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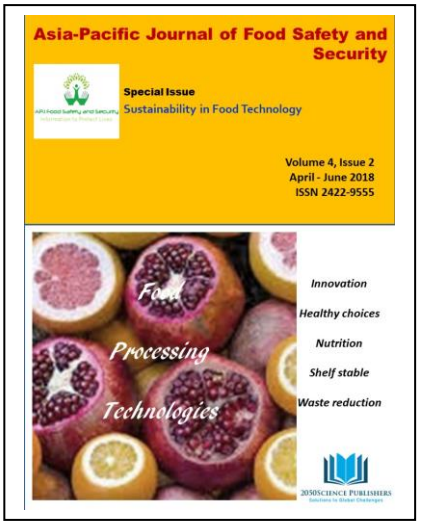

Research

Analysis of 129 Global Cases of *Cronobacter sakazakii* Infection During 1961-2017

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Highlights

- *Cronobacter sakazaki*i is a global pathogenic bacterium with a wide geographical distribution.
- The main symptoms of the infection are bacteremia, septicemia, meningitis and enterocolitis.
- The main source of infection is infant formula and related feeding-equipment.

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Abstract

To understand the incidence rate and situation of global *Cronobacter sakazakii* infection cases and to provide valuable information for future prevention of infections. Statistics, classification and analysis were made on global 129 reported *C. sakazakii* infection cases occurred during 1961-2017 in different parts of the world. The main symptoms of the infection are bacteremia, septicemia, meaningitis and enterocolitis. The infection was equally distributed between sexes. *C. sakazakii* infection cases were widespread across six continents and it was the highest in European, followed by North America and Asia. From the infection, 36 people died and 93 people survived for antibiotic treatment. Many types of treatments were given for the 129 people, but there was no report about the best treatment regime at present. Of the 129 cases, 114 were infants, classified as mostly the premature, low-birth weight, low immunity newborns. The main source of *C. sakazakii* infection is infant formula and equipment of milk powder. *C. sakazakii* is a worldwide probelm, as this pathogenic bacterium associated with milk powder poses a risk to infants. Therefore, more attention is needed to prevent and mitigate this pathogen in the food industry.

Key words: *Cronobacter sakazakii*; infant; infection cases; case study

Introduction

*C. sakazaki*i is a gram-negative bacillus which can produce yellow pigments. It is a conditional pathogenic bacterium which can become pathogenic under certain condition (Farmer et al., 1980). This bacterium could be isolated from a wide spectrum of food like vegetables, cheese and meat, as well as from the environment, soil, air and water (Mosso et al., 1994; Khan et al., 1998; Kim and Beuchat, 2005; Osterblad et al., 1999). It has been speculated that infant formula and infant feeding equipment like feeding bottles, nipples and blenders are the main sources of the infection based on the cases. However, the major source of contamination has not been determined yet. In the past, there were no reports of *C. sakazakii* infection cases caused by infant formula in China, but several infection cases have been reported recently. People focus on the safety of infant formula increasingly because the tests have isolated 11 samples positive for *C. sakazakii* in 87 poor quality powder milk samples in Fuyang, Anhui province in 2004 (Liu et al., 2005). The testers isolated *C. sakazakii* from commercialized infant formula in Beijing, Chengdu, Guangzhou, Gansu, Guangxi, Zhangzhou, Longyan, and Shijiazhuang (Lu et al., 2008; Li et al., 2009; Zhang et al., 2010; Quan et al., 2013; Li et al., 2009; Zhong et al., 2010; Yuan et al., 2016; Li et al., 2010). In China, the opening of "second child" policy is expected to increase the number of infants in the near future, causing people to demand more infant formula, especially imported infant formula. Therefore, it is vital to intensify the

monitoring of infant formula to assure the safety of infants. For these reasons, the presence of *C. sakazakii* in infant formula should not be ignored.

C. sakazakii is able to survive in environment mainly in the form of bacteria biofilms, which are more resistant than planktonic to adverse environmental conditions (Iturriaga et al., 2007). In addition, *C. sakazakii* has abnormal viability in dry environment like infant formula because it can produce trehalose. Also, improper cleaning and disinfection of related appliances can also increase the possibility of infection during the preparation of infant formula (Iversen et al., 2004). The main path of transmission and the origin of *C. sakazakii* have not been determined until now, but the infection cases reported are almost exclusively caused by infant formula. Thus, it is particularly important to strengthen the detection of organisms in infant formula. The purpose of this paper was to collect worldwide reported infection cases from 1961 to 2017 and to analyze those cases for the risk assessment of infant formula food and safety control of children.

