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CLINICAL INVESTIGATION

Prospective Analysis of Antibiotic Susceptibility Patterns of MRSA in a Turkish University Hospital

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Abstract: Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important nosocomial pathogen. The prevalence of MRSA in many countries is increasing and, in some hospitals, more than half of all *S. aureus* disease isolates are MRSA. MRSA strains are becoming increasingly multiresistant, and have recently developed resistance to vancomycin, which has been used successfully to treat MRSA for more than 30 years. *In-vitro* determination of resistance patterns of *S. aureus* is critical in terms of administering suitable antimicrobial treatments. The objective of this study was to identify the frequency of MRSA from various clinical samples and resistance patterns against various antibiotics used broadly for treatments. All isolated *S. aureus* strains were identified using standard procedures and tested for oxacillin resistance according to methods of the National Committee for Clinical Laboratory Standards. A total of 345 coagulase-positive Staphylococci and 187 MRSA were isolated. We found that the incidence of MRSA in intensive care units (ICUs) and burn center was 23.4% (145/620) and 29.6% (32/108), respectively. This rate was 7% (10/143) in the other units. Resistance rates of MRSA were 29.9% for trimethoprim-sulfamethoxazole, 60.8% for clindamycin, 71.8% for erythromycin, 7.7% for teikoplanin, 90.1% for gentamycin, 88.8% for ofloxacin, 88.1% for norfloxacin and 100% for penicillin. All isolates were found to be sensitive against vancomycin. In our region, although methicillin resistance increased in *S. aureus* strains, teicoplanin resistance remained low in MRSA, suggesting an effective alternative treatment for *Staphylococcus aureus* infections. These results indicated that vancomycin seemed to be the only antimicrobial agent effective against MRSA and it could be the choice of medicine in treating multidrug resistant MRSA infection.

Key Words: *Staphylococcus aureus*, MRSA, antibiotic, resistance, susceptibility.

Introduction

Staphylococcus aureus is recognized as one of the most important bacterial pathogens seriously contributing to the problem of hospital infections in Turkey as well as world wide. Since the first isolation of methicillin-resistant *S. aureus* (MRSA) in the United Kingdom in 1961, increasing rates of methicillin resistance among *S. aureus* strains have been a cause for concern (1). MRSA is a major nosocomial pathogen that causes severe morbidity and mortality worldwide (2).

MRSA strains spread more readily than others once introduced into hospitals, and are often difficult to eradicate once established. Presently in some countries they can constitute up to 80% of all *S. aureus* isolates in hospitals (3,4). Transmission of MRSA occurs primarily from colonized or infected patients to other patients or staff, or vice versa5. Among the resistant pathogens, MRSA is of great concern because of the predominance of this organism that causes various clinical infections (5,6).

Antimicrobial drug resistance has become a great public health problem worldwide (7-9). As MRSA incidences increased, the efficiency of penicillins and sephalosporins has been questioned. Essentially, many MRSA strains acquired resistance to both beta lactam and aminoglycosides. Therefore, it is necessary to know the MRSA prevalence and to choose suitable antibiotics with respect to their antimicrobial profiles for treating the infections (7-9).

Resistance to multiple antibiotics among the MRSA isolates in hospitals has been recognized as one of the major challenges in controlling hospital infections. The pattern of bacterial resistance is important for epidemiological and clinical purposes. The results of antimicrobial resistance patterns are of great concern due to the predominant bacterial isolates which are highly resistant to the commonly available antimicrobial agents. Recently, a marked increase in the number of hospital infections caused by MRSA has been reported in many countries (7-11).

It was reported that the percentage of MRSA ranged from 29% to 35% of all clinical isolates in many American and European hospitals. On the contrary, information about the distribution of MRSA in the global community appears to be tentative because majority of data was obtained from developed countries while data was imprecisely obtained from underdeveloped or developing countries. Meanwhile, information from developing countries was provided by relatively sophisticated hospitals (11-13).

