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Emergence of multi-drug-resistant *Klebsiella pneumoniae* in Neonatal Intensive Care Units: concern about antimicrobial policies

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Abstract

Antimicrobial abuse is a serious risk factor for the emergence of multi-drug-resistant (MDR) pathogens. Multidrug resistant (MDR) Klebsiella pneumoniae is an increasing cause of neonatal infections in India and in other developing countries. Objective of this study was designed to monitor temporal change in prevalence of K. pneumoniae as a causative organism for neonatal infections and its antimicrobial sensitivity pattern. Neonatal infections are clinical syndromes characterized by signs and symptoms of infections in the first month of life. 550 blood cultures were studied from suspected babies and the prevalence of K. pneumoniae among them was checked with its antimicrobial susceptibility and case fatality rate at Department of Microbiology, SRICEAS, Surat, Gujarat. Among 550 suspected neonates in the study period, positivity was found in 110 cases. Among them, 23 cases were found due to Klebsiella pneumoniae infections, 60.86% of them were fatal. High degree of resistance to many antibiotics can be seen(%). Most of our strains were shown their resistance to most of the third generation of cephalosporins used. The incidence of neonatal infections due to K. pneumoniae was higher. All spp. of K. pneumoniae found as M.D.R., which was in co relevance with the mortality caused by them which knocking and shocking data, indicating the emergence to check on the cruelty use of antimicrobials in NICUs.

Key words: Multi drug resistant, neonatal infections, klebsiella pneumoniae, case Fatality

Introduction

Neonatal deaths account for over a third of the global burden of child mortality[1]. In many developing countries neonatal mortality rates (deaths in the first 28 days of life) are as high as 40–50 per 1000 live births[2,3], with infections being the major cause of death[4,5]. Sepsis is a significant cause of morbidity and mortality in neonates[6].

Neonatal sepsis is defined as a disseminated disease with positive blood culture during the first month of life[7], and is more common in developing countries compared with developed countries[8]. Sepsis with Gram negative microorganisms is increasingly reported nowadays particularly in Asian countries[9,10]. The inadvertent use of broad-spectrum antibiotics has led to the emergence of multidrug resistant Gram-negative bacteria[11]. *Klebsiella* species are of significant importance in this regard[12]. The most common pathogens of bacterial sepsis and antibiotic sensitivity patterns vary in different parts of the world[13-15]. The potential for antimicrobial resistance is particularly important for the treatment of systemic infections as initial antimicrobial chemotherapy is almost invariably empiric and must be based on knowledge of the most frequently isolated etiological agents and their antimicrobial susceptibility patterns. Early initiation of appropriate antimicrobial treatment is critical in decreasing morbidity and mortality among patients with bloodstream infections.

Knowledge of local epidemiology is required for optimal management of neonatal sepsis. This study was undertaken to monitor temporal change in prevalence of K. pneumoniae as a causative organism for neonatal infections and its antimicrobial sensitivity patterns from blood cultures of neonates admitted to neonatal care unit, Surat, Gujarat, India.

Material and Methods

Blood samples were collected from 550 clinically suspected neonates (<30 days) admitted to the Neonatal Intensive Care Unit (N.I.C.U.), Surat, Gujarat, India over a period of 10 months. Their blood samples were inoculated into previously sterilized Brain Heart Infusion Broth (BHI, Himedia, and Mumbai, India) in ratio of 1:10. The inoculated blood culture bottles were incubated at 37°C for 24 hours and the growth of the microorganisms was observed. The culture bottles showing turbidity were used for the isolation and cultivation of bacteria using generalized, enriched and selective media. Isolates were identified using standard biochemical tests.

Antimicrobial susceptibility tests: Antimicrobial susceptibility tests were performed using the Kirby Bauer

disc diffusion method as per CLSI guidelines. Antimicrobial used were Amikacin (30µg), Augmentin(50µg), Ceftriaxone (30µg), Cefotaxime (30µg), Ceftazidime (30µg), Cefazoline (30µg), Cefpirome (30µg), Cefipime (30µg), Cefotaxime/sulbactum (30/15µg), Clindamycin (2µg), Ciprofolxacin (5µg), Chloramphenicol(25µg), ,Gentamycin (10µg), Imipenum(10µg), Kanamycin (30µg), Meropenum (10µg), Methicillin (30µg), Nalidixic acid (30µg), Netromycin (30µg), Piperacilin / Tazobactum (100/10µg), Vancomycin (30µg).

