Eur J Clin Microbiol Infect Dis (2009) 28:1297–1304
DOI 10.1007/s10096-009-0779-4

ARTICLE

Epidemiology of invasive neonatal *Cronobacter* (*Enterobacter sakazakii*) infections

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Received: 9 April 2009 / Accepted: 10 July 2009 / Published online: 7 August 2009

Abstract About 120–150 neonatal *Cronobacter* spp. (*Enterobacter sakazakii*) infections have been described. An analysis of current case numbers, epidemiological measures and risk factors is warranted. Data of microbiologically confirmed cases, published between 2000 and 2008, have been analysed statistically. More than 100 neonatal *Cronobacter* infections have been reported in this period. The overall lethality of the 67 invasive infections was 26.9%. The lethality of *Cronobacter* meningitis, bacteraemia and necrotising enterocolitis (NEC) was calculated to be 41.9% ($P<0.0001$), <10% and 19.0% ($P<0.05$), respectively. Logistic regression models ($P<0.0001$) revealed a higher gestational age at birth and parentage not from Europe as significant factors for a higher reporting probability of neonatal *Cronobacter* meningitis. Neonates with *Cronobacter* meningitis not originating from North America have a higher risk for lethal outcome than other neonatal *Cronobacter* infections ($P<0.0001$). Continental differences of risk factors for *Cronobacter* meningitis and for the lethal outcome of neonatal meningitis should be elucidated. Neonatal *Cronobacter* infections are mainly associated with the contamination of infant formula and of the relevant cleaning and preparation equipment. Eleven neonatal *Cronobacter* infections, not caused by contaminated infant formula, have been retrieved. Other environmental sources of infection should be considered. Consistent and sufficiently informative data of invasive neonatal *Cronobacter* infections should be recorded in a centralized reporting system.

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Introduction

Cronobacter spp. (*Enterobacter sakazakii*) is a ubiquitous agent causing infrequent infections in immunologically incompetent patients of all age groups. In 2008, *E. sakazakii* was reclassified as the new genus *Cronobacter* spp. including the six species *C. sakazakii*, *C. turicensis*, *C. muytjensii*, *C. malonaticus*, *C. dublinensis* and *Cronobacter* genomospecies I [1]. The limited epidemiological information about invasive neonatal *Cronobacter* infections warrants a summary of the current knowledge regarding case numbers, frequency, fatality rates and risk factors of neonatal meningitis, bacteraemia and necrotising enterocolitis (NEC). Globally, about 120–150 cases have been reported in the high-risk group of infants up to 2 months of age [2, 3]. The main clinical features of *Cronobacter* infections in neonates are meningitis, septicaemia and NEC [4–6]. The relevance for public health is due to the high rate of fatal outcome and neurological complications of neonatal *Cronobacter* infections. Diarrhoea, urinary tract infections and conjunctivitis [4, 7] occur even less frequently in neonates. In extensive outbreaks, more than ten neonates may be affected simultaneously [7–9]. In 2–12-month-old infants, some single *Cronobacter* infections (bacteraemia, urinary tract infections) have been described [10–12]. Recently, suspicious cases of *Cronobacter* meningitis have been reported in infants >2 month of age [13]. A further 18 cases of (meningitis or) bacteraemia in infants aged 1–11 months have been reported by the laboratory summary of the United Kingdom 1997–2007 to the FAO/WHO [14]. Hence, *Cronobacter* infections in neonates are very rare acute diseases, reliable incidence rates are not available. In the USA, incidences of one *Cronobacter* infection per 100,000 infants, 8.7 per 100,000 low-birth-weight neonates [8] and one *Cronobacter* infection per

10,660 very-low-birth-weight neonates [15] have been reported. In addition to powdered infant formula (PIF) as the main source of neonatal *Cronobacter* infections, contamination of the preparation and cleaning equipment and the hospital environment should be considered [16]. Some reports describe the problem of contaminated infant formula [17–20] and *Cronobacter* infections [21–23] in less developed countries with complicated climatic and hygienic conditions. In young children, six cases of bacteraemia [4, 14, 24, 25] and a case of an infected intradural dermoid cyst [24] have been known. Further 27 clinical *Cronobacter* isolates from young children aged 1–4 years have been reported in England and Wales to the FAO/WHO in 2008 [14]. In general, *Cronobacter* infections in infants are associated with intensive medical interventions or immunodeficiency syndrome. In 2008, the FAO/WHO summarised the current knowledge about invasive *Cronobacter* infections in infants and young children in a detailed meeting report. The main purpose of this expert group was to examine the risk of infection by follow-up-formula in infants >6 months of age [14]. Because of the less severe nature of the illness, little attention is focused on *Cronobacter* infections in adults. Recently, the FAO/WHO cited interesting cases of colonisation and infection with *Cronobacter* spp. in the elderly population [26, 27] and mentioned the necessity of systematic reviews of *Cronobacter* infections in adults [13]. The majority of *Cronobacter* infections in infants [28] and adults [11, 29, 30] is health care-related. In the European Union, the Rapid Alert System for Food and Feed (RASFF) and the Early Warning and Response System (EWRS) are tools to promote the prevention and control of communicable diseases, including (risk factors for) *Cronobacter* infections. Microbiological criteria for food and process hygiene, relevant for the European Economic Area (EEA), consider *Cronobacter* spp. as a possible risk factor in PIF and dried dietary foods for special medical purposes for infants <6 month of age [31].

