**Reviewer’s Comments**

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

**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. MRSA is a significant burden on healthcare systems and societies all throughout the world, but it is most acute in developing nations. 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 initial empirical antimicrobial therapy. However, more than 7 years have passed since the last report on this topic from our center.

**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 and patient traits and sample types. A crucial p-value of less than 0.05 was utilized with the Chi-squared test.

**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 abscess, tissue, bone, and intra-articular fluid samples with an OR = 1.9 (p = 0.057). 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: clindamycin (93%), erythromycin (81.8%), imipenem (100%), ciprofloxacin (89.9%), levofloxacin (71.7%). Zero resistance rate to linezolid, and vancomycin was observed for the MRSA and MSSA strains while the resistance rate to nitrofurantoin was zero with MSSA versus 3.8% for MRSA. The prevalence of multidrug resistant (MDR) isolates was 60.4%. Significantly higher in MRSA (68.7%) versus 55.4% for MSSA with an average difference of 13.3% (p = 0.03).

**Conclusion:** The prevalence of MRSA in this study was higher than in other studies 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.

**Key words**: Antibiotic patterns; multidrug resistant ( MDR); MRSA, MSSA, *S. aureus,* Sana’a, Yemen.

**INTRODUCTION**

*S. aureus* is one of the most common colonizers and a cause of various infections1. It was found that *S. aureus* was the second leading pathogen of antimicrobial resistance-related deaths in 20192. 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 use3, and vancomycin after about 40 years 4 since its introduction into clinical use. Since the mechanism of resistance changes the target of the antibiotic, resistance against an agent in vitro usually indicates clinical resistance against all other agents in the same class, even though one of them may appear to be effective in vitro5. Penicillinase, a type of *beta-lactamase* that cleaves the -lactam ring of the penicillin molecule and renders the antibiotic ineffective, is produced by *Staphylococcus* bacteria as a means of resisting the antibiotic. 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 resistance7. It is associated with several epidemiological features8 and may indicate increased resistance against other agents (eg, 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.

In the current era, due to the recent development and clinical approval of new, powerful antibiotics as new potent antibiotics, it is becoming more important to use anti-staphylococcal agents judiciously; try the older agents with a narrow/targeted spectrum at the first lines by an appropriate dose and duration; hesitate prescribing antibiotics where no evidence- proven indication exists; and wait for the antibiogram results if the situation permits. Additionally, due to the quick establishment of resistance mutations, rifampin (RIF) or fluoroquinolones (FQ) monotherapy of S. aureus infections should be avoided10. Another promising finding is the "seesaw effect," which shows increased beta-lactam activity when antibiotics targeting glyco- and/or lipo-peptides are less effective 11.

 For patients for whom there are no yet available microbiological test results to target treatment, the Clinical and Laboratory Standards Institute (CLSI) M39 recommends analyzing and presenting cumulative antibiogram reports at least annually12. The current study concentrate on the issue that more than a 8 years had passed since the last such report for *S. aureus* from the 48 Military Hospital in Sana’a city, Yemen.

 **SUBJECTS AND METHODS**

This cross-sectional retrospective study was conducted at the 48 Military hospital, a tertiary referral care hospital in Sana’a city, Yemen. Clinical samples of various specimen types were collected from hospitalized in- patients and patients attending the outer clinic of the hospital from 1st of January 2022 to December 2022. Sample types were considered as follows: blood; Wound secretions Respiratory secretion and sputum. Abscess, tissue, bone and intra-articular fluid. urine. pleural, peritoneal, and pericardial fluids; Catheters and devices and others. Data for *S. aureus* isolates were collected from medical records. Replication isolates were excluded following CLSI M39 recommendations on a patient basis; The first isolate was analyzed for each patient at a one-year period, regardless of the body site from which the sample was obtained or the antimicrobial susceptibility pattern 13. Isolates with missing data were also excluded.

***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:** In Mueller-Hinton agar, the modified Kirby-Bauer disc diffusion technique was used to test the antibiotic sensitivity of bacterial isolates. The 2017 Clinical Laboratory Standards Institute recommendation was used to interpret the inhibitory zone diameter14.

**Detection of MRSA**: Cefoxitin disc diffusion was used to detect MRSA strains as recommended by CLSI to detect methicillin resistance14, 15. Cefoxitin is a better inducer of mec-A gene expression than oxacillin or methicillin, and can be used to screen heterogeneous MRSA populations.

**MDR determination**: MDR was defined as no susceptibility to ≥ 1 agent in ≥ 3 antimicrobial categories . To compare rates of MDR between isolates of methicillin-susceptible Staphylococcus aureus (MSSA) and MRSA, we omitted the beta-lactamse as being an antimicrobial category. In this study, the antibiotic susceptibility (or resistance) pattern indicates the antibiotics to which an isolate is simultaneously sensitive (or resistant).

