding the rates determined in Addis Abeba by Dilnessa and Bitew[9] and Iran by Qodrati *et al*.,[23] (48.5%). Additionally, it was significantly lower than what Kim *et al*.,[25] studied with a tailored definition (97.7%) and significantly higher than what Wiliamson *et al*.,[26] reported from New Zealand (6%).

Table 3: Prevalence of MDR degree among *S. aureus* of MSSA strains comparing with MRSA strains isolated from clinical specimens.

Antimicrobial class used to define MDR	Degree	Total *S. aureus* N=265, N (%)	MSSA N=166 N (%)	MRSA N=99 N (%)	Difference %	*p*
1-Glycopeptide (Vancomycin)	R0	50 (18.9)	37 (22.3)	13 (13.1)	9.2	0.64
2-Aminoglycosides (Gentamicin)	R1	10 (3.8)	2 (1.2)	8 (8)	6.8	0.004
4-Quinolone (Ciprofloxacin)	R2	45 (17)	35 (21.1)	10 (10)	9.2	0.09
5-Sulfonamides (Cotrimoxazole)	R3	20 (7.5)	17 (10.2)	3 (3)	7.2	0.03
6-Oxazolidinones (Linezolid)	R4	65 (24.5)	35 (21.1)	30 (30.3)	9.2	0.92
7-Macrolides (Erthromycin)	R5	35 (13.2)	19 (11.4)	16 (16.2)	4.8	0.26
Total MDR=160 (60.4%)	R6	25 (9.4)	12 (7.2)	13 (13.1)	5.9	0.11
	R7	15 (5.7)	9 (5.4)	6 (6)	0.6	0.83
	MDR	160 (60.4)	92 (55.4)	68 (68.7)	13.3	0.03

R0: Sensitive against all selected antibiotic class; R1: Resistant to at least one antibiotic class; R2: Resistant to two antibiotic class; R3: Resistant to three antibiotic class; R4: Resistant to four antibiotic class; R5: Resistant to five antibiotic class; R6: Resistant to six antibiotic class; R7: Resistant to all seven antibiotic class; MDR: Resistant to at least three antibiotic class.

Inpatients had a higher chance of being infected with MRSA isolates with an OR of 2.7 (p<0.001) compared to outpatients. The above result is reasonable; Most infections occur in the community, which are linked to organisms that are least resistant. The infections that appear in hospital acquired infections are caused by pathogens that are more resistant to antibiotics and that also increase the overall resistance rate of *S. aureus*. MRSA rates were significantly different between sample types; Abscess, tissue, bone, and intra-articular fluid had a higher chance of with MRSA with *OR*=1.9 (p=0.057) and catheters and devices with *OR*=3.7 (p=0.003). This was contrary to what Mehraz *et al*.,[20] found Waitayangkun *et al*.,[8] or Dilnessa and Bitew[9] .

Methicillin resistance considerably increased the resistance status against the majority of antibiotics. It was usual to anticipate 100% resistance to other beta-lactams (imipenem). Levofloxacin, clindamycin, tetracycline, erythromycin, gentamicin, rifampicin, and trimethoprim/sulfamethoxazole are likely to be ineffective against the MRSA isolate, and no difference was seen between MSSA and MRSA when tested with chloramphenicol, nitrofurantoin, linezolid (LZD), and vancomycin. These findings concurred with those of earlier studies[9,23,27,28]. The prevalence of clindamycin resistance in the current investigation, which also included inducible clindamycin resistance, was 56.2% overall and 93% for MRSA isolates. When there is a low resistance rate (e.g., 10%), the Infectious Diseases Society of America (IDSA) guidelines advice[28] empirically treating skin and soft tissue MRSA infections with clindamycin. As a result, the current findings do not support the use of clindamycin in Sana'a, Yemen. Although high-level vancomycin-resistant aureus isolates from Yemen were reported before (40%)[6], the prevalence rate of vancomycin intermediate *S. aureus* was reported by Al-Shami *et al.*, (1.4%)[30]. In Yemen, the results of the current study appear promising with the result of Al-Safani *et al*.,[6] (40%) and also according to Al-Shami *et al*.,(1.4%)[30]. Out of the three newer antibiotics, LZD has the highest clinical availability and is the only oral option with a 100% susceptibility rate in current study. Similar rates were seen in previous studies[31,32], but Baddour *et al*.,[5] with a 4.1% resistance rate demonstrated that the establishment of LZD-resistance has already started and is a progressive trend over time. Although these drugs are beneficial additions to Yemen's antimicrobial options, their usage should be restricted to patients who actually need them in order to delay the evolution of antibiotic resistance in Yemen and globally.

