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To Study and Compare the Antimicrobial Susceptibility Pattern of Methicillin Resistant Staphylococcus Aureus (MRSA) and Methicillin Resistant Coagulase Negative Staphylococci (MRCONS)

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Methicillin resistant staphylococcus aureus (MRSA), antimicrobial resistance (AMR), antimicrobial susceptibility testing (AST), healthcare worker (HCW), methicillin resistant coagulase negative staphylococci (MRCONS), multidrug resistant organisms (MDROS), health care-associated infection (HAI)

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Abstract

Antimicrobial resistance (AMR) is a leading cause of death around the world, with the highest burden in low-resource settings. It is important to expand microbiology laboratory and pharmacy capacity for surveillance. Empirical antibacterial therapy should be based on several considerations, including patient risk factors, expected pathogens and local / regional susceptibility profiles, among others. Hence, Antimicrobial Susceptibility Testing (AST) is the most important investigation carried out by a clinical microbiology laboratory and it plays a vital role to guide the clinician in tailoring the empirical antimicrobial therapy to pathogen-directed targeted therapy. It is also important to monitor antimicrobial susceptibility pattern of common hospital pathogens. The guidelines on AST are regularly revised and need to be consulted regularly. Most of the studies done previously have concentrated on studying the antimicrobial susceptibility pattern of clinical isolates from patients. In contrast, in our study, we evaluated the antimicrobial susceptibility patterns of the staphylococcal isolates obtained from the healthcare workers (HCWs) during their screening for MRSA carriage. As the pathogenic role of coagulase negative staphylococci is increasingly being reported, a detailed AST for MRCONS was also done and compared with the patterns in MRSA isolates. All the staphylococcal isolates were sensitive to vancomycin, teicoplanin and linezolid whereas no isolate was sensitive to penicillin G. MRCONS isolates were found to be more sensitive to many common antibiotics like co-trimoxazole, ciprofloxacin, erythromycin, gentamicin, amikacin and rifampicin as compared to MRSA isolates but the differences were not statistically significant (p-value > 0.05). The high antibiotic resistance of MRSA is very concerning because it can lead to treatment failure in clinical practice. A robust antimicrobial stewardship and strengthened infection control measures are required to prevent spread and reduce emergence of resistance. Continuous surveillance of multidrug resistant organisms (MDROs) in a healthcare setting is a necessity to have optimum treatment outcome and less of treatment failures.

INTRODUCTION

Health care-associated infection (HAI) is defined as a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s). There must be no evidence that the infection was present or incubating at the time of admission to the acute care setting[1]. HAIs may be caused by infectious agents like bacteria, viruses, parasites or fungi from endogenous or exogenous sources. Endogenous sources are body sites, such as the skin, nose, mouth, gastrointestinal tract, or vagina that are normally inhabited by microorganisms. Exogenous sources are those external to the patient, such as health care personnel, visitors, patient care equipment, medical devices, or the health care environment[1]. Corticosteroids, cancer chemotherapy, and antimicrobial agents all contribute to the likelihood of HAI by suppressing the immune system or altering the host's normal flora. Likewise, foreign objects, such as urinary or intravenous catheters, break the body's natural barriers[2]. HAIs result in excess length of stay, mortality and healthcare costs. In 2002, an estimated 1.7 million HAIs occurred in the United States, resulting in 99,000 deaths[3].

HAIs with Staphylococcus aureus, especially methicillin resistant Staphylococcus aureus (MRSA) infections are a major cause of illness and death and impose serious economic costs on patients and hospitals[4]. S. aureus is the most virulent species of staphylococci encountered. A wide spectrum of factors, not all of which are completely understood, contribute to the organism's ability to cause infections and diseases[5].