Material and Methods

Data were collected from the published literature between 1961 and 2017 by using of the keywords *Enterobacter sakazakii*, *C. sakazakii* without limitation of language (updated 25 October 2017) to search from Web of Science and CNKI. Some reports were excluded based on the same location and time of the event after sorting out and summarizing. The data were analysed using Excel 2007 software.

Results

Infection cases

There were 129 *C. sakazakii* infection cases that were reported globally during 1961-2017. The 129 cases were reported in 28 journals over last 34 years.

Table 1. Reported case of *C. sakazakii* infection worldwide during 1961-2017

Year of report （Year of occurrence）	Country	Number of Cases	Source
1961（1958）	England	2	Urmenyi and Franklin, 1961
1965（1958）	Denmark	1	Joker et al., 1965
1979（1958）	Georgia, USA	1	Monroe and Tift., 1979
1981（1958）	Indiana, USA	1	Kleiman et al., 1981
1981（1958）	Oklahoma, USA	2	Adamson and Rogers, 1981
1982（1980）	Spain	1	Jimenez and Gimene, 1982
1983（1978-1983）	Netherlands	8	Muytjens et al., 1983

1985（1985）	Missouri, USA	1	Naqvi et al., 1985
1987（1984）	Athens, Greece	11	Arseni et al., 1987
1988（1984）	Massachusetts, USA	2	Willis and Robinson, 1988
1989（1986）	Iceland	2	Biering et al., 1989
1989（1987）	Iceland	1	Biering et al., 1989
1989（1988）	Tennessee, USA	4	Simmons et al., 1989
1989（1989）	Portugal	1	Lecour et al., 1989
1990（1988）	Maryland, USA	1	Noriega et al., 1990
1991（1990）	Ohio, USA	1	Gallagher and Ball, 1991
1996（unspecified）	Canada	1	Tekkok et al., 1996
2000（1996）	American	1	Burdette and Santos, 2000
2001（1995-1996）	Massachusetts, USA	5	Lai, 2001
2001（1998）	Belgium	12	Van Acker et al., 2001
2001（1999）	Israel	2	Bar-Oz et al., 2001
2002（1993-1998）	Israel	4	Block et al., 2002
2002（2001）	Tennessee, USA	1	Himelright, 2002
2004（2001）	Indiana, USA	1	Stoll et al., 2004
2007（2002）	India	1	Ray et al., 2007
2007（2006）	India	1	Ray et al., 2007
2008（1994）	France	17	Townsend et al., 2008
2008（2006）	Singapore	1	See et al., 2008
2008（2008）	Korean	4	Beom et al., 2008
2010（2008）	Japan	1	Teramoto et al., 2010
2011（2009）	Tanzania	17	Mshana et al., 2011
2011（2010）	Mexico	2	Flores et al., 2011
2012（2010）	Japan	3	Hamada et al., 2012
2013（2002-2011）	Taiwan, China	5	Tsai et al., 2013
2013（2009-2010）	Argentina	3	Asato et al., 2013
2014（2014）	Sichuan, China	1	Yang et al., 2014
2015（2010）	Mexico	2	Jackson et al., 2015
2017（2015）	Hunan, China	1	Long et al., 2017
2017（2016）	Pennsylvania, USA	1	Bowen et al., 2017
2017（unspecified）	Hubei, China	2	Cui et al., 2017

Typical Cases

In 1961, Urmenyi and Franklin (1961) were the first authors to report two cases of neonatal meningitis caused by *C. sakazakii* in England. Since then a series of infection cases caused by *C. sakazakii* have been reported in the world.

In 1983, Muytjens, et al. (1983) investigated eight neonatal cases of meningitis due to *C. sakazakii* which occurred in the Netherlands with the fatality rate of 75% even though they had been treated using antibiotics. One of the female neonates (2,400g), whose gestational age was at 39 weeks, on the third day of birth, her skin gradually turned yellow-gray and snored frequently. The gram-negative bacteria were shown by Gram staining, and *C. sakazakii* infection was identified after culture identification. Chloramphenicol treatment was stopped and gentamycin was immediately used (5 mg/kg every 24 h), but unfortunately, she died on the fifth day of birth. *C. sakazakii* was isolated and cultured from her brain; thus, the caused bacteremia and meningitis were confirmed. A boy (2,085 g), one of twins, a low birth weight baby, was delivered by caesarian section. After five days of birth, this baby showed abdominal distention and grey skin, leukocyte count of 1,000/mm^3, most of which were neutrophils tested from the extremely low level of cerebrospinal fluid. The baby died on the sixth day and was confirmed to suffer from meningitis and enterocolitis.