The rate of MRSA resistance against gentamicin in the current study was 61% versus 3.01% for MSSA. Streptomycin, kanamycin, and gentamicin were once effective against *staphylococcal* infections until strains developed resistance against them. Aminoglycosides work by interfering with ribosomal RNA of the 30S subunit of the ribosome through amine and/or hydroxyl interactions[33]. Aminoglycoside-modifying enzymes, ribosomal mutagenesis, and active efflux of the drug out of bacteria are the three primary mechanisms of aminoglycoside resistance that are currently and widely acknowledged[6]. By covalently joining a phosphate moiety, a nucleotide, or an acetyl to either the primary amine or alcohol functional group (or both groups) of the antibiotic, aminoglycoside-modifying enzymes

render aminoglycosides inactive. Aminoglycoside adenylyltransferase 4' IA (ANT(4')IA) is the amino-glycoside modifying enzyme that has been most studied in *S. aureus*. X-ray crystallography has been used to identify this enzyme[34]. Many aminoglycosides, notably kamamycin and gentamicin, have a 4' hydroxyl group that the enzyme is able to link an adenyl moiety to. The current investigation found a 0.0% MRSA resistance rate to glycopeptides and vancomycin. The Tn1546 transposon, which was discovered in a plasmid in *enterococci*, is the source of the van-A gene, which codes for an enzyme that creates an alternate peptidoglycan that vancomycin will not bind to[35]. This alternative peptidoglycan is what mediates glycopeptide resistance.

Non-lactam antibiotics, such as clindamycin (a lincosamine) and trimethoprim/sulfamethoxazole, are frequently used to treat MRSA infections in both the hospital and the community. Due to linezolid's accessibility as an oral medication, resistance to these antibiotics has also prompted the adoption of new, broad-spectrum anti-Gram-positive antibiotics. Glycopeptide antibiotics (vancomycin and teicoplanin) are presently the first-line treatment for significant invasive infections caused by MRSA. These antibiotics have a variety of drawbacks, including the requirement for intravenous administration, toxicity, and the requirement to routinely check medication levels. Additionally, glycopeptide antibiotics do not penetrate infected tissues very well (this is especially problematic for endocarditis and infections of the brain and meninges). Methicillin-sensitive *S. aureus* (MSSA) should not be treated with glycopeptides because the results are subpar[36]. Due to the high rate of penicillin resistance and the potential for MRSA to develop vancomycin resistance, the U.S. Centers for Disease Control and Prevention have produced guidelines for the appropriate use of vancomycin. In situations where the prevalence of MRSA infections is known to be high, the attending physician may choose to use a glycopeptide antibiotic until the identity of the infecting organism is established. Once a MSSA strain of *S. aureus* has been identified as the cause of the infection, the appropriate course of treatment can be altered to flucloxacillin or even penicillin[23].

Limitations of the study

The shortcomings of the study were as follows. First of all, because the data came from a single center, it was unable to accurately identify multidrug resistance in each MRSA isolate for each hospital in Sana'a. Second, no molecular research has been performed on these isolates to support the findings.

CONCLUSIONS

Overall, this study found that MRSA frequency was alarmingly high compared to earlier studies conducted at the same hospital eight years earlier. Additionally, there appeared to be an unacceptable level of resistance to popular alternative antibiotics as clindamycin and trimethoprim-sulfamethoxazole, while a *S. aureus* infection is detected, it may be more fair to empirically begin with first-generation cephalosporins rather than clindamycin, and the natural course and response to therapy should be further taken into account while escalating the antimicrobial regimen. Vancomycin is now the gold standard for treating MRSA infections due to its low resistance rate and availability in comparison to newer drugs that are more expensive and have more adverse effects. The sole oral medication that has gained popularity for treating MRSA infections is linezolid, although it is best to save these medications for last-resort use if the rate of vancomycin resistance rises significantly in the future.

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AUTHOR'S CONTRIBUTIONS

Al-Huraibi BS: writing, review and editing. **Al-Shehari M:** formal analysis, data curation. **Al-Moyed KA:** writing, review, and editing. **Al-Shami HZ:** supervision, review. **Al-Hymia FM:** writing, review and editing, data curation. **Al-Shamahy HA:** formal analysis, supervision. All authors read and approved the final manuscript for publication.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

Regarding this project, there is no conflict of interest.

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