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Prevalence of Antimicrobial Resistance among Gram-Positive Isolates in an Adult Intensive Care Unit at a Tertiary Care Center in Saudi Arabia

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Abstract- *Objectives:* To estimate the prevalence of Grampositive infections in intensive care units (ICU), and to observe the patterns of resistance against different antibiotics.

Methods: A retrospective cross-sectional study was conducted of all reports of Gram-positive isolates from adult ICU of King AbdulAziz Medical City, Riyadh between 2010 and 2014. Organisms were identified and tested by an automated system and the antibiotic susceptibility was confirmed by manual method.

Results: Among 2155 Gram-positive isolates, methicillinsusceptible Staphylococcus aureus (MSSA) were the most commonly isolated organism followed by Enterococcus, Methicillin-resistant Staphylococcus aureus (MRSA), Streptococcuspneumonia andCoagulase-negative Staphylococci. MRSA resistance decreased to clindamycin, erythromycin, and trimethoprim/sulfamethoxazole. Coagulasenegative Staphylococcishowed a significant increase in the resistance to cefazolin, and erythromycin. There was an increase in resistance to ampicillin, and vancomycinamong Enterococcus, however there was a decrease in the resistance to ciprofloxacin, and nitrofurantoin. Streptococcus pneumoniae showed a significant decrease in resistance to cefotaxime (50% to 0%). Vancomycin showed 100% sensitivity to MSSA, MRSA, Coagulase negative Staphylococcus, and Streptococcus pneumoniae.

Keywords: *resistance; multidrug resistance; grampositive bacteria.*

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Conclusion: Our study revealed that antibiotic resistance among Gram-positive organisms remains a continuous issue in the healthcare setting. To reduce further progression in the emergence of MDR organisms, a continuous surveillance program for bacterial resistance is advised.

Keywords: resistance; multidrug resistance; gram-positive bacteria.

I. Introduction

During the course of management of bacterial infections, bacteria might develop the ability to resist the bactericidal or bacteriostatic effects of one or more antibiotic class (multidrug resistance (MDR)) [1]. This is usually a result of the frequent and widespread use of potent antibiotics, which is the main reason why antimicrobial resistance is more noted in the intensive care units (ICUs) in comparison to the other inpatient departments in hospitals worldwide [2]. According to the national healthcare safety network report in the United States, host risk factors for developing a nosocomial infection are age, comorbid diseases, duration of hospitalization, length of ICU stay, immune status, and disease severity. It was reported that the incidence of ICU nosocomial infections worldwide is between 5%-30% [3]. A study conducted in 8 European countries concluded that overuse was one of the factors associated with increased antibiotic resistance [4].

The patterns of antimicrobial resistance vary between ICUs in different countries due to the various factors leading to such a resistance including different patterns of infections and antibiotic use, the variations in local infection control policies, and the effective usage of the local resistance reports directing the suitable antibiotic therapies in practice, all of which will lead to different resistance patterns, and outcomes on patients and healthcare systems accordingly [5]. Over the past few years, the efficacy of antibiotics against various ICU pathogens has been decreasing, with MDRs on the rise [6]. Globally, Antibiotic resistance is still a continuous issue however due to the differences in international and national data, a local continuous surveillance studies should be conducted to identify the emergence of different bacterial resistance patterns in order to establish local guidelines. This study was done to estimate the prevalence of Gram-positive infections in intensive care units (ICU), and to observe the patterns of resistance against different antibiotics.

II. Methods

a) Study Design and Setting

A cross-sectional retrospective study was conducted on Gram-positive isolates from the adult ICU of King Abdulaziz Medical City (KAMC) between the period of 2010 and 2014. The ethics committee and

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institute review board in King Abdullah International Medical Research Centre approved this project.

b) Study Sample and Technique

The annual antibiogram data was used to calculate the percentage of resistance in Gram-positive bacteria with a total of 2155 isolates from blood, urine, sputum and respiratory aspiration. All isolates were analyzed per the guidelines of the Clinical and Laboratory Standards Institute (CLSI).The species level and AST performed using an automated system (The VITEK®2 system, BioMariex, France) to characterize all Gram-positive bacteria. All antimicrobial susceptibility testing was confirmed by manual method. Only one isolate per patient per year was used for analysis. Ampicillin, ceftazidime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, and trimethoprim-sulfamethoxazole were tested either by the breakpoint method (with the vitek 2 system) or by the ETEST method using the previously mentioned antibiotics on a Muller Hinton Agar Plate. The proportion of susceptible isolates was calculated as the sum of susceptible organisms (neither intermediately susceptible nor resistant) relative to the total number of organisms tested. Multidrug resistance was defined as resistance to three or more antimicrobials (imipenem, ceftazidime, ciprofloxacin, pipracillin-tazobactam, and/or an aminoglycoside).