Penicillin, a ß lactam antibiotic, was initially used as the drug of choice for treating serious S. aureus infections[6]. The family ß lactam consists of four major groups of antimicrobials: penicillins, cephalosporins, monobactams, and carbapenems[7]. Soon after the introduction of penicillin, microorganisms able to destroy this ß lactam antibiotic were reported, thus emphasizing the facility of pathogenic microorganism to develop ß lactam resistance[8]. At least three different types of ß lactamase enzymes are produced by S. aureus. Production of these enzymes may be inducible or constitutive and render these organisms resistant to penicillin. Genes coding for these enzymes usually reside on plasmids that also carry genes for resistance to several antibiotics, such as erythromycin and tetracycline. These resistance genes may be transferred to other bacteria by transformation or transduction rendering them resistant to ß lactams[9]. In the 1950s, penicillinase-producing strains of S. aureus were so common that penicillin was becoming useless against staphylococcal infections[10]. The introduction of methicillin, the first of the penicillinase-resistant semisynthetic penicillins, into clinical practice in 1959 and 1960 solved this problem, for a time[10]. Strains of S. aureus resistant to methicillin were identified almost immediately. The first methicillin-resistant S. aureus (MRSA) infection was reported in England in 1961 in the hospital environment. The CLSI defines MRSA as strains of S. aureus with an oxacillin minimal inhibitory concentration (MIC) of 4µg/ml or greater[11]. Methicillin resistance is associated with production of a novel Penicillin Binding Protein (PBP) that is not present in susceptible staphylococci. Resistant strains of S. aureus produce an additional 78-kilodalton PBP, termed PBP2a or PBP2', that has a low binding affinity for ß lactam antibiotics[12,13]. Once the normally present PBPs have been inactivated by a ß lactam agent, PBP2a continues to function and allows the synthesis of a stable peptidoglycan structure, thereby allowing the organism to grow and divide[6]. PBP2a is encoded by the gene mecA, which is located within a large mobile genetic element called the staphylococcal chromosomal cassette mec (SCCmec). Currently, there are 5 types of SCCmec distinguished by their genetic sequence, labelled SCCmec I to SCCmec V[14]. Methicillin resistance among S. aureus isolates was found to be 15-30% according to studies conducted in the 2000s[15,16]. However, recent studies[17,18] have shown methicillin resistance among S. aureus isolates to be as high as 41.5%. MRSA has remained a major nosocomial pathogen in India. Percentage of MRSA among the S. aureus isolates varied from 20-80%[19,20] in the 1990s. Other studies conducted all over India from 2000-2009 have shown this percentage to vary from 30-55%[21-24]. MRSA carriage at hospital admission is far more prevalent than MRSA-positive clinical specimens. Screening cultures at admission help to identify the reservoir of unknown MRSA patients[9]. According to various studies conducted worldwide, the prevalence rate of MRSA carriage among hospitalized patients was found to vary from 3% to as high as 24%[25,26]. MRSA are generally found to be multidrug resistant as depicted in various studies[19-21]. The glycopeptide antibiotic vancomycin was first released in 1958. Subsequently, vancomycin has been the treatment of choice for serious infections caused by MRSA[19]. MRSA strains usually remain sensitive to vancomycin as shown by various studies[19-21], although resistance to this agent has emerged[22], the first case of fully vancomycin-resistant strains of S. aureus (VRSA) due to the acquisition of the van A gene from vancomycin resistant enterococci being reported from the United States in 2002[27,28]. Other drugs which can be used in treatment of MRSA infections are dalbavancin, telavancin, linezolid, daptomycin and tigecycline[21], teicoplanin and quinupristin-dalfopristin[21] Combination of daptomycin and rifampicin could prevent S.aureus from developing

resistance[20]. The regular monitoring antibiotic sensitivity pattern of MRSA and formulation of definite antibiotic policy may be helpful for reducing the incidence of MRSA infections[21].

The present study was conducted with the objectives to study the antimicrobial susceptibility profile of staphylococcal isolates and to compare the antimicrobial susceptibility pattern of MRSA and MRCONS.

MATERIALS AND METHODS

This prospective study was conducted on 88 staphylococcal isolates obtained during screening of HCWs for MRSA carriage.

Confirmation of Staphylococcal Isolate: The isolate was identified by colony morphology, Gram's staining and various biochemical tests like catalase, coagulase and mannitol fermentation test[29].

Antimicrobial Susceptibility Testing (AST): AST was performed using Modified Kirby-Bauer disk diffusion method.

Media Used: Mueller-Hinton agar[30].

