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ORIGINAL ARTICLE

Emergence of Colistin Resistance against Multi-Drug Resistance Microorganisms and its Clinical Outcomes

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ABSTRACT

Background: Over the past decade, excessive use of Colistin against multidrug-resistant, Gram-negative bacteria have resulted in the evolution of resistance to Colistin.

Objective: To evaluate efficacy of Colistin against multidrug-resistant organisms (MDRO), the emergence of Colistin resistance and its effects on clinical outcomes.

Study Design: Retrospective study

Place and Duration of Study: King Saud Medical City (KSMC) from 1st October 2015 till 31st January 2016.

Methodology: Forty-three patients, resistant to Colistin on blood culture and sensitivity were enrolled.

Results: Colistin was not effective at breaking the MDRO. The results revealed no significant impact of Colistin on site of infection such as chest, urinary tract or skin (p=0.612), types of organisms (p=0.629), length of hospital stay and the IV Colistin days (p=0.097 and p=0.166 respectively) in the past 12 months. The positive finding was that more than two third (76.7%) of the ICU patients were alive.

Conclusion: Emergence of Multi drug resistance organism is matter of global concern that caused the ineffectiveness of many potent antibiotics and led to the drastic clinical outcomes. Collaboration between medical, paramedical, and administrative staff, with strict implementation of preventive protocol can slow down the velocity of microbial multidrug resistance.

Keywords: Multi-drug resistant, Colistin, Outbreak, Intensive care unit, critically ill patients

INTRODUCTION

Since long ago, nosocomial infections have been recognized as a significant health care challenges that causes drastic complications in critically sick hospitalized patients. The majority of these infections are caused by bacterial pathogens (prevalence of gram negative or positive bacterial infections are variable among different institutions) which are usually responsible for hospital associated pneumonia, surgical site infection (SSI), urinary tract infections (UTI), central line associated blood stream infection (CRBSI) and sepsis.[1,2] Patients admitted to the intensive care unit (ICU) are more vulnerable to get the infections and have a higher risk of infection related complications.[3] International data showed association between the hospital-related infections and length of ICU and hospital stay which in turn affects patient morbidity, mortality and health institution expenditures.[4] King Saud Medical City (KSMC) is one of the largest hospitals in Saudi Arabia that has experienced serious issues related to the Colistin resistant organism outbreak.

Infections caused by multi-drug resistant organisms (MDRO) mainly Gram-negative bacteria have a special concern and require an immediate attention to provide appropriate controlling measures and initiate specific treatment modalities to prevent deleterious sequels.[5] A special attention should be paid on the infections caused by multi-drug resistant Klebsiella pneumonia and Acinetobacter baumanii which are considered to be the common causative organisms of severe hospital acquired infections that have the capability to resist the effect of routinely used antibiotics and require specific therapeutic regimens.[6]

Klebsiella spp. are gram-negative, non-motile, usually encapsulated rod-shaped bacteria of the family Enterobacteriaceae, usually associated with nosocomial pneumonia with specific radiological findings and considered second most common causative organism in UTI. Some Klebsiella strains are also able to resist the effect of extended spectrum cephalosporins by producing ESBL hydrolyzing enzyme.[7] Similarly, Acinetobacter spp., which is aerobic, non-motile, catalase-positive, Gram-negative bacteria that cause a variety of health care-associated infections, including bacteremia, pneumonia, meningitis, UTI and wound infection are also recognized as a drug resistant pathogen. It has shown resistance against all type of penicillin, cephalosporins, fluoroquinolones, and aminoglycosides particularly in ICU settings.[8-10] Due to their resistance pattern, Carbapenem antibiotics are considered to be the drug of choice for infections caused by Klebsiella pneumonia and Acinetobacter baumanii.[11] However, these bacteria continue to develop antibiotic resistance and carbapenems resistant strains have now been isolated. This has decreased the choice in selecting effective therapeutic agents for such infections and has forced the specialists to reconsider an old antibiotic as an effective treatment for the highly resistant isolates.[12,13] In recent

years, the use of colistin has reached an important position in the treatment of MDRO, especially in intensive care settings.