c) Statistical Analysis

The trend in the resistance rate over a 5-year period (between 2010-2014) was analyzed to identify a statistically significant increasing or decreasing trend using chi-square for linear trend analysis and chi-square test was used for testing the association between categorical variables. The percent of change of antibiotic susceptibility was calculated as the difference between the later (e.g. 2014) and earlier (e.g. 2010) susceptibilities percentages divided by the earlier one. P value $<.05$ was considered as statically significant. All P values were two-tailed. SPSS software package for Windows (version 22.0, IBMCorp, Armonk, NY, USA) was used for all statistical analyses

III. Results

a) Descriptive Statistics of the Included Samples

From 2010 to 2014, there were 6611 isolated organisms in total, out of which 2155 (33%) were Gram-positive. There were 285 Gram-positive organisms isolated in 2010, 294 in 2011, 334 in 2012, 632 in 2013, and 610 in 2014. Among all isolated Gram-positive organisms, *methicillin-susceptible Staphylococcus aureus* (*MSSA*) were the most commonly isolated 849 (39%) followed by *Enterococcus* 590 (27%), *methicillin-resistant Staphylococcus aureus* (*MRSA*) 462 (21%), *Streptococcus pneumoniae* 135 (6%), *Coagulase negative Staphylococcus* 113 (5%), and *Streptococcus viridans* 6 (0.27%). All screening samples were not included to avoid false representation of colonization rather than true infection.

b) Prevalence of Antimicrobial Resistance

Over the study period, *MSSA* resistance increased to clindamycin until 2013 (5% to 12%, $p=0.15$), erythromycin (5% to 13%, $p=0.001$), and trimethoprim/sulfamethoxazole(TMP/SMX) (1% to 4%, $p=0.19$). There was no resistance to vancomycin, and penicillin throughout the study period (0%), however, from 2010 to 2013, *MSSA* was 100% resistant to moxifloxacin.

Of 590 *Enterococcus* isolates, there was an increase in ampicillin (59% to 71%, $p=0.003$), and in vancomycin resistance (37% to 46%, $p=0.170$); a decrease in the resistance to ciprofloxacin, and nitrofurantoin (96% to 76% and 66% to 54%), respectively.

MRSA resistance decreased to clindamycin (72% to 52%, $p<0.0001$), erythromycin (72% to 53%, $p<0.0001$), and TMP/SMX (60% to 46%, $p<0.0001$). However, no change was seen in *MRSA* resistance to cefazolin (1%) from 2012 to 2014, and to vancomycin (0%) throughout the study period.

Streptococcus pneumoniae showed a significant decrease in resistance to cefotaxime (50% to 0%, $p=0.003$); an increase in resistance to erythromycin (25% to 50%, $p=0.428$), and to penicillin (0% to 7%). On the other hand, there was no change in the resistance to moxifloxacin, and vancomycin (0%) throughout the study period.

Coagulase negative Staphylococcus showed significant increase in the resistance to cefazolin (54% to 90%, $p<0.0001$), and erythromycin (65% to 90%, $p=0.02$). On the other hand, *Coagulase negative Staphylococcus* resistance to TMP/SMX decreased (62% to 20%, $p=0.001$) and showed no resistant to vancomycin from 2010 to 2014.

IV. Discussion

Antimicrobial resistance is a global concern [1]. ICU is a potential source of multidrug resistance due to the widespread use of multiple antibiotics compared to other hospital departments [2]. *Methicillin sensitive Staphylococcus aureus* was found to be the most commonly isolated organism in the adult ICUs of KAMC (849 isolates). Savas et al. reported that from 597 ICU isolates, 241 were *Staphylococci*, and *MSSA* was not the most common isolates 24 (9.96%) [7]. In this study, among 1,424 *Staphylococcus isolates*, MSSA was the most commonly isolated organism 849 (59.6%). Savas et al evaluated the resistance of MSSA to clindamycin, erythromycin, and TMP/SMX, and it was 25%, 27%, and 21%, respectively [7].Looking at the ranges of MSSA resistance in this study, MSSA resistance increased to clindamycin (5% to 12%), erythromycin (5% to 13%), and

TMP/SMX (1% to 4%). In our study, vancomycin, and cefazolin remain the most effective antibiotics against *MSSA*. Comparison of the overall resistance pattern is illustrated in table-1.

Although *MRSA* is considered an endemic in many hospitals worldwide, it is still difficult to be eradicated, and remains a major concern in all ICUs [8].*MRSA* is showing a significant increase in prevalence in many ICUs reaching to 60% of all isolates [9]. In this study, from 2010 to 2014 and among 2155 Gram-positive isolates, *MRSA* were the third most common isolates in KAMC adult ICU 462 (21%).Vancomycin is considered the most important antibiotic used for *MRSA* till date [10].However, *MRSA* showed a resistance against vancomycin in other reported studies [10].Fortunately enough, throughout our study period, *MRSA* showed no resistance to vancomycin in KAMC adult ICUs. Comparison of the overall resistance pattern is illustrated in table-1.