**Statistical analysis:** The Epi Info statistical tool version 6 (CDC, Atlanta, USA) was used to analyze the data. The association of MRSA with baseline characteristics of clinical samples received for *S. aureus* were determine by calculating *OR*, 95% *CI, X2* 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 Chi squared test was used to determine the significance of the observed difference between groups, considering the critical *p*-value to be ≤ 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).

**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 M3912. 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 found against linezolid (LZD), and vancomycin (VAN). Although this was the case, MRSA generally remained a rare finding, even in hospital settings, until the 1990s, at which point its prevalence in hospitals surged and it is now endemic16. Now, methicillin-resistant *S. aureus* (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) sickness17. In the current study, the prevalence of MRSA was lower than previous reports by Al-Safani *et al* in the same center6 (19%), Khalili *et al.*18 and Mehrez *et al.* 19 in Iran, as well as less than that reported in Yemen by Al-Akwa *et al* 20 (23.5%). Alyahawi *et al*. (17.6%) 21 but similar to that recently reported by Qodrati *et al.* 22 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 report23. In the present study, the overall prevalence of MDR isolates was 60.4%, exceeding the rates determined in Addis Abeba by Dilnessa and Bitew9 and Iran by Qodrati *et al.* 22 (48.5%). Additionally, it was significantly lower than what Kim *et al*. 24 studied with a tailored definition (97.7%) and significantly higher than what Wiliamson *et al.* 25 reported from New Zealand (6%).

 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*. found. 19, 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 studies9,22, 26,27. 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 advise28 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%) [29]. 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%)29. Out of the three newer antibiotics, LZD has the highest clinical availability and is the only oral option with a 100% susceptibility rate in our study. Similar rates were seen in previous studies30,31, 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. Amino glycosidic antibiotics, such as streptomycin, kanamycin, and gentamicin were once effective against staphylococcal infections until strains developed mechanisms to inhibit the action of aminoglycosides, which occurs via amine and/or hydroxyl interactions with ribosomal RNA of the 30S subunit ribosomal32 . 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 acknowledged6. 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. This alters the antibiotic's charge or sterically inhibits it, lowering its affinity for attaching to ribosomes. Aminoglycoside adenylyltransferase 4' IA (ANT(4')IA) is the aminoglycoside-modifying enzyme that has been most studied in *S. aureus*. X-ray crystallography has been used to identify this enzyme33. 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 vanA gene, which codes for an enzyme that creates an alternate peptidoglycan that vancomycin will not bind to34. 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 (no oral preparation is available), toxicity, and the requirement to routinely check medication levels through blood testing. 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 subpar35.

The U.S. Centers for Disease Control and Prevention have developed guidelines for the proper use of vancomycin due to the high rate of penicillin resistance and the possibility for MRSA to develop vancomycin resistance. The attending physician may decide to employ a glycopeptide antibiotic until the identity of the infecting organism is determined in circumstances where the incidence of MRSA infections is known to be high. Once a methicillin-susceptible 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 penicillin22.

**Limitations of the study**

**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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**CONFLICT OF INTEREST**

There is no conflict of interest around this work.

**AUTHOR CONTRIBUTIONS**

The research was given their unanimous approval after being revised, drafted, and data-analyzed by all authors.

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Table 1: Association of MRSA with baseline characteristics of clinical samples received for *Staphylococcus aureus* in the 48 Military Hospital in Sana'a City for the year 2022 (n = 265)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Type of specimens | MSSAn=166N (%) | MRSAN=99N (%) | *OR* | *CI* | *X2* | *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 in the 48 Military Hospital in Sana'a City for the year 2022 (n = 265)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Antibiotics  | Total*S. aureus* n=265N (R %) | MSSA n=166N (R %) | MRSA n=99N (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 | - |

*MSSA* methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *S. aureus*,

Table 3: Prevalence of MDR degree among *S. aureus* of MSSA strains comparing with MRSA strains isolated from clinical specimens in the 48 Military Hospital in Sana'a City for the year 2022 (n = 265)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Antimicrobial class used todefine MDR | Degree | Total*S. aureus* n=265N ( %) | MSSAN=166N ( %) | MRSAN=99N ( %) | Difference % | P |
| 1-Glycopeptide (Vancomycin)2-Aminoglycosides (Gentamicin)4-Quinolone (Ciprofloxacin)5-Sulfonamides (Cotrimoxazole)6-Oxazolidinones (Linezolid)7-Macrolides (Erthromycin)Total MDR=160 (60.4%) |  R0 | 50 (18.9) | 37 (22.3) | 13 (13.1) | 9.2 | 0.64 |
|  R1 | 10 (3.8) | 2 (1.2) | 8 (8) | 6.8 | 0.004 |
|  R2 | 45 (17) | 35 (21.1) | 10 (10) | 9.2 | 0.09 |
|  R3 | 20 (7.5) | 17 (10.2) | 3 (3) | 7.2 | 0.03 |
| R4 | 65 (24.5) | 35 (21.1) | 30 (30.3) | 9.2 | 0.92 |
|  R5 | 35 (13.2) | 19 (11.4) | 16 (16.2) | 4.8 | 0.26 |
|  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.