The focus of this project was to examine the effect of Colistinon Multi Drug Resistance Organism (MDRO). The MDRO bacteria organism has been a real concern in many hospitals where the patients in intensive care units (ICU) are more vulnerable to the bacterial organism. The aim of this study was to reveal that Colistinis capable of breaking the resistance of MDRO. In addition, the study demonstrated that the main factors affecting the outcome of the outbreak of resistance include the site of infection, patient's length of stay, organism type, and number of days Colistin was used.

MATERIALS AND METHODS

This prospective analysis carried out between from 1st October 2015 till 31st January 2016 at King Saud Medical City (KSMC). It is a tertiary referral hospital and the largest Ministry of Health Hospital in Riyadh/Saudi Arabia. The hospital's intensive care unit includes surgical, medical and trauma units with the total bed capacity of 127 beds. An outbreak investigation started immediately after the detection of culture-confirmed infections with Acinetobacter Baumanniior Klebsiella pneumonia strains that were Colistin resistant in February 2016 among 10 patients admitted in ICU. Isolates obtained after two or more calendar days of admission to ICU were labelled as ICU acquired, otherwise incidence is linked to trans-outward, referred hospital or the community based on the source of admission to ICU (Transfer rule). The outbreak was declared, and all required demographical, microbiological and clinical data was collected and interpreted. It was done by a management committee that was formulated and led by the medical director with key partners, including the representatives from the Infection Control Unit, Intensive Care Unit, Nursing, Pharmacy and Infectious Disease physicians. Bed management and housekeeping service representatives were also included in this committee to initiate, coordinate, and follow implementation of the containment plan on daily basis.

RESULTS

The results showed, out of forty-three Colistin resistance patients admitted to ICU 78.1% were the male and the rest of the population were the female. The mean weight and age calculated were the 68.37 kg and 52.51 years respectively. During the study duration the readmission rate was very low only 3 (0.605%) patients were readmitted, and the average length of ICU stay was 41.372 days (Table 1).

The results revealed that the 65.1% admmited patients were not given Colistin before but they developed resistance against Colistin, which was very high. The major micobes isolaed from the culture of ICU admitted patients were Acinetobacter (83.7%) and Klebsiella (16.3%). The mortality estimation showed there were 33 (76.7%) patients discharged alive from ICU during study duration. The most common site of infection was the chest infection (pneumonia 46.5%). Data demonstrates out of 43 the bacteremia was found in 4 (9.3 %), skin infection in 9 (20.9%) and urinary tract infection (UTI) in 10 (23.3%). Chi square analysis showed no significant difference in treatment of different type of microorganisms (p= 0.629), site of infection (p=0.612) and mortality outcome (p=0.111) with Colistin in selected population (Table 2). Similarly results of logistic regression also revealed no significant results with Colistin use, such as length of ICU stay (p=0.097) and impact of IV Colistin days (p=0.166) (Table 3)

Table 1: Demographic characteristics and length of ICU

Variable	Mean±SD
Age (14-81 years)	52.51±18.993
Weight (24-103 kg)	68.37±17.0905
Number of previous ICU admissions within the past 12 months (0.0-3.0)	0.605±0.9294
ICU Los (2.0-117.0)	41.372±28.3524

Table -2: Comparison of different variables

Variable	No.	%	P value
ICU outcome			
Alive	33	76.7	0.111
Died	10	23.3	
Colistin used before			
No	28	65.1	0.539
Yes	15	34.9	
Orgamism type			
Acinetobacter	36	83.7	0.629
Klebsiella	7	16.3	
Site of infection			
Bacteremia	4	9.3	0.612
Pneumonia	20	46.5	
Skin Infection	9	20.9	
UTI	10	23.3	
Location at first culture			
ICU	22	51.2	0.284
Non-ICU	21	48.8	

Table 3: Logistic regression model

Model		Sum of Squares	df	Mean Square	F	Sig.
IV Colistin days	Regression	2301.429	1	2301.429	1.989	.166
	Residual	47448.850	41	1157.289		
	Total	49750.279	42			
ICU Los	Regression	2224.968	1	2224.968	2.893	.097
	Residual	31537.079	41	769.197		
	Total	33762.047	42			

