

Neonatal Sepsis due to *Klebsiella*: Frequency, Outcome and Antibiotic Sensitivity

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Abstract

Sepsis is a significant cause of morbidity and mortality in neonates. The most common pathogens of bacterial sepsis and antibiotic sensitivity patterns vary in different parts of the world. The aim of this study was to determine the most common pathogens and outcome of neonatal sepsis and also antibiotic sensitivity patterns of *Klebsiella* species. A retrospective descriptive study was carried out. The study was performed at a neonatal care unit in Kashan between October 2000 to October 2003. Only those neonates with positive blood culture were included. Patients with *Klebsiella* septicemia were categorized into two groups of early and late-onset sepsis. Patterns of the antibiotic resistance of the bacterial isolates were studied by disc diffusion technique. Frequencies and Fisher's Exact test was used to compare the early-onset outcome versus late-onset outcome. One hundred and thirty-six neonates had positive blood cultures out of 453 cases. The most common pathogens were *Pseudomonas*, *Klebsiella* and coagulase negative *Staphylococci* respectively. Overall crude mortality rate was 39% (*Pseudomonas* was the predominant cause). All *Klebsiella* species were resistant to ampicillin. Twenty-three percent of *Klebsiella* species were multiresistant considering our most common etiologic pathogens of bacterial sepsis and the significant number of resistant bacteria to ampicillin and gentamicin; it seems prudent to consider revising the present choice of empirical antibiotic treatment.

Keywords: Neonatal sepsis, Antibiotic sensitivity, *Klebsiella*, Iran

Introduction

Sepsis is a significant cause of morbidity and mortality in neonates (1). Sepsis with Gram-negative microorganisms is increasingly reported nowadays particularly in Asian countries (2, 3). The inadvertent use of broad-spectrum antibiotics has led to the emergence of multi-drug resistant Gram-negative bacteria (4). *Klebsiella* species are of significant importance in this regard (5). The most common pathogens of bacterial sepsis and antibiotic sensitivity patterns vary in different parts of the world (6- 8). Knowledge of local epidemiology is required for optimal management of neonatal sepsis. This study was undertaken to determine:

1) the most common causes and outcome of neonatal sepsis and 2) antibiotic sensitivity patterns of *Klebsiella* isolates from blood cultures

of neonates at a neonatal care unit in Kashan during a three-year period.

Materials and Methods

A retrospective descriptive study was carried out on 453 neonates who were admitted with clinical syndrome of sepsis at the neonatal ward of Martyr Beheshti's General Hospital between October 2000 to October 2003 (three years). This neonatal care unit is the sole center for admitting ill neonates after their first discharge from hospital after birth in Kashan. Therefore studying the bacteriologic and antibiotic sensitivity profile of the admitted neonates can provide a useful guide to the existing pattern of neonatal sepsis in this area. Patients were included if they had clinical signs of sepsis, abnormal erythrocyte sedimentation rate (ESR)

and/or positive C-reactive protein (we cannot measure serum CRP level quantitatively in our hospital laboratory). Normal ESR was defined by adding three to the age of the infant in days up to the first two weeks of life. After the first two weeks, an ESR of more than 17 was considered as abnormal (9). Those with known problems simulating sepsis (such as metabolic diseases, congenital adrenal hyperplasia, hypoglycemia and asphyxia...) were excluded from the study. Out of a total number of 453 neonates, only patients with positive blood culture (30%) were enrolled in our study (n=136). According to the time of presentation of symptoms, we categorized the study population into two groups. Group one with early onset sepsis was defined as time of onset ≤ 7 days and group two with late-onset sepsis with presentation >7 days after birth. Patterns of the antibiotic resistance of the bacterial isolates were studied by disc diffusion technique (the HIMEDIA products). For ampicillin and gentamicin, 10 micrograms discs and for ceftriaxone, cefazidime, ceftizoxime and amikacin, 30 microgram discs were used. Mono-phasic BHI broth media (manufactured by Difco Laboratories) were used for cultures. All the records of the study population (n=136) were carefully reviewed and data including sex, age, pertinent hematologic laboratory findings, results of cultures, antibiotic sensitivity and clinical outcome (death versus survival) of the patients were entered into a questionnaire. Frequencies and other statistical analyses were calculated by Statistical Package for Social Sciences (SPSS version 9.05). Fisher's Exact Test was used to compare the outcome of neonates with early-onset versus late-onset sepsis. *P* value less than 0.05 was considered significant. For ethical issues, confidentiality of the entire patient's information was considered.

Results

Patient's characteristics are presented in Table 1. The contributions of bacterial pathogens to neonatal sepsis are illustrated in Fig. 1.

As shown in Fig. 1, *Pseudomonas aeruginosa* (n=58), *Klebsiella* species (n= 43) and coagulase-negative *Staphylococci* (n= 20) were the most common pathogens, causing approximately ninety percent of cases with culture-proven bacterial neonatal sepsis.

