

Brief Report**How Safe are Infant Formulas?**

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Preamble

Enterobacter sakazakii causes invasive infection with high mortality rates in neonates. *Enterobacter sakazakii* is a gram-negative rod within the family Enterobacteriaceae, genus *Enterobacter*. The organism was called “yellow-pigmented *Enterobacter cloacae*” until 1980 when it was renamed *Enterobacter sakazakii*. Urmenyi and Franklin (1) reported the first two known cases of meningitis caused by *E. sakazakii* in 1961. Subsequently, cases of meningitis, septicemia, and necrotizing enterocolitis due to *E. sakazakii* have been reported worldwide (2). When meningitis occurs, severe neurological complications, including cerebral abscess formation, are common, and death occurs in 33%—80% of cases. *Enterobacter sakazakii* has been detected in tins and packages of powdered infant formula. The pathogen is able to grow in infant formula milk during storage at refrigeration temperatures and attach to infant-feeding equipment, which may become reservoirs of infection. *Enterobacter sakazakii* appeared to be one of the most thermo tolerant organisms (3,4). Risk for infection might depend on several factors, including the number of bacteria present in the product, handling after preparation, and underlying patient characteristics (e.g., immunosuppression, prematurity, or low birth weight (2).

Evidence

In one of the prospective study (5), a quantity of dehydrated powdered infant formula was prepared to contain *Enterobacter sakazakii* strain 607 at approximately 106 CFU/ml when rehydrated,

according to the manufacturer’s instructions. The survival of the microorganism in the dry formula was followed for 2 years, during which samples periodically were rehydrated and analyzed for viable *Enterobacter sakazakii*. During the initial 5 months of storage at room temperature, viable counts declined approximately 2.4 log cycles. During the subsequent 19 months, the concentration of viable *E. sakazakii* declined an additional 1.0 log cycle. These results indicate that a small percentage of *E. sakazakii* cells can survive for extended periods in dehydrated powdered infant formula.

In a report from the Department of Neonatal Intensive Care, the National University Hospital, Reykjavik, Iceland (6) three cases of neonatal infection caused by *Enterobacter sakazakii* were reported. These infections occurred during a 9-month period in 1986 and 1987. Two of the neonates, who were normal at birth, survived but were left with brain damage. The third, which had Down’s syndrome and severe cardiac malformations, died. The same organism was also grown from groin and anal swabs from a healthy neonate. *Enterobacter sakazakii* was not isolated from any environmental sources in the neonatal wards or in the milk kitchen, but it was grown from several lots of the powdered-milk formula used in the hospital. The four *E. sakazakii* strains isolated from the neonates were indistinguishable from 22 strains grown from the formula. Their biotypes, plasmid DNA profiles, and antibiograms were identical.

A report from Belgium (7) has linked *Enterobacter sakazakii* infection with occurrence of an outbreak of necrotizing enterocolitis (NEC) that occurred in the neonatal intensive care unit of Academisch

Ziekenhuis Vrije Universiteit Brussel hospital, Brussels. A total of 12 neonates developed NEC in June-July 1998. For two of them, twin brothers, the NEC turned out to be fatal. *Enterobacter sakazakii*, a known contaminant of powdered milk formula, was isolated from a stomach aspirate, anal swab, and/or blood sample for 6 of the 12 neonates. A review of feeding procedures revealed that 10 of the 12 patients were fed orally with the same brand of powdered milk formula. *Enterobacter sakazakii* was isolated from the implicated prepared formula milk as well as from several unopened cans of a single batch. Molecular typing by arbitrarily primed PCR (AP-PCR) confirmed, although partially, strain similarity between milk and patient isolates. No further cases of NEC were observed after the use of the contaminated milk formula was stopped. With this outbreak we show that intrinsic microbiological contamination of powdered milk formula can be a possible contributive factor in the development of NEC, a condition encountered almost exclusively in formula-fed premature infants.

The US Centers for Disease Control and Prevention reported an outbreak of *Enterobacter sakazakii* infection associated with the use of powdered infant formula in a neonatal intensive care unit (2). The index case in the outbreak was a male infant born at 33.5 weeks who was admitted to the NICU because of prematurity, low birth weight and respiratory distress. The infant developed fever, tachycardia, decreased vascular perfusions and suspected seizure activity at 11 days. Culture of cerebrospinal fluid (CSF) grew *E. sakazakii*. Intravenous antibiotics for meningitis were administered, but the infant died 9 days later.

Enhanced case surveillance of 49 infants in the NICU identified 9 additional cases — 2 cases of “suspected infection” (*E. sakazakii*-positive culture from a nonsterile site, i.e., tracheal aspirate, with documented clinical deterioration) and 7 “colonized cases” (*E. sakazakii*-positive culture from a nonsterile site, i.e., stool or urine, without documented deterioration).