In 1991, Gallagher, et al. (1991) reported an infection case caused by *C. sakazakii* in Ohio, USA. A 5-week-old full-term male (2,520g) developed poor feeding, lethargy and apnea after two days. *C. sakazakii* was isolated by blood cultures. After 28 days of ampicillin and cefotaxime treatment, the baby remained asymptomatic and was discharged. Infant was re-admitted to hospital due to fever, drowsiness and poor feeding after 12 days. Meningitis was diagnosed and then recovered following re-treatment with ampicillin and cefotaxime.

The above typical cases demonstrated that neonates, especially low birth weight and preterm infants are susceptible to *C. sakazakii* infection. Chloramphenicol and gentamicin were not effective against the bacteria, but ampicillin and cefotaxime were effective in timely treatment.

Infection symptoms

The symptoms of 129 infection cases are summarized in table 2. Bacteremia was the most common (27 cases, 20.93%), followed by septicemia (24 cases, 18.60%), meningitis (21 cases, 16.28%), and enterocolitis (19 cases, 14.73%). It can be concluded from the table that the most common symptoms are bacteremia, and some patients developed simultaneous meningitis and bacteremia (16 cases，12.40%), simultaneous meningitis and septicemia (2 cases, 1.55%). Patient may show bloody diarrheic syndrome (6 cases, 4.65%) and pneumonia (2 cases, 1.55%), however, some infected patients

did not show obvious symptoms (9 cases, 6.98%). According to reports in the literature, many patients were accompanied by high fever, shortness of breath, seizures, spastic quadriplegia.

Table 2. Symptoms of *C. sakazakii* infection in 129 cases

Infection	Number of Cases	%
Bacteremia	27	20.93
Septicemia	24	18.60
Meningitis	21	16.28
Enterocolitis	19	14.73
Simultaneous bacteremia and meningitis	16	12.40
Bloody diarrheic syndrome	6	4.65
Simultaneous meningitis and septicemia	2	1.55
Pneumonia	2	1.55
No significant symptoms	9	6.98
Unknown	3	2.33
Total	129	100

Patient sex

In 129 cases, only 88 patients were indicated sex in the literature (Table 3). The 88 cases include 46 females and 42 males, showing females are a little more susceptible to infection than males due to probably lower born immunity of the females.

Table 3. Sexual distribution of *C. sakazakii* infection in 88 cases

Sex	Number of Cases	%
Female	46	52.27
Male	42	47.73
Total	88	100

Infection geography

The geographical infection distribution of the 129 cases reported in the literature was shown in table 4. All six continents, except the Oceania, had *C. sakazakii* infection cases. Europe was the highest with 53 cases (41.09%), followed by the North America with 27 cases (20.93%), the Asia with 26 cases (20.16%) and the Africa with 17 cases (13.18%). The South America with three cases (2.32%) was the lowest infection location to *C. sakazakii*. It is worth noting that there were few residents in the North Atlantic with infection reports (3 cases, 2.32%). There was no infection report in the South Atlantic. However, there would be infection with *C. sakazakii* as long as there are residents as *C. sa-*

kazaki seems extremely geographical adaptable with human resident.

Table 4. Geographical distribution of *C. sakazakii* infection in129 cases

Location	Number of Cases	%
Europe	53	41.09
North America	27	20.93
Asia	26	20.16
Africa	17	13.18
South America	3	2.32
North Atlantic	3	2.32
Total	129	100

Antibiotic therapy

Of the 129 cases, 38 patients died of antibiotic resistance and low immunity, and lack of timely treatment or improper treatment. The remaining 91 patients survived following antibiotics treatment, but most survivors were accompanied by sequelae, especially for neonates, such as mental decline, delirium, hearing and vision loss. Different hospitals had different antibiotics therapy. However, there were no treatment report in those publication.

Characteristic of infant infection

Of the 129 cases, 15 patients were in adults, accounting for 11.63%. Except for one patient with 37 years old, all patients were over 60 years old and over half were over 70 years old. Those patients usually had diabetes, congenital heart disease or cancer before *C. sakazakii* infection.