DISCUSSION

Colistin has long been retained as a back-up agent due to serous nephrotoxicity and neurotoxicity problems and the introduction of less toxic antibiotics.[14] A rapid increase in the microbial resistance has been seen in any countries around the globe against Gram-negative bacteria. They are found to be resistant against aminoglycosides as well as all other lactams, including monobactam, carbapenems, cephalosporins and penicillin. This emergence of resistance compelled the doctors to reconsider the use of colistin for the MRDO as an option for critically ill patients in ICU.[15] Colistin-resistant Acinetobacter spp. and Pseudomonas spp. as well as Enterobacteriaceae have been mentioned in

literature worldwide. Species of Proteus and Serratia has also been reported intrinsically resistant to colistin.[16]

Although Colistin was discovered long ago and showed effectiveness in treatment, it poses some health-related threats by the isolation of Colistin resistant gram-negative bacteria. Colistin inhibits bacterial growth through interaction with anionic lipopolysaccharides (LPS) of the external membrane of bacteria. This electrostatic interaction displaces magnesium ions (Mg+2) and calcium ions (Ca+2) and makes the cell content leaky. Microbial cells died as a result of this process.[17,18]

Colistin also binds to the endotoxin of gram-negative bacteria, the lipid A part of LPS molecule, and neutralizes bacterial LPS, most of the patients developed Colistin resistance which was given to them for the first time. There are two ways bacteria can make changes in the LPS and become resistant to Colistin. First the hereditary mutation, low level, and independent of the ongoing presence of the antibiotic, while the second one is an adaptation and develop with the subsequent use of colistin. Thus, in light of the above-mentioned mechanism, we can infer that the outbreak of KSA was due to transport of resistant bacteria from the outside or has developed resistance due to previous Colistin over-use. The results depicted that Colistin did not have an impact on the site of infection, types of organisms, location of organisms and the IV Colistin days in the past 12 months. The results are consistent with the study[19] who observed that the use of Colistin alone cannot be effective in managing MDRO. A combination of Colistin with other antibiotics is effective in managing MDRO. Colistinis frequently used to increase the permeability of other antibiotics through the bacterial outer membrane by a detergent mechanism. In addition, the study by Sobieszczyk et al[20] indicated that the use of Colistin in combination with other antibiotics is effective in reducing MDRO.

The researchers indicated that the efficacy reduces if an antibiotic is used individually. The antimicrobial resistance to antibiotics is an emerging problem of word that should be given a proper attention otherwise there is a chance of microorganism dominance and increase probability of epidemics or even pandemics. So, the strict measure should be taken in this scenario, these measures can be classified into two major types, including standard preventive measures and specific controlling interventions that involve administrative measures, adherence monitoring, MDRO education, judicious antimicrobial use, surveillance cultures, infection control precautions to prevent transmission, as well as environmental measures and decolonization. The nature of these measures and interventions requires a collaborative effort among administrative and infection control committees, health care providers and all other staff and employees in the institution down to housekeepers. This outbreak required around 2 months to be controlled in KSA. By the end of April 2016, the MDR infection incidence reports returned back to the usual rate (1-2 cases/ month). Standard controlling measures had been implemented, including a stopping admission to or transferring out from the ICU till all investigations were completed grouping all patients with laboratory reported isolate of Acinetobacter Baumannii or Klebsiella pneumonia resistant to Colistin under strict contact precautions within isolated area. By applying the measures KSA ICU team manage to discharge 33 patients alive (76.6%). But this was the retrospective analysis, to study the exact method of developing resistance and the how to avoid it need double blind experimental design.

CONCLUSION

The unjust use of antibiotic causes the emergence of microbial resistance that can take the form of a serious outbreak. By proper surveillance, implementation of prevention protocol and collaborative effects of ICU and hospital administrative staff can avoid this global issue of emergence of multidrug resistance in microorganisms.

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