RESEARCH

STUDY OF COLISTIN AND TIGECYCLINE SENSITIVITY FOR CARBAPENEM RESISTANT ISOLATES OF KLEBSIELLA PNEUMONIAE (CRKP) PATIENTS IN THE INTENSIVE CARE UNIT (ICU) OF HIMS, DEHRADUN UTTARAKHAND

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Abstract

Background: Study of colistin and tigecycline sensitivity for carbapenem resistant isolates of Klebsiella pneumoniae patients in the intensive care unit (ICU) of HIMS, Dehradun, Uttarakhand. **Materials and Methods:** 274 consecutive ICU admission patients with Klebsiella pneumoniae (KP) infection were enrolled in this prospective cross-sectional study from June 2019 to January 2020. **Result:** Of the total 274 isolates of Klebsiella pneumoniae, 131 (48.1%) strains were carbapenem resistant. These CRKP strains, are isolated from respiratory specimens (62.9%), including 75 (30.9%) from endotracheal aspirate (ETA), 38(15.6%) from sputum, 28 (12.2%) from blood 20 (8%) from urine and 19 (7.8%) from broncho alveolar lavage fluid (BAL) in the ICU. Gender, Duration of stay in ICU, BMI did not have much significant difference between the two CRKP and CSKP. Out of these 131 strains of CRKP (120) 92% and (113) 87 % was found to be sensitive to colistin and tigecycline respectively and (128) 98% to colistin & tigecycline together. **Conclusion:** CRKP infections are the major public health threat in ICU, still rising .Appropriate and adequate use of antibiotics should be done in the ICU. Most of the CRKP infections were isolated from respiratory tract specimens. In our study the sensitivity as well as clinical outcome of colistin and tigecycline therapy was comparable for CRKP patients. Tigecycline and colistin was well tolerated. However, combination therapy is more effective and have more success rate in treating CRKP infections as compared to monotherapy.

INTRODUCTION

Infectious disease is one of the leading causes of mortality and morbidity in intensive care unit (ICU) admission patients, and multidrug-resistant (MDR) bacteria isolates are not uncommon among them.[1] Of these MDR pathogens, carbapenem-resistant Klebsiella pneumoniae (CRKP) poses a significant threat to public and clinical health due to its high levels of resistance to most alternative antibiotics. Despite improvements in hospital infection control and antimicrobial scientific stewardship, CRKP is still on the rise.[2] Various infections like bacteremia, pneumonia caused by Carbapenem resistant klenbsiella pneumoniae (CRKP) are very common in ICU. The management of such infections is difficult. The emergence of Carbapenem resistant Klebsiella pneumoniae (CRKP) ,a rapidly evolving global public health problem ,has made the compulsory use of other antibiotics like colistin and tigecycline, in addition of having bactericidal activity they have strong post antibiotic effect against multidrug resistant gram negative bacteria like Klebsiella pneumoniae.[3] Clinical studies have shown high mortality rate among patients with CRKP .Tigecycline and colistin are considered to be the last options for these infections.[4,5,6] The above antibiotics are used in CRKP infections in ICU without other comorbidities.[7] These drugs have a number of disadvantages but remain the mainstay of treatment. Colistin increased used has become a problem because of the development of resistance and its nephrotoxicity.[8,9,10] So in combination with tigecycline it is used in ICU .Tigecycline is a very good drug for soft tissue and intraabdominal infections in ICU.[11,12] The aim of our article is to the study of colistin and tigecycline sensitivity for

carbapenem resistant isolates of Klebsiella pneumoniae patients in the intensive care unit (ICU) of HIMS, Dehradun Uttarakhand.

MATERIALS AND METHODS

This prospective cross-sectional study was conducted from June 2019 to January 2020 in ICU of HIMS, Jolly Grant, Dehradun after obtaining ethical clearance from research committee of HIMS. 274 critically ill patients admitted in ICU with infectious diseases caused by Klebsiella pneumoniae were included. Information of the patients enrolled in the study was obtained from ICU, while the antimicrobial susceptibility results were collected from the microbiology laboratory reports. The criterion for variable selection were in accordance with previous studies and specifically related to ICU patients. The clinical characteristics of each patient will be composed of three parts: (1) Basic information, including age, sex, comorbidity, body mass index (BMI), history of nursing home residence, and history of Klebsiella pneumoniae colonization or infection in the preceding year (both the susceptible and the resistant strains will be included). (2) Status at ICU admission, including acute physiology and chronic health evaluation II (APACHE II) score, previously performed procedures. (3) Antibiotic prescriptions within 30 days prior to Klebsiella pneumoniae infection. Inclusion criteria: 1) Patients diagnosed with infectious diseases (bacteremia, pneumonia, skin and soft tissue infection, urinary tract infection, and abdominal infection) caused by Klebsiella pneumoniae admitted in ICU. The diagnostic criteria of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) were applied to diagnose these infectious diseases. The presence of Klebsiella pneumoniae infection was defined as positive culture result from clinical sample of the patient admitted in ICU.2) Patients between 18 and 80 years of age. Exclusion criteria: 1) Patients having more than one pathogen isolated during their ICU stay. 2) If their medical history will be incomplete. Klebsiella pneumoniae strains were identified and antimicrobial susceptibility results were obtained by automated VITEK system in the microbiology laboratory as per CLSI (Clinical and Laboratory Standards Institute) guidelines. Klebsiella pneumoniae ATCC 700603 was used as quality control strain for antibiotic susceptibility testing. CRKP was defined as Klebsiella pneumoniae isolates that were resistant to at least one of the carbapenem agents like imipenem, ertapenem or meropenem.[13] The antibiotic susceptibility test was conducted for various drugs like Piperacillin, Piperacillin-tazobactam, ampicillin sulbactam, ciprofloxacin, levofloxacin, ceftazidime, cefipime, gentamicin, amikacin, cotrimoxazole, imipenem, meropenem, ertapenem, tigecycline, colisin.