Procedure: Four or five similar-appearing, well-isolated colonies on blood agar plate were touched with a wire loop and the growth was transferred to a tube containing 4-5 ml of sterile normal saline.The density of the suspension was adjusted to approximately 108 colony-forming units (CFUs) per millilitre by comparing its turbidity to a McFarland 0.5 BaSO4 standard. The standard was prepared by adding 0.5ml of 0.048 M BaCl2-99.5ml of 0.36N H2SO4. Aliquots of 4-6ml of the barium sulfate turbidity standard were distributed to screw-capped tubes, sealed tightly and stored in the dark at room temperature. The degree of cloudiness in the broth was compared with the standard, visualizing the two against a white background with contrasting black lines.Within 15 minutes of adjusting the turbidity, a sterile cotton swab was dipped into the inoculum suspension. The swab was rotated several times with firm pressure on the inside wall of the tube to remove excess fluid.A dried Mueller-Hinton agar plate was inoculated by swabbing the plate three times over the entire agar surface, rotating the plate approximately 60 degrees each time to ensure an even distribution of the inoculum. Antibiotic disks were placed on the surface of the agar, using forceps, within 15 minutes of swabbing Mueller-Hinton agar plate.Each disk was gently placed onto the agar to provide uniform contact. Disks were evenly distributed on the agar so that they were no closer than 24mm from center to center.The plates were incubated at 35oC for 24 hours. ATCC strain S. aureus 25923 was used as quality control. The following antimicrobial disks obtained from HIMEDIA®, were used.

The plates were examined after overnight incubation at 35°C. The zones of growth inhibition around each disk were measured using a scale. An interpretive correlate (susceptible, intermediate, or resistant) was provided by reference to published guidelines (Performance Standards for Antimicrobial Susceptibility Testing provided by CLSI).Resistance to methicillin/oxacillin was confirmed as per CLSI guidelines, using cefoxitin 30µg disks[31].

RESULTS AND DISCUSSIONS

A total of 88 staphylococcal isolates were analyzed. Out of 88 staphylococcal isolates, 42 (48%) were identified as Staphylococcus aureus and 46 (52%) were coagulase negative staphylococci (CONS). Out of 42 isolates of S. aureus, 21 (50%) were MRSA and out of 46 CONS, 34 (74%) were MRCONS.

MRCONS isolates were found to be more sensitive to co-trimoxazole, ciprofloxacin, erythromycin, gentamicin, amikacin, netilmicin and rifampicin as compared to MRSA isolates but the differences were not statistically significant ($p>0.05$). All the isolates were sensitive to vancomycin, teicoplanin and linezolid whereas no isolate was sensitive to penicillin G [Table 1].

The epidemiology of MRSA is gradually changing since its emergence was reported. The association of multidrug resistance with MRSA has added to the problem[21].

In our study, no MRSA isolates were found to be sensitive to penicillin G. Tahnkiwale[20] and Vidhani[32], in their respective studies reported similar finding. Farzana *et al* in their study found that less than 20% of S.aureus isolates were sensitive to penicillin and ampicillin[33]. Sensitivity to co-trimoxazole was found to be 47.6%. Other studies, however, have shown lower sensitivity (3%-40%) to co-trimoxazole[19-21]. Erythromycin proved to be 33% sensitive in MRSA isolates in our study. A sensitivity ranging from 20% to

Fig. 1: Antimicrobial susceotibility profile (MRSA vs MRCONS)

Table 1: Comparison of antimicrobial susceptibility profile of mrsa and mrcons.

Antimicrobial	MRSA (n=21) (%)	MRCONS (n=34) (%)	p-value
Penicillin G	0	0	-
Co-trimoxazole	10 (47.61%)	13 (28.23%)	0.4931
Ciprofloxacin	5 (23.80%)	17 (50.00%)	0.0541
Clindamycin	15 (71.42%)	24 (70.58%)	0.9468
Erythromycin	7 (33.33%)	13 (38.23%)	0.7135
Gentamicin	16 (76.19%)	31 (91.17%)	0.2552
Amikacin	16 (76.19%)	32 (94.11%)	0.1281
Netilmicin	19 (90.47%)	33 (97.05%)	0.6648
Vancomycin	21 (100%)	34 (100%)	-
Teicoplanin	21 (100%)	34 (100%)	-
Linezolid	21 (100%)	34 (100%)	-
Rifampicin	18 (85.71%)	32 (94.11%)	0.5683

Table: The following antimicrobial disks obtained from HIMEDIA®, were used.

