A STUDY ON OUTBREAK OF CARBAPENEM PLUS COLISTIN-RESISTANT KLEBSIELLA PNEUMONIAE SEPSIS IN NEWBORNS IN A NURSERY OF A TERTIARY CARE HOSPITAL

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ABSTRACT

BACKGROUND

A retrospective study was performed in a nursery of a tertiary care hospital in Jamshedpur, India, between March 2016 and July 2016. There was an outbreak of carbapenem+colistin resistant Klebsiella during that period. We identified all blood culture results that had yielded a growth of carbapenem+colistin resistant Klebsiella pneumoniae during the study period. Only the blood cultures showing growth of Klebsiella pneumoniae were included under study. Medical records of these babies were reviewed for demographic and clinical data.

MATERIALS AND METHODS

Clinical parameters analysed included severity of illness and various factor affecting outcome. The records of 60 patients with bacteraemia caused by Klebsiella pneumonia were identified and analysed. The mean age of patients was 3 days and 32 (53%) were male.

RESULTS

The mean duration of hospital stay was 12 days. The mean time for onset of bacteraemia was 2.4 days after admission. The most common co-morbid condition was prematurity (31.6%) followed by birth asphyxia (HIE) (20%). All patients received IV tigecycline with a dose of 1.2 mg per kg with 1:10 dilution of normal saline over 15 minutes of IV infusion twice daily. Mean duration of antibiotics was 7.8 days. Minor drug reactions like generalised rash, vomiting and diarrhoea were documented. Serious adverse reaction of tigecycline therapy like ARF was reported in 3 babies. The overall survival at 30 days was 76.6% in our study with lowest survival rate of 50% was for babies undergoing surgery followed by preterm babies <32 weeks with survival rate of 63.3%, while survival rates for HIE and RDS babies were 84.4%, 66.6%, respectively. We also found that patients treated with combination therapy had lower mortality (64.28%) compared with tigecycline monotherapy (35.71%), although this was statistically not significant.

CONCLUSION

Carbapenem+colistin resistant K. pneumoniae is a serious healthcare-associated infection in critically ill-patients in NICU with co-morbidities and prior antibiotic exposure; K. pneumoniae was the most common organism at our center. Thirty day survival rate was only 76.6% and even lower for premature <32 weeks. Klebsiella pneumonia was highly sensitive to only tigecycline and was the cornerstone of therapy, but its safety in newborn may need to be studied to optimise the outcome; neonatal hepatitis and ARF was seen in 15% of patients only and was reversible in most of the cases. Combinations of other antibiotics with tigecycline may result in a lower mortality compared with monotherapy; however, this needs to be explored by randomised-controlled studies.

KEYWORDS

Carbapenem-Resistant Klebsiella Pneumoniae, Colistin-Resistant Klebsiella Pneumoniae, Tigecycline in Neonates.

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BACKGROUND

Klebsiella pneumoniae is the most important organism responsible for a significant proportion of hospital-acquired infections in the neonate.[1] Carbapenem-resistant K. Pneumoniae (KPC) isolates are emerging as a cause of MDR gram-negative infections in healthcare settings.[2,3] Clinically, a limited number of antimicrobial options remain for the treatment of KPC-producing K. pneumoniae, especially colistin. KPC-producing K. pneumoniae isolates are typically resistant to carbapenems as well as penicillins, cephalosporins, fluoroquinolones and frequently also to aminoglycosides. Infection due to KPC-producing K.

pneumoniae is therefore commonly treated with a regimen-containing colistin[2] and especially for the carbapenem-resistant K. pneumoniae, colistin is used as the cornerstone of therapy.[4] Colistin is used extensively to treat infections with this organism. Klebsiella pneumoniae that produces K. Pneumoniae Carbapenemase (KPC) has rapidly spread across hospitals worldwide in the past decade.[4] Colistin, which had been in disuse for decades due to concerns about toxicity and availability of other safer antimicrobial agents, now constitutes a first line regimen for treatment of infection caused by this organism. With the increased use of colistin, emergence of multiclonal clusters of colistin-resistant K. pneumoniae isolates have been described from various centres.[5,6,7,8,9,10] There are very few reports of colistin-resistant Klebsiella pneumoniae in our country; however, reports of carbapenem resistance in gram-negative organisms are being increasingly encountered in healthcare-associated infections in India. Bacteraemic episodes due to these organisms carry a high mortality as shown by previous studies from other countries.[9,10] Colistin-resistant organisms have a potential to persist in the patients and the hospital environment and cause subsequent transmission. With the continued use of colistin for treatment of infection with various multidrug-resistant gram-negative pathogens, it is likely that we will see an increasing number of instances of both, de-novo emergence of resistance and nosocomial spread.[11]