The remaining 114 cases were infants, accounting for 88.37% of the total. Most patients suffered from low immunity and they tended to have fever, skin discoloration, and a decrease in leukocyte count before the infection. Therefore, the susceptible population to *C. sakazakii* infection is infants with low immunity, followed by the elderly with chronic disease.

Of the 114 infant cases, only 99 patients were reported their specific age (Table 5). The most susceptible population were neonates within one month old (75 cases), followed by infants elder than 1 month and within 1 year old (19 cases, 19.19%). Children over 1 year old had a very low probability of infection (5 cases, 5.05%). Therefore, more concern should be taken on infants within 1 year old of age, especially in neonates.

Table 5. Age distribution of *C. sakazakii* infection in 99 cases

Age	Number of Cases	%
Neonates (0-1 months)	75	75.76
Infant (1-12 months)	19	19.19
≥1 year old	5	5.05
Total	99	100

Gestational age

Gestational age (<37 weeks) is called as pregnancy and 37-42 weeks called full term. The 68 cases of infants reported in literature were classified by stages of pregnancy as shown in table 6. The remaining 46 cases had not been described. Premature baby were 50 cases, accounting for 73.53% whereas full term pregnancy baby were 18 cases, accounting for 26.74%. Thus, patients are mainly preterm infants while the infants with full term has a low chance of infection (18 cases, 26.47%).

Table 6. Stage of pregnancy of *C. sakazakii* infection in 68 cases

Pregnancy	Number of Cases	%
Premature	50	73.53
Full term	18	26.47
Total	68	100

Birth weight

For this study, birth weight <1,000 g was classified as extremely low birth weight (ELBW), <1,500 g as very low birth weight (VLBW), <2,500 g a low birth weight (LBW) , and normal weight is 2,500-4,000 g. The 52 cases of infants reported in literature were classified by birth weight and the remaining 62 cases had not been described (Table 7). Within these 52 infection cases, 13 (25%) had ELBW, 11 (21.15%) VLBW, and 13 (25%) LBW, accounted for 71.15% of the total, while 15 (28.85% had normal weight. So, the birth weight of the main patient group was lower than normal birth weight.

Table 7. Birth weight of *C. sakazakii* infection in 52 cases

Birth weight	Number of Cases	%
ELBW	13	25
VLBW	11	21.15
LBW	13	25
Normal weight	15	28.85
Total	52	100

Results from table 6 and table 7 indicated that the susceptible population of *C. sakazakii* are neonates with premature birth, low birth weight and low immunity.

Cause of infection

The causes for infection of 114 infants were considered mainly as infant formula and feeding utensil like bottles, spoons, powdered milk cans and medical equipment which were not completely disinfected. Therefore, the key for the risk reduction of infant infection is to prevent possible contamination with *C. sakazakii* during the production and consumption of infant formula.

Conclusion

There were continuous reports of infection cases worldwide after the first case of *C. sakazakii* was reported in England. *C. sakazakii* was a global pathogenic bacterium with a wide geographical distribution. The prevalence in Europe, North America and Asia were high, with 41.09%, 20.93%, and 20.16% respectively. Most of the cases were reported away from China, which showed that China must pay attention to the existence of *C. sakazakii* while importing infant formula. The main susceptible population is infants, especially for neonates with premature birth, low birth weight, and low immunity, followed by the elder with chronic disease. There was no significant difference of infections with sexual distribution. Patients were susceptible to bacteremia, septicemias, meningitis, and enterocolitis, and the proportions were 20.93%, 18.60%, 16.28%, and 14.73% respectively. These infections had an effect on the growth of infants. The mortality rate of the 129 cases reported in the literature was about 30%, but it can be up to 75% in an infection event. The best antibiotic treatment regime has not been reported. Many patients died of improper treatment or survived with sequelae. *C. sakazakii* is easy to survive in infant formula. The main source of infection is infant formula and related feeding-equipment. *C. sakazakii* is the main threat to the health of infants, attracting a great concern from manufacturers, governments, regulators and consumers. The key to avoid the risk of infection is to prevent the contamination of infant formula and milk powder products from the bacteria during the production process. The proper disinfection of related utensils is also a step that should not be overlooked. The available literature showed that research on the treatment for *C. sakazakii* infection will need further attention in the future.

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