Reports of microbiologically confirmed *Cronobacter* infections in neonates, published between 2000 and 2008, have been included in this literature and data analysis. More than 100 cases of neonatal *Cronobacter* infections have been reported in this period. The overall lethality of the 67 invasive cases with known outcome data was 26.9%. The lethality of *Cronobacter* meningitis, bacteraemia and NEC was 41.9% ($P<0.0001$), <10% and 19.0% ($P<0.05$), respectively.

Logistic regression models ($P<0.0001$) revealed a higher gestational age at birth and parentage not from Europe as significant factors for a higher reporting probability of neonatal *Cronobacter* meningitis. Neonates with parentage from North America have a lower probability ($P<0.01$) of dying from *Cronobacter* meningitis. These epidemiological measures of lethality and risk factors are based on limited numbers of reported cases and on different case recruitment strategies. Further consistent and sufficiently informative data of neonatal *Cronobacter* infections should be recorded in a centralised reporting system.

Materials and methods

Data of microbiologically confirmed neonatal *Cronobacter* spp. (*E. sakazakii*) infections have been extracted from scientific publications and from international (FAO, WHO), European (RASFF, EWRS) and national epidemiological reports or reporting systems. PubMed, ISI (Web of Science) and Scopus abstract and citation databases, as well as the alert systems of big publishers (ASM, Blackwell, Elsevier, Oxford and Springer), were searched using the following keywords: *E. sakazakii*, *Cronobacter*, neonate, infant, newborn, NICU; described anywhere in the text; without limitation of language; published between 2000 and 2008 (updated 31 March 2009). Cases of haemorrhagic colitis have been coded as cases of NEC for statistical modelling. Bacteraemia, sepsis and septicaemia have been used synonymously. Colonisations without clinical signs of infection have not been considered as cases of infection. Information about continental parentage, kind and outcome of infection was available for 67 invasive *Cronobacter* infections in neonates (aggregated data sets). Information about further risk factors like gestational age at birth, birth wight, onset of infection and gender has been available for 59 cases (complete data sets). Calculations have been carried out with SAS 9.1.—Enterprise Guide 2.1. Logistic regression models are based on the complete data set for dependent and effect variables of invasive neonatal *Cronobacter* infections during the period 2000–2008. Logistic regression models have been performed for the dependent variables ‘kind of infection’ (i.e. meningitis, sepsis or NEC) and ‘outcome of infection’ (i.e. death), respectively. Birth weight, day of onset, gender, gestational age at birth, kind of infection and parentage have been investigated as effect (or independent) variables in the relevant univariate logistic regression models, respectively. In the following model steps, significant variables have been included in multivariate logistic regression models (forward selection procedure), respectively. P-values≥ 0.05 were considered as statistically not significant (n.s.).

Results

Epidemiology of neonatal *Cronobacter* infections published 2000–2008

Microbiologically confirmed cases of *Cronobacter* infections in neonates published 2000–2008 are summarised in Table 1.

The overall case fatality rate of invasive neonatal *Cronobacter* infections was 26.9%. The lethality of *Cronobacter* meningitis, *Cronobacter* septicaemia and *Cronobacter* NEC were calculated to be 41.9% ($P<0.0001$), <10% (n.s.) and 19.0% ($P<0.05$), respectively.

Significant logistic regression models for all kinds of invasive neonatal *Cronobacter* infections in the years 2000–2008 have been summarised in Table 2 according to the goodness of fit. The model with the best adaptation to the data comprises the bivariate model no. 5 with the significant