Continued collaborative efforts are required on national, provincial and regional levels to control the antibiotic resistance. The number of studies about the prevalence of MRSA strains and their resistance patterns against antibiotics was inadequate in Turkey as in many other countries. The prevalence of MRSA was found to differ tremendously among the cities of Turkey (7-9,12).

The present study was undertaken to ascertain the relationship among MRSA strains isolated from various clinical specimens in Baskent University Hospital, Adana, Turkey. Our objective was to determine the percentage of *S. aureus* among all nosocomial isolates and the percentage of MRSA among these *S. aureus* isolates. In addition, we investigated the resistance patterns of the isolated MRSA strains for various antibiotics.

Materials and Methods

This study was performed to find the prevalence of hospital-acquired MRSA infection from several departments and intensive care units (ICUs) between 2001 and 2002 in Baskent University Hospital in Adana, Turkey. In this study, the isolation rate of coagulase positive Staphylococci was 39.6% (345/871) from various clinical samples such as respiratory tract, blood, urine, catheters, surgical wound.

Bacterial strains

The present study involved a total of 345 consecutive isolates of *S. aureus* collected from Başkent University Hospital. Numbers of clinical specimens and their rates were as follows: surgical wounds (n = 90, 26.1%), urine (n = 98, 28.4%), burns (n = 60, 17.4%), blood (n = 52, 15.1%), catheters (n = 30, 8.7%), and other sources (n = 15, 4.3%). To isolate Staphylococci, samples were inoculated onto sheep blood-agar plates and phenol-red mannitol salt agar plates. The plates were incubated at 37 °C for 48 h. Identification of *S. aureus* was based upon colony morphology, biochemical activities and coagulase tests (6).

Identification of *S. aureus* was confirmed by standard methods and susceptibility testing was performed by disc diffusion on Mueller-Hinton agar (Difco, USA) with 24-h incubation at 35 °C. Interpretation criteria were those of the National Committee for Clinical Laboratory Standards (NCCLS) (14). Resistance to oxacillin was confirmed by the screen agar test. Oxacillin discs (1µg) were obtained from the Oxoid firm (Oxoid, USA). Strains producing inhibition less than 10 mm zone diameter or producing no inhibition were considered resistant to oxacillin.

Susceptibility of isolated MRSA strains to penicillin (10 µg/disc), gentamycin (10 µg/disc), trimethoprim-sulphamethoxazole (1.25/23.75 µg/disc) erythromycin (15 µg/disc), clindamycin (2 µg/disc), teicoplanin (30 µg/disc), ofloxacin (5 µg/disc), norfloxacin (10 µg/disc), and vancomycin (30 µg/disc) was tested. All antibiotic discs were obtained from Oxoid. ATCC 25923 was used as the control strain for identification and susceptibility tests.

Statistical analysis

Statistical analysis was performed using a chi squared test and P values less than 0.05 were considered statistically significant. The statistical analyses were performed by using Statistical Package for Social Sciences (SPSS, ver. 10.0) software.

Findings

In this study, *S. aureus* was present in 39.6% (345/871) of the samples taken from the clinics [18.1% MRSA and 21.5% methicillin sensitive *S. aureus* (MSSA)]. They were isolated from the following clinical specimens:

burns (n = 60, 17.4%), surgical wounds (n = 90, 18.0%), urine (n = 98 28.4%), blood (n = 52, 15.1%), catheters (n = 30, 8.7%), and and other sources (n = 15, 4.3%). The rate of MRSA was 54.2% (187/345) of isolated *S. aureus*. While the isolation rate of *S. aureus* was 69.9% (241/345) in ICUs and burn centers, it was 30.1% (104/345) in the other departments.

Figure 1 shows the departments from which MRSA were isolated. The isolation rate was 27.4% (45/164) in general surgical ICU, 17.8% (18/101) in burn centers and 17.2% (31/180) in internal ICU, and these units were followed by cardiovascular surgical ICU and coronary ICU as 11.8% (22/187) and 7.5% (14/187), respectively.