Enterococci are considered one of the most common causes of hospital-acquired infections. In the past 20 years, *Enterococci* have become increasingly resistant to many antibiotics [9]. Recent studies conducted to assess the incidence of multidrug resistant Gram-positive pathogens showed that *Enterococcusfaecalis* accounted for 15.7% of all Gram-positive isolates. In our study, we found that 27% of all Gram-positive isolates were *Enterococcus*. Hällgren A et al. Evaluated the resistance of *Enterococcusfaecium* to ampicillin, vancomycin, and ciprofloxacin and it was 74.3%, 1.4%, and 82.4% respectively [11]. In this study the resistance pattern of *Enterococcus* to ampicillin, and ciprofloxacin was almost the same as the resistance that was reported by Hällgren A et al., 71% and 76% respectively. However, *Enterococcus* was highly resistant to vancomycin 46%. Comparison of the overall resistance pattern is illustrated in table-2.

In this study, from 2010 to 2014 and among 2155 Gram-positive isolates, *Streptococcus pneumoniae* accounted for 6%, and *Coagulase-negative Staphylococci* accounted for 5% of all Gram-positive isolates. On the other hand, in a recent study, among 1416 pathogens isolates, *Streptococcus pneumoniae* accounted for 6% and *Coagulase-negative Staphylococci* accounted for 8.3% of all isolates in the ICU with 99.1%, and 71% susceptibility to vancomycin, respectively [12]. In ourstudy, *Streptococcus pneumoniae* showed almost no resistance to ceftriaxone, moxifloxacin, andvancomycin. *Coagulase-negative Staphylococci*is 100% sensitive to vancomycin. Comparison of the overall resistance pattern is illustrated in table-2.

V. Conclusion

Our study revealed that antibiotic resistance among Gram-positive organisms remains a continuous issue in adult ICU, KAMC- Riyadh. Among all isolated Gram-positive organisms, the most commonly isolated were *MSSA* (39%), *Enterococcus* (27%), and *MRSA* (21%). Vancomycin remains the most effective drug against *MSSA, MRSA*, *Streptococcus pneumonia*, and *Coagulase-negative Staphylococci.* The overuse of multiple antibiotics in ICU is considered one of the reasons behind the significant resistance. Therefore, strict adherence to infection prevention guidelines and continuous monitoring to antimicrobial resistance are essential to avoid major outbreak in the future.

Limitation: This study was conducted in a single center in Riyadh (KAMC) and in a limited period of time 2010-2014 which could be considered as a limitation to our findings.In addition, the data was collected from the yearly antibiogram. Therefore, Patients data such as age, sex and antibiotic use were not possible to obtain to study some of the risk factors

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Appendix 1: Table 1-2

Table 1: Comparison between 2010 and 2014 antibiotic resistance of *Methicillin sensitive Staphylococcus aureus*and*Methicillin-resistant Staphylococcus aureus*

Antibiotic	Resistance (%) in 2010	Resistance (%) in 2014	Trend
Methicillin sensitive Staphylococcus aureus (MSSA)			
Trimethoprim/sulfamethoxazole	1%	7%	↑
Clindamycin	5%	7%	↑
Erythromycin	5%	13%	↑
Cefazolin	2%	0%	↓
Vancomycin	0%	0%	–
Methicillin-resistant Staphylococcus aureus (MRSA)			
Trimethoprim/sulfamethoxazole	60%	46%	↓
Clindamycin	72%	52%	↓
Erythromycin	72%	53%	↓
Cefazolin	1%	1%	–
Vancomycin	0%	0%	–

Table 2: Comparison between 2010 and 2014 antibiotic resistance of *Enterococcus, Streptococcus pneumonia* and *Coagulase-negative staphylococci*

Antibiotic	Resistance (%) in 2010	Resistance (%) in 2014	Trend
Enterococcus			
Ampicillin	51%	71%	↑
Nitrofurantoin	66%	54%	↓
Vancomycin	37%	64%	↑
Streptococcus pneumonia			
Cefotaxime	50%	0%	↓
Erythromycin	25%	50%	↑
Moxifloxacin	0%	0%	–
Penicillin	0%	7%	↑
Vancomycin	0%	0%	–
Coagulase-negative Staphylococci			
Trimethoprim/sulfamethoxazole	62%	20%	↓
Clindamycin	62%	67%	↑
Erythromycin	65%	90%	↑
Vancomycin	0%	0%	–