Statistical Analysis

The data was descriptively analyzed using Microsoft Excel 2010 software.

RESULTS

Of the total 274 culture confirmed cases of Klebsiella pneumoniae in ICU 131 (48%) were found to be CRKP (Carbapenem Resistant Klebsiella pneumoniae) and 143 (52%) were CSKP (Carbapenem Sensitive Klebsiella pneumoniae). These CRKP strains, are isolated from respiratory specimens (62.9%), including 75 (30.9%) from endotracheal aspirate (ETA), 38(15.6%) from sputum, 28 (12.2%) from blood 20 (8%) from urine and 19 (7.8%) from broncho alveolar lavage fluid (BAL) in the ICU. Gender, Duration of stay in ICU, BMI did not have much significant difference between the two CRKP and CSKP. Most of the CRKP patients had previous history of Klebsiella pneumoniae infection in the preceding year or had present colonization with the same bacteria or had other resistant bacterial infection in the past. These are also considered as risk factors for the development of CRKP.APACHE II score was highest among CRKP patients admitted in the ICU and also in the patients having various procedures performed. CRKP was found to be more in patients on steroid therapy or taking other immunosuppressive treatment, as well as in patients on invasive mechanical ventilation, central venous line and on parenteral nutrition for more than 2 days. The mortality was also found to be higher in CRKP group as compared to CSKP group. Most of the patients of CRKP were in the age group of 51-60 years in both the genders. Comorbidities were found to be more in CRKP patients like Diabetes mellitus, Chronic renal failure, Chronic pulmonary disease, Hematologic diseases, and Neurological diaseases. Therapeutic procedures performed in ICU like any surgery, hemodialysis, bronchoscopy, endoscopy, also found to be more in case of CRKP patients mentioned in [Table 1]. [Table 2] shows out of these 131 strains of CRKP (120) 92% and (113) 87 % was found to be sensitive to colistin and tigecycline respectively and (128) 98% to colistin & tigecycline together. (123) 94% showed sensitivity to amikacin, (105) 80% to gentamicin, cephalosporins showed (55) 42% sensitivity, fluoroquinolones showed (51) 39% susceptibility and (69) 53 % sensitivity was shown by beta lactamase inhibitors. Table 3 shows the clinical characteristics of colistin and tigecycline sensitivity in CRKP patients. Clinical outcomes of CRKP study patients are shown in [Table 4]. Combination therapy (colistin and tigecycline) outcomes are clearly depicted in [Table 5].

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Table 1: Demographic and clinical characteristics of CRKP and CSKP groups

Characteristics	CRKP		CSKP	
	No. of patients	Percentage	No.of patients	Percentage
	131	48	143	52
Comorbidities				
Diabetes Mellitus	24	18	21	15
Hyperytension	17	13	14	10
Chronic renal failure	16	12	15	11
Chronic pulmonary diaseases	46	35	36	25
Hematologic diaseases	07	05	06	05
Neurologic diseases	11	14	11	08
APACHE II score	84	64	46	32
Therapeutic procedures performed				
Surgery	41	31	37	26
Blood transfusion	12	09	07	05
Endoscopy	04	03	03	02
Bronchoscopy	38	29	27	19
Hemodialysis	13	10	12	09
Invasive mechanical ventilation	46	35	27	19
Central venous line	100	76	95	67
Parenteral nutrition	51	39	20	14
Corticosteroid therapy	18	14	06	04
Immunosuppressive therapy	14	11	04	03

Table 2: Sensitivity percentage in CRKP (131) patients

Antibiotic	No. of patients	Percentage
Colistin	120	92
Tigecycline	113	87
Colistin + Tigecycline	128	98
Amikacin	123	94
Gentamicin	105	80
Cephalosporins	55	42
Fluoroquinolones	51	39
Betalactamase inhibitors	69	53