The most effective antibiotics against MRSA are glycopeptide antibiotics and of 187 MRSA strains, no resistance was acquired against vancomycin although resistance against teicoplanin, trimethoprim-sulfamethoxazole and clindamycin were 7.7%, 29.9%, 60.8%, respectively. Resistance to norfloxacin and oflaxacin from the quinolone group was 88.8% and 88.1%, respectively. All strains were resistant to penicillin (resistance rate: 100%) and the resistance to gentamycin and erythromycin were 71.8%, 90.1, respectively (Figure 2).

Discussion

MRSA prevalence has been increasing from the first day it was identified. Although it was rarely reported at first, it has become most resistant not only to all beta-lactams but also to a wide range of other antibiotics, and has emerged as the major nosocomial pathogens during the past two decades. Furthermore, multi-drug resistant MRSA has become a major problem (1,2,5,6). Considerable variations in the prevalence of MRSA exist among institutions and geographic areas. In Turkey, there are a number of studies for comparing methiciline and other antibiotic resistance of Staphylococci. Results of these studies differed with respect to the research centers (7-9,12).

Resistance to multiple antibiotics among the Staphylococci isolates in hospitals has been recognized as one of the major challenges in controlling hospital infections. The pattern of bacterial resistance is important for epidemiological and clinical purposes. The results of the antimicrobial resistance pattern give serious cause for concern because the predominant bacterial isolates were highly resistant to the commonly available antimicrobial agents. Recently, a substantial increase in the number of hospital infections due to MRSA has been reported in many countries (4,9-15,16-19). Although MRSA prevalence was found between 16-59% in Turkey (7-9,12) this range is reported between 1-40% in Europe (5,12) and 6-50% in the U.S.A. (15,20).

The proportion of MRSA in the various European countries ranged from <1% in Scandinavia to >30% in Spain, France and Italy. In Europe in general, a north-south gradient is observed, MRSA strains being rare in Scandinavian hospitals (<2%) and far more prevalent in

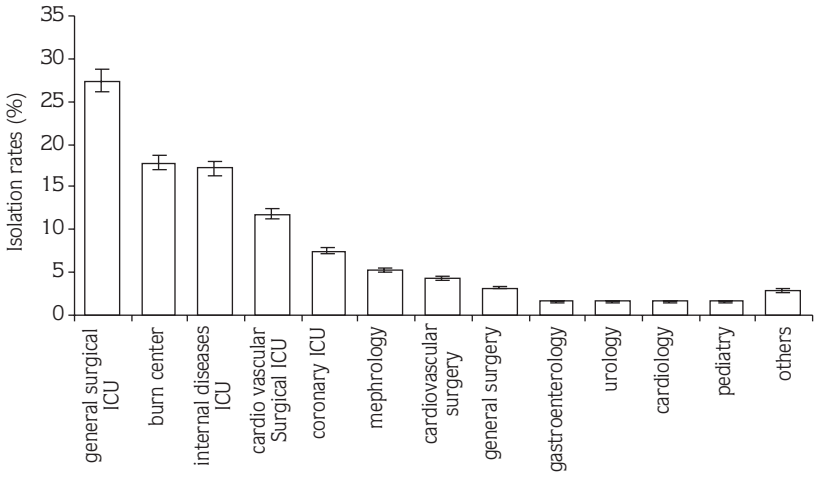

Figure 1. Isolation percentages of MRSA strains according to departments.

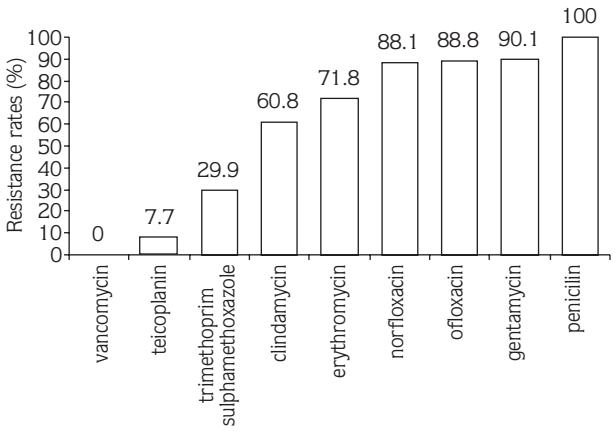

Figure 2. Resistance patterns of MRSA strains.