The other ten percent were due to microorganisms such as *E.coli*, *Enterococci*, *Micrococci*, *Citrobacter*, *Staphylococcus aureus* and *Streptococcus* group B. Overall mortality is depicted in Fig. 2. Forty-three patients had *Klebsiella* septicemia.

Of these, thirty-one (72%) were male and twelve (28%) were female. Early-onset and late-onset sepsis were present in 76% and 24%, respectively. Among neonates with *Klebsiella*, mortality was higher in neonates with early-onset sepsis than those with late-onset (25% versus 14%, Fisher's Exact Test, *P*=0.043).

Overall mortality rate due to *Klebsiella* was 22%. Antibiotic sensitivity results of the isolated *Klebsiella* species are shown in Fig. 3. Ten cases (23%), were resistant to all four drugs and also ceftazidime and ceftizoxime, but proved to be sensitive to carbenicillin in vitro. All of these newborns were successfully treated with imipenem.

Table 1: Patients' distribution according to early onset versus late onset sepsis

Patients' characteristics	Early onset sepsis	Late onset sepsis	Total
No. of neonates (%)	104(76%)	32(24%)	136(100%)
Number of male neonates (%)	82(60%)	22(70%)	104
Number of female neonates (%)	22(40%)	10(30%)	32
Birth weight of neonates (mean \pm SD), grams	3150 \pm 530	3250 \pm 650	3200 \pm 570

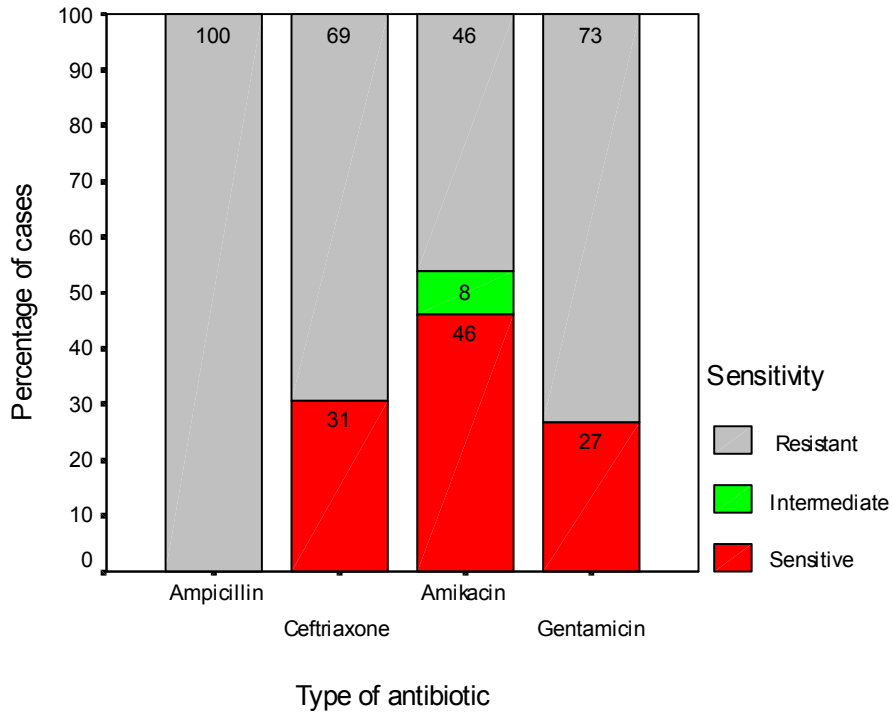


Fig. 1: Pattern of antimicrobial sensitivity of *Klebsiella* species isolated from blood cultures of neonates with bacterial sepsis (between October 2000 to October 2003).