Analysis of possible risk factors such as gestational age, birth weight, mechanical ventilation, humidified

incubators, oral medications, feeding type and feeding method found that only the use of a specific powdered infant formula product developed for infants with malabsorption problems (Portagen, Mead Johnson Nutritionals, Evansville, Ind.) was significantly associated with the cases. Cultures taken from opened and unopened cases from a single batch of Portagen grew *E. sakazakii*. Cultures from other sources such as the water and surface environments were negative. Mead Johnson Nutritionals voluntarily recalled batch BMC17 of Portagen on Mar. 29, 2002, and in April, 2003, the US Food and Drug Administration distributed a letter to health professionals about the risk posed by powdered infant formulas.

In the year 2004, a case of *E. sakazakii* meningitis occurred in a neonatal intensive care unit in New Zealand. As soon as the Ministry was notified, the Ministry and the Food Safety Authority issued advice recommending against powdered formula for pre-term babies where an alternative was available and reinforcing good handling practices when the formula was being prepared. *Enterobacter sakazakii* (*E. sakazakii*) invasive disease notification enables both identification of instances of invasive disease and consideration of the need for public health action (9).

Global response (10,11,12)

Global response to this threat has been swift. The issue of pathogens and in particular *Enterobacter sakazakii* in infant formula was brought to the attention of the 35th session of the Codex Committee on Food Hygiene (CCFH) by two separate processes. The 24th session of the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) requested the CCFH to revise the Recommended International Code of Hygienic Practices for Foods for Infants and Children (CAC/RCP 21-1979) in order to address concerns raised by pathogens that may be present in infant formula. At the same time, the United States of America and Canada introduced a risk profile for *E. sakazakii* in powdered infant formula for

consideration by the committee. The profile documented the severe life-threatening nature of *E. sakazakii* infections in susceptible neonates and infants and the sporadic, low levels of pathogen found in implicated formula products. Implicated products were generally in conformance with the microbiological requirements of the current Codex Alimentarius Code of Hygienic Practices for Foods for Infants and Children.

As a result, the 35th Session of the CCFH: (1) set up a drafting group led by Canada to initiate revision of this code; (2) noted that, as well as *E. sakazakii*, there were a number of other pathogens of concern that may be present in powdered infant formula such as *Clostridium botulinum*, *Staphylococcus aureus* and other *Enterobacter* species; (3) requested the United States and Canada to update the risk profile to include other pathogens of concern, and (4) requested FAO and WHO to convene an expert consultation on pathogens of concern in powdered infant formula, at the earliest opportunity.

Consistent with the need to provide safe feeding for all infants, the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) jointly convened an expert meeting on *Enterobacter sakazakii* and other microorganisms in powdered infant formula (WHO, Geneva, 2 to 5 February 2004). The workshop was organized in response to a specific request to FAO/WHO for scientific advice from the Codex Committee on Food Hygiene to provide input for the revision of the Recommended International Code of Hygienic Practice for Foods for Infants and Children. It also aimed to provide pertinent information to the member countries of both organizations.

After reviewing the available scientific information, the expert meeting concluded that intrinsic contamination of powdered infant formula with *E. sakazakii* and *Salmonella* has been a cause of infection and illness in infants, including severe disease which can lead to serious developmental

sequelae and death. No link has been established between illness and other microorganisms in powdered infant formula, although such a link was considered plausible for other *Enterobacteriaceae*. Severe outcomes are especially serious in preterm, low birth-weight and immunocompromised infants.

World Health Assembly Resolution (WHA58.32) (13)

With keeping in view various documented proofs, World Health Assembly meeting in May 2005 discussed the serious issue of infant milk formula contamination with *Enterobacter sakazakii* and other pathogenic organisms and urged Member States to ensure:

- That clinicians and other health-care personnel, community health workers and families, parents and other caregivers, particularly of infants at high risk, are provided with enough information and training by health-care providers, in a timely manner on the preparation, use and handling of powdered infant formula in order to minimize health hazards
- Are informed that powdered infant formula may contain pathogenic microorganisms and must be prepared and used appropriately
- Where applicable, that this information is conveyed through an explicit warning on packaging

Conclusion

An association between fatal infection attributed to *Enterobacter sakazakii* and use of a commercial powdered infant formula in a NICU is a matter of serious concern for all those who are helping these sick, tiny neonates to fight for their life. Although the literature from the developing countries says that *Enterobacter sakazakii* is a rare cause of invasive disease in neonates; the situation in developing countries like India may be more serious. As *Enterobacter sakazakii* infection, including sepsis, meningitis, or necrotizing enterocolitis, has been associated with use of powdered infant formula, clinicians should be aware that powdered formulas

are not sterile products and might contain opportunistic bacterial pathogens such as those in the family Enterobacteriaceae. Because powdered formula is not sterile and can provide a good medium for growth, prolonged periods of storage or administration at room temperature might amplify the amount of bacteria already present. In developed countries the laboratory facility exists to trace the killer organism back to its powdered formula origins. In less privileged countries, these deaths might be occurring unnoticed. It is possible to avoid the risks by opting for expressed breast milk and breastfeeding. In situations where mothers cannot breastfeed or choose not to breastfeed for any reason, the caregivers should be warned that the powdered formula product, which they are using, is not a sterile product.

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