Results and Discussion

Blood samples for culture were obtained from 550 suspected cases of neonatal infections, of which 110 (20%) were positive. Table1 shows the gender wise distribution, indicating the high ratio of male patients (71%) dominating female (29%), therefore the ratio of male: female is 2.5:1.
The Gram-negative bacterium most commonly isolated was *Escherichia coli* (n=35) followed by *Klebsiella* spp. (n=23). The positivity as per isolates presented in figure 1. Among 110 culture positive cases, 36 (32.72%) of neonates died.
In our study, mortality caused by neonatal infections had surprising results. If we see the distribution of isolates, Gram negative *E.coli* found as the most prominent organisms among all Gram negative organisms causing infections, but the mortality rate was highest in neonates infected with *Klebsiella* spp. (14/60,86%) and therefore found *Klebsiella sp.* as the most important organisms of concern.

Very different, susceptibility pattern was found in *Klebsiella spp.* compare to all other isolates and can be correlated with its high fatality rate. Table 2 shows antibiogram results and presence of high frequency of MDR (21/23) knocking the emergence of prevention of neonatal infections.

Most of the isolates of *Klebsiella* spp. were found to be more susceptible to Amikacin, Imipenum, and Piperacillin/Tazobactam, but they were resistant to the third generation of Cephalosporins. Figure 2 shows the antimicrobial susceptibility test.

Figure 3 represented outcome of cases of neonatal patients, 54 patients were recovered from illness and discharged while 23 patients were discharged against medical advice (DAMA). Case fatality rate of sepsis was 33 (four cases among these were due to the infections with *C. albicans*). A large number of neonatal deaths are still due to infection etiology and it is mainly in the premature and low birth weights babies.

Formulation of strict antibiotic-prescription guidelines by the policy makers and their ground level implementation by the concerned authorities is the need of the hour for India. Frequent surveillance studies from different regions across the world that could help in updating the empirical antibiotic regimen for the neonates admitted to NICUs are highly recommended.

Gram-negative bacilli are frequently associated with infections in the patients admitted to the intensive care units of hospitals[16], and the incidence of infection is higher in the neonatal period than at any time of life[17]. Moreover, the problem of global antibiotic resistance continues to worsen[18]. In this study, the prevalence of documented neonatal infection with positive blood culture was 20%. This incidence was lower than the prevalence of positive blood cultures in Rahman et al.[19] study (62.8%) and Bhttacharjee et al., study (48%)[20]. The lower prevalence of documented neonatal sepsis with positive blood culture in our study had different reasons such as antibiotic administration in mother or neonate, difficulty in sampling, blood culture technique[21] or sepsis due to anaerobic, viral or fungal pathogens[22] and misdiagnosis because of some similarities between the clinical signs of sepsis with other diseases like metabolic disorders[23].

The mortality was higher in neonates whose blood culture were positive for isolates as shown above, Similar results were obtained by many studies in Iraq[24-27].
In case of *Klebsiella sp*., high degree of rrsistance to many antibiotics can be seen. Most of our strains were shown their susceptibility to amikacin and to the comnbinstion of cavulinic acid+ sulbactum and show 100% sensitivity ti imipenum, while resistance to most of the third generation of cephalosporins used.

Neonatal infections remain a major cause of mortality in this age group. As there is a trend of changing pattern of organisms responsible for bacterial infection in the newborn, the possible changing nature of the bacterial pathogen at the neonatal unit needs further monitoring and periodic surveillance, and there is a need to establish and review local antibiotic sensitivities of pathogens for optimal therapy. With early diagnosis and treatment, introduction of new antibiotics and increased awareness of proper hand washing practice, the neonatal mortality and morbidity can be reduced markedly.

Conclusion

Neonatal infection, a clinical syndrome, characterized by systemic signs and symptoms of first month of life. It encompasses systemic infections of newborn including meningitis, pneumonia, arthritis osteomyelitis and urinary tract infections of the newborn. It is one of the commonest causes of Neonatal mortality and morbidity and estimated that 20% of all neonates develop infections, and it is responsible for 30-50% of total neonatal dearth in developing countries. As Neonatal infections are a life-threatening emergency and delays in diagnosis and treatment may have adverse consequences, surveillance is needed to identify the

common symptoms and signs, causative agents and their antibiotic sensitivity patterns.