Mediterranean hospitals (>40%). Whether low or high, the rates of MRSA prevalence in European countries have remained approximately the same during the last decade. Recent findings suggest that MRSA might also be emerging as a community-acquired pathogen (4,5).

It was reported that the rates of resistance among non-glycopeptide antibiotics were lowest for rifampin and highest for ciprofloxacin, and MRSA was found more frequently in intensive care patients (13,16). MRSA seems to be a growing problem, especially in southern Europe, where incidence and rates of antibiotic resistance are alarmingly high (4,5,17).

MRSA is a pathogen of special concern in ICUs. The burn units are especially a very susceptible niche for colonization and infection events by this organism (16,19).

In the present study, among the *S. aureus* isolated from patients in the various departments, ICU and burn centers, the general incidence of MRSA was noticeably higher than those reported from other countries (16-18). In our study, the incidence of MRSA was 23.4% (145/620) in ICUs whereas it was17.8% (18/101) in burn centers. While the MRSA rate in ICUs was 23.4% (145/620), it was 16.7% (42/251) in burn centers and the other department patients. There was a significant difference between ICU patients and the others department patients according to occurrence of MRSA rate, ($P<0.01$).

The majority of MRSA is resistant to erythromycin, clindamycin, gentamycin and quinolons (9-11). In this study, we found that penicillin was not effective for MRSA strains. Penicillin resistance rate was identified as 100% and gentamycin resistance rate was 90.1%. Resistance to quinolons was also quite high (88.1% for norfloxin, 88.8% for ofloxacin).

The most active drugs against *S. aureus* are vancomycin, teikoplanin and trimethoprim-suplhamethoxazole (11). The incidence of MRSA resistant to clindamycin (60.8%), erythromycin (71.8%), norfloxacin (88.1%), gentamycin (90.1%) and penicillin (100%) were very high.

Susceptibility to gentamycin from glycopeptide antibiotics was found quite low (9.9%). Although ofloxacin susceptibility was higher than that of other quinolones (norfloxacin; 11.9%) it was not recommended for empiric treatments of MRSA infections.

Results about resistance rates found in Turkey were in accordance with those in other parts of the world. Susceptibility to glycopeptide antibiotics was found to be maximum in gentamycin (9.9%), and lowest in clindamycin (39.2%). Strains were also susceptible to erythromycin 28.2%. The reason that we found higher MRSA prevalence may be due to haphazard antibiotic usage.

Vancomycin continues to be the drug of choice for treating most MRSA infections caused by multidrug resistant strains. In recent years, reports of the existence of moderately susceptible isolates among MRSA strains in many countries including the USA, Korea and Hong Kong and of vancomycin resistant *S. aureus* strains in the USA in 2002 makes it necessary to search for the resistance patterns to vancomycin. In our study, all strains were found to be susceptible to vancomycin (20-24). Additionally, MRSA strains sampled from the ICUs and various departments were found to have high resistance to widely used antibiotics for treatments.

Vancomycin seemed to be the only antimicrobial agent effective against MRSA and it could be the choice of medicine in treating multidrug resistant MRSA infections. However, vancomycin susceptibility should be regularly inspected and routine tests should be done for new glycopeptides such as teicoplanin. Furthermore, regarding hospital-related infections, constant studies monitoring antibiotic susceptibility patterns of MRSA should be performed.

It was claimed that the rates of MRSA colonization may vary in terms of both risk factors and geographical

regions (17). In this study, it was found that, especially intensive care patients were at great risk to MRSA infection. Surveillance studies should be carried out in every geographical region to detect the prevalence of MRSA strains, and appropriate infection control measures should be performed to prevent infection with corresponding strains. In conclusion, considering the increasing occurence of MRSA infections, highly reliable, accurate, and rapid testing for methicillin resistance is essential for both antibiotic therapy and infection control regimens.

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