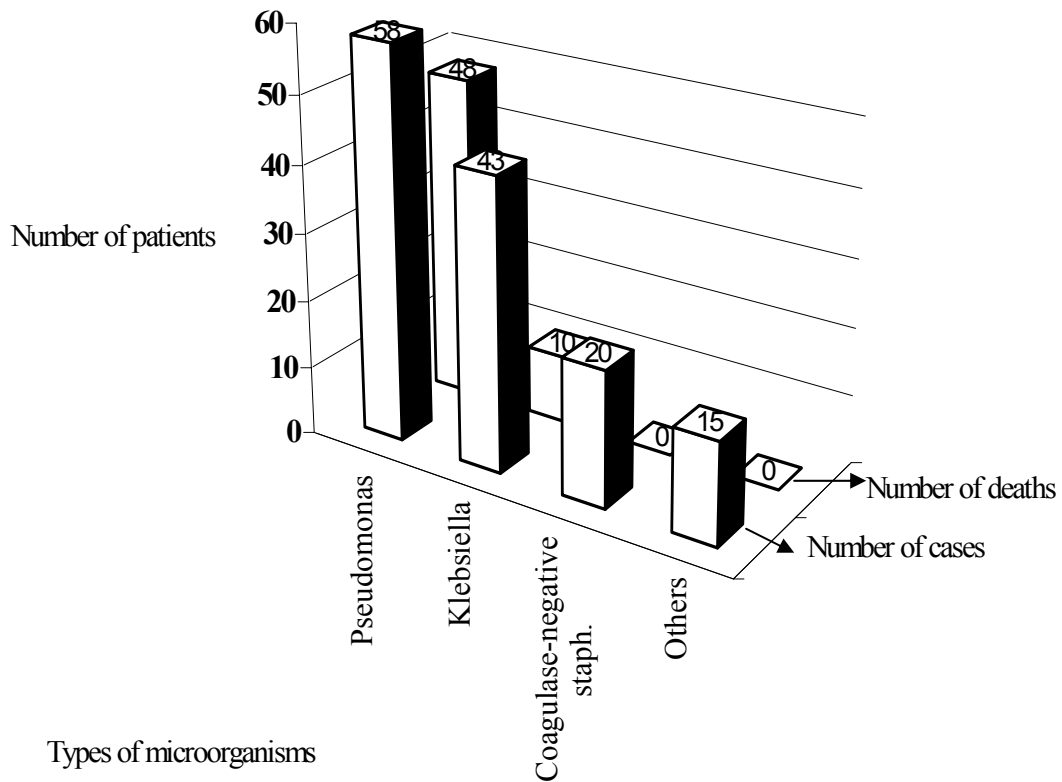


Fig. 2: Mortality of neonatal sepsis according to the pathogenic bacteria

Discussion

In our study the most common etiologic agent was *Pseudomonas aeruginosa*. This is in contrast to reports from other parts of the world. In western countries, group B *Streptococci* and *E.coli* are the most common Gram-positive and Gram-negative microorganism respectively (1, 9). In our study 43 % of neonatal sepsis are caused by *Pseudomonas* species while Gladstone et al in a ten-year review reported *Pseudomonas* species as just comprising 6% of all cases with neonatal sepsis (10). According to our findings, *Klebsiella* species were the second most common cause of neonatal sepsis in this area. All the isolated *Klebsiella* species were resistant to ampicillin. In a study performed on 124 blood culture-positive neonates with sepsis at neonatal ward of Ali Asghar's Children Hospital during the years 1990 and 1992 (11) the most common pathogens were *Enterobacter* (27%), *Staphylococcus aureus* (23%) and *Klebsiella* (24%), respectively. In this study the positivity rate of blood cultures was 41% and almost all Gram negative bacteria were resistant to ampicillin. In another study in Iran (12) on 242 neonates, *Staphylococcus aureus* was the leading cause of neonatal sepsis and *Klebsiella* was found to be the third most common etiologic agent in this respect. Antibiotic sensitivity was not studied. Missallati et al reviewed 36 cases of blood-culture-proven neonatal septicemia. They found *Klebsiella* as the most common microorganism (13). In their study, similar to ours, the bacterial isolates were resistant to ampicillin.

However, they reported sensitivity of the isolates to cefotaxime. In our study the percentage of extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella* species that were resistant to all the third generation cephalosporins, was 23 %. Jain et al reviewed blood samples of 728 neonates with suspected sepsis and reported that 86.6% of *Klebsiella* species were extended-spectrum beta-lactamase producing (14).

Extended-spectrum beta-lactamase (ESBL), first detected in Germany, now is a worldwide problem (13). However because of technical limitations we could not document production of ESBL by double-disk synergy test or the E-test strip (14). The positivity rate of our blood cultures was 30 %. Kumhar et al carried out a study on neonates of a tertiary care hospital in India and showed a blood culture positivity of 42%. *Klebsiella* was the most common etiologic microorganism in their study (17). However Mokuolu et al in a two-year review reported a positivity rate similar to us (30.8%) (18). *Staphylococcus aureus* was the most common pathogen in their research. However Rahman et al in a retrospective review of 1598 blood cultures in Pakistan reported a positivity rate of 62.8% with the *E.coli* as the most common organism (19). Twenty-three Percent of our *Klebsiella* isolates were resistant to amikacin, while in a review of blood cultures drawn from 520 newborns in Pakistan, the majority of the isolated Gram-negative rods were susceptible to amikacin, but similar to us more than 90% of *Klebsiella* isolates were resistant to ampicillin. Therefore the authors suggested vancomycin and amikacin as empirical treatment of choice for neonatal sepsis (20). The mortality rate of neonatal sepsis due to *Klebsiella* was 22 % in our study. Ahmed et al performed a descriptive analysis of clinical and bacteriological profile of neonatal septicemia in Bangladesh. *E.coli* and *Klebsiella* were the most common pathogens in their study. Forty percent of their neonates with positive culture (n =30) had died (21). In summary we reviewed the prevalence of various etiologic agents in a three-year period. We showed that our bacterial profile is not the same as western countries, Gram-negative bacteria and in particular *Pseudomonas* and *Klebsiella* species are the leading causes of neonatal sepsis. However the prevalence of resistant *klebsiella* spp. is significant and deserves more consideration.

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