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ENTEROBACTER SAKAZAKII IN INFANTS: NOVEL PHENOMENON IN INDIA

P Ray, A Das, V Gautam, N Jain, A Narang, M Sharma

Abstract

E. sakazakii has been implicated in necrotizing enterocolitis, bloodstream and central nervous system infections, with mortality rates of 40-80%. Two cases of E. sakazakii infections; one preterm very low birth weight neonate with meningitis and a two month infant with bacteraemia, are described for the first time in India. The first baby succumbed to the infection while the other responded to appropriate therapy. Powdered infant milk formulae have been implicated in causing neonatal infections and the first baby was on formula feed with classic signs of sepsis and meningitis. The second infant was on breast feed and probably developed nosocomial E. sakazakii bacteraemia.

Key words: Enterobacter sakazakii, formula-feed, neonates, nosocomial

Enterobacter sakazakii, introduced as a new species in 1980, has been implicated in several invasive infections, sporadically or as outbreaks, especially in premature infants.\(^1\,^2\) E. sakazakii has been implicated in the causation of necrotizing enterocolitis, bloodstream and central nervous system infections, with mortality rates of 40-80%.\(^2\,^9\) Disease epidemiology and reservoir of the bacterium has not been characterized. It have been reported to be a frequent contaminant of powdered milk formulae, but other environmental sources of infection cannot be ruled out.\(^2\) E. sakazakii strains described in literature are either clinical isolates or recovered from unused formula products. Neonatal E. sakazakii infections have been well described in many reports, case series and extensive reviews, but to the best of our knowledge no cases have been reported from India.

In this report, two cases of E. sakazakii infections are being described from PGIMER, Chandigarh, a tertiary medical care centre. The medical records of the infants were reviewed for gestational age, birth weight, feeding practices, surgical/medical interventions, associated infections, antimicrobial therapy and outcome.

Case Reports

Case 1

A 1.4-kg premature (34 weeks, one of triplets) female neonate on tube feed was admitted to the neonatal intensive care unit (NICU) in July 2002. The baby had a respiratory rate of 46/minute, heart rate of 146/minute and polycythemia (PCV 68%, TLC 5000/mm\(^3\), reticulocyte 3%) and was put on oral rehydration. After five days, the baby developed grunting, episodic apnoea, chest retraction, tachypnoea, multifocal clonic movements with tonic posturing and an enlarged liver 10 cm below right costal margin. The child was put on ventilator and developed fulminant sepsis with meningitis. Investigations revealed a TLC of 2800/mm\(^3\) with 90% neutrophils, thrombocytopenia, positive C-reactive protein, metabolic acidosis and intraventricular haemorrhage on ultrasound. CSF showed raised protein, reduced glucose and elevated leukocyte count (3000/mm\(^3\), predominantly neutrophilic) but culture was negative. The baby was started on intravenous ciprofloxacin (3 mg/kg) and netilmicin (7 mg/kg) as per NICU protocol. Blood culture, sterile overnight, grew E. sakazakii, after two days of incubation. The isolate was resistant to cepotaxime, ceftazidime and ciprofloxacin and sensitive to gentamicin, amikacin, netilmicin and co-trimoxazole. The sepsis, developed after five days of hospital stay, was labelled as nosocomial in origin. The baby died before blood culture positivity of E. sakazakii and susceptibility results were available on the eighth day.

Case 2

A two month female infant on breast feed was admitted in July 2006 with cough and respiratory distress (respiratory rate 94/minute) and a provisional diagnosis of bronchiolitis. The baby’s mother had hypertension and diabetes mellitus requiring insulin and the baby suffered from neonatal jaundice on day 3. After three days of hospital stay, the baby developed signs of sepsis (considered nosocomial) and was transferred to the paediatric intensive care unit (PICU). Blood collected grew E. sakazakii resistant to gentamicin, amikacin, cefotaxime and ceftazidime, intermediately resistant to ciprofloxacin and sensitive to co-trimoxazole and ceftriaxone–sulbactam combination. The baby was initially started on intravenous ceftriaxone–sulbactam and vancomycin (as per policy for treatment of sepsis in PICU) for five days and, on availability of susceptibility data, ceftriaxone–sulbactam was continued for another two weeks. Subsequent blood cultures were negative; the child became afebrile and was discharged.