In our study, the incidence of culture proven sepsis was observed to be 20 %. Epidemiologically infections were predominantly seen in males. Among blood culture isolate, Gram negative organisms were most common in compare to Gram positive, fungal sepsis was observed in 9% of the cases. High degree of antibiotic resistance seen in Klebsiella isolates and can be correlated with the fatality rate caused by them.

Most of the isolates of Klebsiella spp. were susceptible to amikacin, but shown resistant to third generation of cephalosporins. High prevalence of MDR was the stinking feature of this study and justifies the purpose of the study.

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Table-1
Gender wise distribution of patients

Patient's characteristics	No of suspected septicemias	No of positive blood cultures
No. of neonates	550	110
No. of male	390	78
No. of female neonates	160	32

Table-2
Antibiogram of *Klebsiella sp.*
ISOLATES-NO

Antibiotics	2	12	23	30	31	34	35	45	48	54	76
Amikacin	S	S	S	S	S	S	R	S	S	S	S
Augmentin	R	R	R	R	R	R	R	S	S	S	R
Ceftriaxone	S	R	R	R	R	R	R	S	R	S	R
Cefotaxime	R	R	R	R	R	R	R	S	S	S	R
Ceftazidime	R	R	R	R	R	R	R	S	R	S	S
Cefazoline	R	R	R	R	R	R	R	S	R	S	R
Cefpirome	M	R	R	R	S	M	S	M	R	R	R
Cefipime	S	R	R	R	S	M	S	S	S	M	M
Cefotaxime+sulbactum	S	S	S	S	S	S	S	S	S	S	S
Clindamycin	S	S	S	S	S	S	M	R	R	M	R
Ciprofolxacin	R	S	S	S	S	S	M	S	M	M	S
Chloramphenicol	S	S	S	S	R	S	S	S	S	S	S
Gentamycin	S	R	R	R	R	S	S	M	S	M	R
Imipenum	S	S	S	S	S	S	S	S	S	S	S
Kanamycin	S	R	R	R	R	S	S	S	S	S	S
Meropenum	S	S	S	S	S	S	R	R	S	R	R
Nalidixic acid	R	R	R	R	R	R	R	S	M	R	S
Netromycin	S	M	S	M	S	S	R	R	R	R	R
Piperacilin + Tazobactum	S	S	S	S	S	S	R	R	S	S	R

Antibiotics	88	89	90	92	93	95	110	125	143	144	159	193
Amikacin	S	S	S	S	S	S	R	S	S	S	S	S
Augmentin	S	R	R	R	S	M	R	R	R	R	R	S
Ceftriaxone	S	R	R	R	S	S	R	R	R	R	M	R
Cefotaxime	S	R	R	R	S	S	R	R	R	R	R	R
Ceftazidime	M	S	S	S	S	R	R	R	R	S	R	R
Cefazoline	M	R	R	R	S	R	S	R	M	R	R	R
Cefpirome	M	R	R	R	S	M	R	S	R	R	R	R

Cefipime	M	M	M	M	S	R	R	M	R	R	R	M
Cefotaxime+sulbactum	S	S	S	S	M	S	R	R	S	R	R	R
Clindamycin	S	M	M	M	R	R	R	R	R	R	S	R
Ciprofolxacin	S	S	S	S	S	R	R	S	S	R	M	R
Chloramphenicol	S	S	S	S	R	S	M	R	R	R	R	S
Gentamycin	M	R	R	R	S	R	R	R	R	R	R	R
Imipenum	S	S	S	S	S	S	S	M	R	M	S	S
Kanamycin	S	S	S	S	S	S	S	S	S	S	S	S
Meropenum	R	R	R	R	R	R	R	R	R	R	R	R
Nalidixic acid	S	S	S	S	S	R	S	S	S	M	R	S
Netromycin	S	R	R	R	S	S	R	R	R	R	R	R
Piperacilin + Tazobactum	S	R	S	S	M	R	S	S	S	S	R	M