AIMS AND OBJECTIVES

To study the outcome of outbreak of carbapenem+colistin resistant Klebsiella pneumoniae infection in neonates in our centre to analyse the clinical parameters, risk factors and severity of illness in the affected neonates, bacteriological response to tigecycline and safety profile of tigecycline in the neonates.

MATERIALS AND METHODS

This is a retrospective study performed in a 30-bedded nursery of a tertiary care hospital in Jamshedpur, India, between March 2016 and July 2016. We identified all blood culture results that had yielded a growth of carbapenem+colistin resistant Klebsiella pneumoniae during the study period. We then reviewed the medical records of these babies.

Only the blood cultures showing growth of Klebsiella pneumoniae were considered for analysis. Blood cultures were performed using BacT/ALERT culture system and species identification was carried out with VITEK-GNI card. Antibiotic susceptibility was performed using disc diffusion interpretive criteria as per revised clinical and laboratory standards institute performance standards.[12]

Medical records were reviewed for demographic and clinical data. Clinical parameters analysed included severity of illness. The source of bacteraemia was defined on the basis clinical and microbiologic evaluation using infections criteria proposed by CDC.[13] Presence of risk factors such prematurity, birth asphyxia, infant of diabetic mother, babies who had surgery, double volume exchange transfusion and prior antibiotic use of colistin or carbapenem group was recorded. Babies were treated with tigecycline and repeat cultures were taken on day 7 for bacteriological clearances were analysed; outcome in the form of mortality and survival after tigecycline treatment were recorded.

The records of 60 patients with bacteraemia caused by Klebsiella pneumonia were identified and analysed. The mean age of patients was 3 days and 32 (53%) were male. The most common co-morbid condition was prematurity (31.6%) followed by birth asphyxia (HIE) (20%). Three patients (5%) needed DVET, while four (6%) had other surgeries. The mean duration of hospitalisation was 12 days. The mean time for onset of bacteraemia was 2.4 days after admission. Of the 60 patients, 46 (76.6%) had already received antibiotics. Among them, 8 cases were exposed to carbapenem group of antibiotics and 6 cases had received colistin while rest were on the first line antibiotics of Inj. Magnex (cefoperazone+sulbactam) and Inj. Amikacin (as proposed by the infection control committee of the institution) (Table 1).

Age in days (Mean)	3
Male:female	1.14:1
Comorbid conditions	
HIE	12
Prematurity	19
Pneumonia	6
RDS	6
IGDM	3
Hyperbilirubinaemia+DVET	3
Surgical cases	4
Congenital anomaly	2
Others	5
Shock at presentation	12 (20%)
Time of onset of bacteraemia	2.4 days
Prior treatment with antibiotics	46 (76.6%)
Carbapenem	8
Colistin	6
Others	12
Culture positive cases while on ventilator	25 (41.6%)
Babies having central lines or PICC lines	48 (80%)
Babies having central line at the time of sampling	21 (35%)

Table 1

RESULTS

Twenty percent (n=12) patients had shock at the time of admission. Forty one percent babies were having Klebsiella growth in their blood culture while were on ventilator. Eighty percent babies (n=48) were having central line in Klebsiella pneumoniae culture positive cases and out of them, thirty five percent (n=21) babies were having central

line in situ while sampling. The mortality was 23.3 percent out of which maximum death occurred in premature babies especially below 32 weeks (Table 2).