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Discussion

The isolates grew as smooth colonies, 2-3 mm in diameter, on 5% sheep blood agar and moist pale pink colonies on MacConkey agar after overnight incubation at 37°C. Conventional biochemical tests were performed and antibiotic susceptibility by disc diffusion on Mueller–Hinton agar (MHA) was done according to CLSI recommendations. Growth on MHA revealed a light yellow pigment. Biochemically (nitrate reduced, glucose fermented with production of acid and gas, catalase positive and oxidase negative), the isolates belonged to the family Enterobacteriaceae. Further analysis showed that indole was not produced, citrate utilized, urea not hydrolysed, VP+MR-, H₂S was not produced and both the isolates were motile. Presumptively, the strains were identified as yellow pigment producing species in the genus Enterobacter. Speciation was done by extended biochemical tests (lysine decarboxylase/LDC, arginine dihydrolase/ADH, ornithine decarboxylase/ODC and sorbitol fermentation) for differentiation between Enterobacter cloacae, Enterobacter sakazakii and Pantoea agglomerans. Both the isolates were LDC-, ADH +, ODC + and did not ferment sorbitol and were finally identified as E. sakazakii. E. sakazakii was the sole bacterial isolate in these patients and the susceptibility patterns of both the isolates were different. The first isolate was resistant to cephalosporins and fluoroquinolones but sensitive to aminoglycosides and co-trimoxazole, whereas the second was resistant to cephalosporins and aminoglycosides, moderately resistant to fluoroquinolones and sensitive to beta lactam-beta lactamase inhibitor combinations and co-trimoxazole.

Powdered infant milk formulae have been implicated in causing neonatal infections and one of our cases was a premature, very low birth weight neonate on formula feed with classic clinical signs of sepsis and meningitis. Since the baby was on tube feed, it may be assumed that E. sakazakii was probably due to contamination of the feed, but this could not be proved because attempt to isolate the organism from the presumed source was not made. The second infant was primarily suffering from bronchiolitis, was on breast feed and probably developed nosocomial E. sakazakii bacteraemia that responded to specific antimicrobial therapy. The source of E. sakazakii in the second case also was unclear and transmission from hospital environment cannot be ruled out. Analyses of host risk factors and disease course in infants have revealed that infants with meningitis and bacteraemia fell into two distinct groups. Infants with meningitis were generally <1 week of age at the onset of infection and suffered a worse outcome, whereas infants with only bacteraemia had generally surpassed the neonatal period at the onset of infection and had a lower mortality rate. The difference in the chronological ages of the infants in the two distinct disease groups (meningitis/bacteraemia alone) was reflected in our cases also and the baby who survived had only bacteraemia although the isolate was more resistant.

Case definition for invasive E. sakazakii infections in infants have been met in only 46 cases worldwide, although there are numerous reports of E. sakazakii isolates from non-sterile sites. Interestingly, all these reports are from the developed countries, whereas the situation seems to be radically different in the developing world. This ambiguity may be attributed to the socio-cultural differences in infant feeding practices, since the use of formula feed is relatively uncommon in developing countries. Powdered infant formula has been found to be contaminated with other gram negative organisms belonging to the family Enterobacteriaceae, but the degree of association of E. sakazakii with formula feeds and neonatal infections needs further studies. The risk factors, reservoirs, disease course and epidemiology of E. sakazakii have to be investigated further, since reports of infections in adults and infants who have never been given powdered feeds imply alternative sources of infection.

This is the first report of E. sakazakii infections in infants from India. We have previously reported one case of fatal postoperative nosocomial E. sakazakii infection in an adult (submitted elsewhere) from PGIMER, Chandigarh and the present report includes two cases of invasive E. sakazakii infections in infants. Nosocomial source of infection seems very likely since all the three cases reported from our centre meet the definition of hospital-acquired infections. Evidence to prove this assumption is presently lacking but plausible since E. sakazakii is a non-fastidious gram negative bacterium and has been isolated from various environmental sites and factories producing milk powder, chocolate, cereal, potato flour, spices and pasta. It has also been isolated from household vacuum cleaner bags and from the guts of the stable fly (Stomoxys calcitrans) and the Mexican fruit fly (Anastrepha ludens). Since the organism has been isolated from varied environmental sites, it seems logical to expect its presence in the hospital environment with a wide variety of inanimate moist niches.

The pathogenesis of infection by this organism is not well elucidated, but since it has been associated with powdered formula feeds and implicated in necrotizing enterocolitis, the gastrointestinal (GI) system seems to be the primary site of colonization or infection, from where it probably spreads to the blood stream and central nervous system. Faecal contamination, directly or indirectly, of the hospital environment may occur and once a niche is established, E. sakazakii can proliferate and may spread nosocomially. The serious nature of the infection is evident from the fact that two of our three cases were fatal. These three cases constitute the first report of E. sakazakii from India and probably greater awareness and intensive biochemical characterization will help in identification of more cases and help in the proper management of these patients.

Carbapenems, newer cephalosporins or beta lactam-beta lactamase inhibitor combinations in combination with aminoglycosides may be of greater utility due to increasing sensitivity.
antimicrobial resistance and production of extended spectrum beta lactamases by *Enterobacter* species. Trimethoprim–sulfamethoxazole has been proposed as a useful alternative and the findings of this report also support this suggestion, as both *E. sakazakii* isolates were sensitive to co-trimoxazole.¹ Timely diagnosis and early institution of proper antibiotic therapy based on susceptibility can reduce the mortality.

References


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