Figure-1
Positivity rate of each isolate

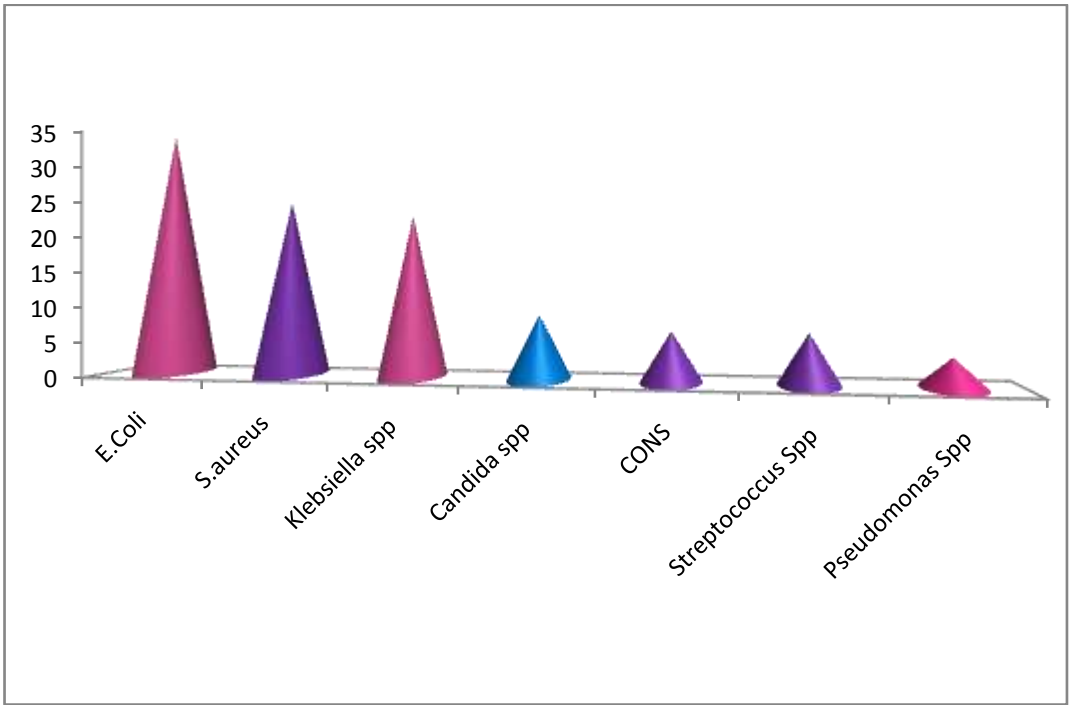

Figure-2
Antimicrobial susceptibility Test

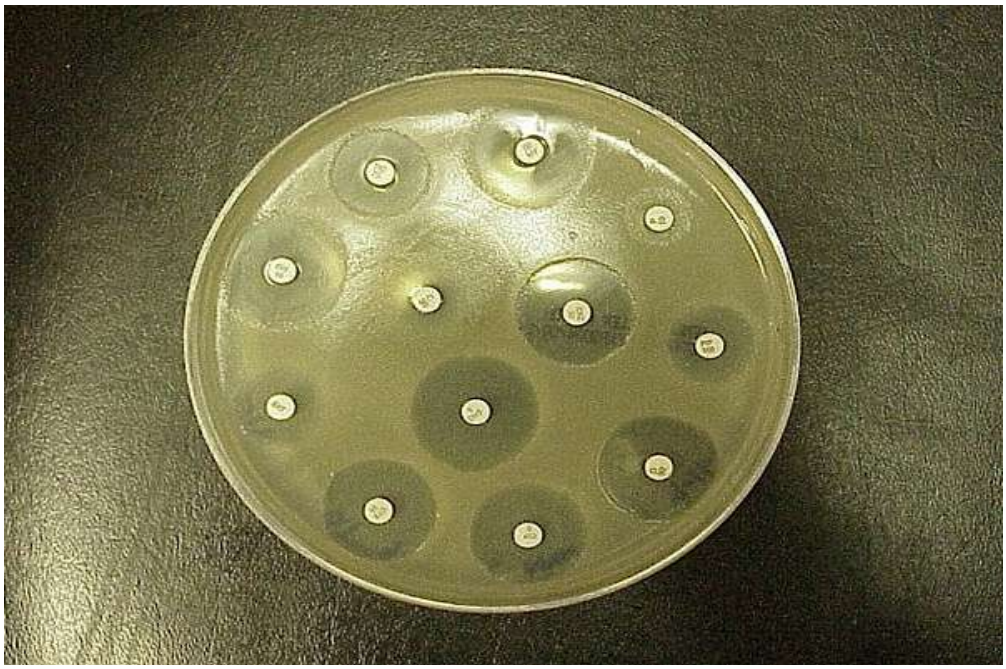

Figure-2
Outcome of patients of NICU