Comorbid Conditions	Number of Colistin-Resistant Cases	Number of Survivors	Number of Non-Survivors
Premature >32 weeks	8	6	2
Premature <32 weeks	11	7	4
HIE	12	10	2
Pneumonia	6	5	1
RDS	6	4	2
IGDM	3	3	0
Hyperbilirubinaemia +DVET	3	3	0
Surgical cases	4	2	2
Congenital anomaly	2	2	0
Others	5	4	1
Total	**60**	**46 (76.6%)**	**14 (23.3%)**

Table 2

All patients received IV tigecycline with a dose of 1.2 mg per kg with 1:10 dilution of normal saline over 15 minutes of IV infusion twice daily. Mean duration of antibiotics was 7.8 days. Minor drug reactions like generalised rash, vomiting and diarrhoea were documented. Serious adverse reaction of tigecycline therapy like ARF were seen in 3 babies, out of which 2 recovered and neonatal cholestasis were documented in 6 cases, out of which 5 recovered to normal. Out of these, 9 serious ADR according to Naranjo scale of causality assessment, 6 cases were having possible ADR and 3 cases were having probable ADR due to tigecycline therapy.

The overall survival at 30 days was 76.6% in our study with lowest survival rate of 50% was for babies undergoing surgery followed by preterm babies <32 weeks with survival rate of 63.3%, while survival rates for HIE and RDS babies were 84.4%, 66.6%, respectively.

We also found that patients treated with combination therapy had lower mortality (64.28%) compared with tigecycline monotherapy (35.71%), although this was statistically not significant (P=0.208) (Table 3).

	Combination Treatment	Tigecycline Monotherapy
Number of babies recovered/transferred	48	12
Number of babies died	9	5
P value (using chi-square test)=0.208		

Table 3

Combination vs. monotherapy- Treatment outcome.

DISCUSSION

In the present study, the most common carbapenem resistant gram-negative isolate was Klebsiella pneumoniae with more than half of all episodes due to EOS and with a mean time of onset of bacteraemia after admission of 2.4 days. These results are in concordance with previous studies implicating these organisms as causes of healthcare-associated infections.[14]

Seriously, ill-neonates in NICU stay for prolonged periods often require femoral lines, umbilical lines, partial or double volume exchange, broad-spectrum antibiotics and mechanical ventilation, which make them susceptible to resistant hospital-acquired infections. Notably, only 8 of our babies had received carbapenem and 6 had received colistin out of total 46 babies who were already receiving antibiotics at the time of KP isolation. Rest of the cases was not exposed to antibiotics. This raises concern about healthcare-associated infections of carbapenem+colistin resistant KP to the antibiotics unexposed neonates.

The overall 30-day survival rate in our cohort was only 76.6%, but it was difficult to assess whether this was due to sepsis itself or due to underlying severe illness and multiple co-morbidities. Mortality in our patients was high for babies who had major surgery and babies who were preterm. We also observed that patients treated with two drug combinations had a trend towards a higher survival rate than those treated with tigecycline alone as observed in other studies also. Small study numbers in the two groups and the fact that more severely ill patients may receive combination treatment may have resulted in the absence of a statistically significant difference.

We acknowledge significant limitations in our study, its retrospective nature, relatively small sample size and absence of a control group for comparison.

CONCLUSION

Carbapenem+colistin resistant K. pneumoniae is a serious healthcare-associated infection in critically ill-patients in NICU with co-morbidities and prior antibiotic exposure; K. pneumoniae was the most common organism at our centre. Thirty-day survival rate was only 76.6% and even lower for premature <32 weeks. Klebsiella pneumonia was highly sensitive to only tigecycline and was the cornerstone of therapy, but its safety in newborn may need to be studied to optimise the outcome; neonatal hepatitis and ARF was seen in 15% of patients only and was reversible in most of the cases. Combinations of other antibiotics with tigecycline may result in a lower mortality compared with monotherapy; however, this needs to be explored by randomised-controlled studies.

ABBREVIATIONS

ADR- Adverse Drug Reaction.
ARF- Acute Renal Failure.
DVET- Double Volume Exchange Transfusion.
HIE- Hypoxic Ischaemic Encephalopathy.
IGDM- Infant of Gestational Diabetic Mother.
K. pneumoniae- Klebsiella pneumoniae

KPC- Klebsiella Pneumoniae Carbapenemase
IV- Intravenous
RDS- Respiratory Distress Syndrome
PICC- Peripherally Inserted Central Catheter

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