Antibiotics	Potency
Penicillin G	10 U
Gentamicin	10µg
Amikacin	30 µg
Netilmicin	30 µg
Erythromycin	15µg
Co-trimoxazole(Trimethoprim/Sulfamethoxazole)	1.25/23.75 µg
Rifampicin	5 µg
Ciprofloxacin	5 µg
Clindamycin	2 µg
Vancomycin	30 µg
Teicoplanin	30 µg
Linezolid	30 µg
Cefoxitin	30 µg

50% was reported in other studies[21,32]. The lower sensitivity of the MRSA isolates against the commonly used antibiotics could be attributed to factors like misuse and overuse of antibiotics. Antibiotic use provides selective pressure favouring resistant bacterial strains. Inappropriate use increases the risk for selection and dissemination of antibiotic resistant bacteria which are placed at competitive advantage[39]. Around 60% of the MRSA isolates were found to be sensitive to rifampicin in studies conducted by Kesah[25] and Pulimood[19]. However, in our study 85.7% of the MRSA isolates were found to be sensitive to rifampicin. Askarian *et al* found that 97% of the MRSA isolates were sensitive to rifampicin[38].

Ciprofloxacin had been proposed as an alternative for treatment of MRSA infection[35]. It is alarming to know that only 23.8% of the isolates were sensitive to this drug. Similarly, Pulimood[19] and Goyal[35] have also shown a lower sensitivity of MRSA isolates towards ciprofloxacin. The development of S. aureus resistance to ciprofloxacin might be due to previous antimicrobial therapy. Moreover, wide use of ciprofloxacin may have resulted in a steady increase in the incidence of fluoroquinolone resistant staphylococci.

MSSA isolates were more sensitive to ciprofloxacin, erythromycin, amikacin, netilmicin and rifampicin as compared to MRSA isolates. This was in agreement with the studies conducted by Askarian[34] and Vidhani[32]. MSCONS isolates were more sensitive to ciprofloxacin, clindamycin, erythromycin, gentamicin, netilmicin and rifampicin as compared to MRCONS isolates. MRCONS isolates were found to be more sensitive to co-trimoxazole, ciprofloxacin, erythromycin, gentamicin, amikacin, netilmicin and rifampicin as compared to MRSA isolates. All the differences were not statistically significant.

Among amino glycosides, sensitivity to gentamicin and amikacin was 76% each, while 90% MRSA isolates were sensitive to netilmicin. Similarly, a higher sensitivity (93.4%) towards gentamicin was reported by Tahnkiwale[20] However, in other studies a lower sensitivity (20%-60%) was observed for amino glycosides[15,19,21,23].

Vancomycin has remained the treatment of choice for serious infections caused by MRSA[36]. MRSA strains usually remain sensitive to vancomycin as shown by variousstudies[15,32,19-21]. This is consistent with the finding in our study also as all the isolates were sensitive to vancomycin.

In recent years, CONS have become increasingly recognized as important agents of nosocomial infections[37]. Many studies have focused on species identification and characterization of CONS[41,42]. Their role as significant pathogens following neurologic[52-55], and cardiothoracic surgery[40,5-11], in immunocompromised patients[41,42] and in patients with prosthetic devices[41,42] has been well established. In our study, about 52% staphylococcal isolates were identified as CONS. Methicillin resistance among CONS was 74%. However, Farzana et al in their study found that only 22% of CONS were resistant to methicillin[33].

A robust antimicrobial stewardship and strengthened infection control measures are required to prevent spread and reduce the emergence of infection.

CONCLUSION

50% of the Staphylococcus aureus isolates were resistant to methicillin (MRSA) and a substantial number of CONS were also methicillin-resistant (MRCONS). All isolates exhibited sensitivity to glycopeptides and linezolid, highlighting these as preferred treatment options for multidrug-resistant MRSA infections. None of the isolates were sensitive to penicillin G, and only a small fraction of MRSA isolates responded to ciprofloxacin. Given the significant burden of MRSA infections and the limited treatment options, understanding the distribution and antimicrobial susceptibility of MRSA isolates is imperative. Continuous monitoring of multidrug-resistant organisms (MDROs) in hospital settings is essential for achieving optimal treatment outcomes, preventing treatment failures, and planning empirical therapies. This practice will also contribute to long-term cost savings and reduce overall morbidity, mortality, and hospital stay durations.

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