Table 3: Clinical characteristics of colistin and tigecycline sensitivity in CRKP patients

Characteristics	Colistin		Tigecycline	
	No. of patients	Percentage	No.of patients	Percentage
	120	92	113	87
Comorbidities				
Diabetes Mellitus	13	11	10	09
Hyperytension	14	12	15	13
Chronic renal failure	05	04	05	04
Chronic pulmonary diaseases	18	15	10	09
Hematologic diaseases	7.2	06	03	03
Chronic liver disease	16	13	02	02
Surgery	06	05	07	06
Corticosteroid therapy	25	21	21	19
Acute respiratory failure	19	16	14	12
Septic shock	19	16	16	13

Table 4: Clinical outcomes of CRKP patients with colistin and tigecycline therapy

Characteristics	Colistin		Tigecycline	
	No. of patients	Percentage	No.of patients	Percentage
	120	92	113	87
Clinical success	23	19	16	15
Microbiological success	14	12	08	07
Recurrence of infection	05	04	02	02
ICU stay	16	13	17	15
Hospital stay	67	56	41	36
Nephrotoxicity	10	08	00	00
Mortality in ICU	19	16	16	14

Table 5: Clinical outcomes of CRKP patients with colistin and tigecycline (combination) therapy

Characteristics	Colistin + Tigecycline	
	No. of patients	Percentage
	128	98
Clinical success	23	18
Microbiological success	13	10
Recurrence of infection	03	02

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ICU stay	36	28
Hospital stay	107	84
Mortality in ICU	11	09

DISCUSSION

CRKP infections has been detected all over the world causing threat to public health. The emerging trend of CRKP may be the result of acquisition of carbapenemase genes, excessive consumption of carbapenems also increases the CRKP.[14] Some studies have shown CRKP risk factors in new borns, childrens, pregnant females.[15,16] There are very few studies focusing on adult ICU patients with CRKP infections. The rising trend of CRKP infections draws major public concern and more effective counteractive measures as well as antibiotic stewardship has been taken by general population.[17] A study by Falagas et al showed mortality in critically ill ICU tends to be on increase in spite of using monotherapy or combination regimens.[18] As per our results , APACHE II score in CRKP group was higher .During any therapeutic procedure, mucosa of trachea and skin was eroded which in turn increases the chances of CRKP infections and colonization.[17] .We also found mechanical ventilation and parenteral nutrition were also risk factors for CRKP infections, so interventional apparatus has to be removed as early as possible to avoid any nosocomial infections. Control of infections in ICU is very difficult due to decreased immunity and critical condition of the patients. Our study indicated that corticosteroid therapy (14%), immunosuppressive therapy (11%) increases CRKP patients. Intravenous immunoglobulins or other immunity boosters has to be given in these patients. ICU patients with CRKP infections have high mortality, so the antibiotic coverage should be adequate and proper, avoiding its indiscriminate use.[19] The previous history of klebsiella pneumoniae infection and colonization was found to be the principal risk factor for CRKP infections.[20]

History of nosocomial infections during ICU stay was also increasing CRKP infections as well.[21] In our study, CRKP strains, are isolated mainly from respiratory specimens 113 (62.9%), including 75 (30.9%) from endotracheal aspirate (ETA), 38 (15.6%) from sputum, 28 (12.2%) from blood 20 (8%) from urine and 19 (7.8%) from broncho alveolar lavage fluid (BAL) in the ICU. Comorbidities like diabetes mellitus, hypertension, chronic renal failure, chronic liver disease, hematological and neurological diseases were also found more in CRKP patients. For CRKP infections colistin and tigecycline remains the antibiotic of choice but now a days resistance to these drugs are also emerging.[22,23] In our study , out of the 131 strains of CRKP (120) 92% and (113) 87 % was found to be sensitive to colistin and tigecycline respectively and (128) 98% to colistin & tigecycline together.In our study, efficacy of colistin and tigecycline was comparable, similar results were obtained by kim et al.[24] Combination therapy with more than one agent is the better option for treating CRKP infections.[25] In our study clinical and microbiological success rate is better with combination therapy (colistin and tigecycline together), Recurrence of infection, ICU stay, hospital stay and mortality rate also reduced by combination therapy. One major limitation of our study is the limited number of cases and limited number of patients with combination therapy.

CONCLUSION

CRKP infections are the major public health threat in ICU, still rising. Appropiate and adequate use of antibiotics should be done in the ICU. Most of the CRKP infections were isolated from respiratory tract specimens. In our study the sensitivity as well as clinical outcome of colistin and tigecycline therapy was comparable for CRKP patients. Tigecycline and colistin was well tolerated. However, combination therapy is more effective and have more success rate in treating CRKP infections as compared to monotherapy.

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