Table 1 Neonatal *Cronobacter* infections published 2000–2008

Year	Cases	Infection	Outcome	Location	Source
1992	1	Meningitis	Death	India	[21]
1994	10	NEC (7), meningitis (1), septicaemia (2)	Death (4)	France	[50]
1998	12	NEC (12), bacteraemia (1)[#]	Death (2)	Belgium	[9]
1998	4	Bacteraemia	Cure	Brazil	[14]
1998	12	Bacteraemia, urinary tract infection	Unknown	Philippines	[14]
1999	1	Meningitis	Neurological complication	USA	[51]
2000	2	Meningitis (1), septicaemia (1)	Cure	Israel	[23]
2001	1	Septicaemia	Cure	USA	[15]
2001	1	Meningitis	Death	USA	[8]
2001	2	Meningitis, urinary tract infection	Cure	USA	[14]
2002	1	Meningitis	Death	Belgium	[52]
2002	1	Meningitis	Death	Brazil	[22]
2002	3	Meningitis	Death (1), neurological complication (1)	USA	[14]
2002	2	Invasive infection	Unknown	USA	[14]
2003	4	Meningitis (2), bacteraemia (2)	Death (1)	USA	[14]
2004	1	Meningitis	Death	New Zealand	[53]
2004	4	Meningitis (2), haemorrhagic colitis (1), conjunctivitis (1)	Death (2)	France	[7, 54]
2004	1	Meningitis	Neurological complication	USA	[14]
2004	1	Invasive infection	Unknown	The Netherlands	[37]
2005	1	Septicaemia	Cure	Slovenia	[55]
2005	1	Meningitis	Neurological complication (1)	USA	[14]
2006	1	Bacteraemia	Cure	Spain	[56]
2006	2	Meningitis	Death (2)	Switzerland	[57]
2006	2	Meningitis	Unknown	Hungary	[58]
2006	3	Meningitis	Neurological complication (2)	USA	[14]
2007	7	Meningitis (3), bacteraemia (3), NEC (1)	Death (1), neurological complication (10)	USA	[14]
2007	1	Meningitis	Unknown	Spain	[59]
2008	1	Meningitis	Neurological complication	Japan	[14]
2008	2	Meningitis	Neurological complication (1)	USA	[14]
2008	1	Meningitis	Cure	Canada	[14]
2008	1	Invasive infection	Unknown	USA	[60]
2008	1	Meningitis	Cure	Korea	[13]
1987–2000	3	Meningitis, septicaemia, conjunctivitis	Unknown	Israel	[14]
1992–2007	14	Meningitis, septicaemia	Unknown	England and Wales	[14]
All	105				
In detail*	67		Death (18)		

*Invasive cases with known outcome

[#] One fatal case with simultaneous NEC and septicaemia

Adapted from Table 3 in Friedemann (2008) [16]

Table 2 Risk factors of neonatal *Cronobacter* infections in 2000–2008

Model		Model quality		Variables		Results					Interpretation
No.	Logistic	Likelihood	BIC[#]	Dependent	Effect	*z*-score	CI_z (95%)	*P*-value	OR	CI (95%)	Reporting probability (RP)*
1	Univariate	<0.0001	64.5	Meningitis	Gestational age**	0.4	0.2–0.6	0.0002	1.4	1.2–1.7	Higher RP of meningitis at a higher gestational age
2	Univariate	<0.0001	70.3	Meningitis	EU	−2.5	−3.8–(−1.4)	<0.0001	0.08	0.02–0.28	Lower RP of meningitis with EU parentage
3	Univariate	=0.0008	78.7	Meningitis	North America	1.9	0.8–3.1	0.002	6.5	2.0–21.0	Higher RP of meningitis with parentage from North America
4	Univariate	=0.0020	80.4	Meningitis	USA	1.7	0.6–3.0	0.003	5.7	1.8–18.0	Higher RP of meningitis with USA parentage
5	Bivariate	<0.0001	54.5	Meningitis	Gestational age**	0.3	0.1–0.5	0.007	1.3	1.1–1.6	Higher RP of meningitis at a higher gestational age with non-EU parentage
					Non-EU	2.8	1.3–4.5	0.0006	15.9	3.3–78.0	
6	Bivariate	<0.0001	63.6	Meningitis	Gestational age**	0.3	0.1–0.5	0.003	1.4	1.1–1.7	Higher RP of meningitis at a higher gestational age with parentage from North America
					North America	1.6	0.2–3.0	0.03	4.8	1.2–19.8	
7	Bivariate	<0.0001	64.2	Meningitis	Gestational age**	0.3	0.1–0.5	0.002	1.4	1.1–1.7	Higher RP of meningitis at a higher gestational age with USA parentage
					USA	1.5	0.1–2.9	0.04	4.4	1.1–17.8	
8	Univariate	=0.0065	71.6	Death	Meningitis	1.7	0.4–3.1	0.01	5.3	1.5–19.0	Higher probability of death in cases of meningitis
9	Bivariate	<0.0001	63.5	Death	Meningitis	3.2	1.5–5.3	0.0007	23.9	3.8–150.4	Higher probability of death in cases of meningitis with Non-North American parentage
					Non-North America	1.4	0.6–2.5	0.003	16.8	2.6–107.5	
10	Bivariate	=0.0002	66.1	Death	Meningitis	2.8	1.3–4.6	0.0009	16.3	3.1–84.5	Higher probability of death in cases of meningitis with non-USA parentage
					Non-USA	1.2	0.4–2.1	0.006	10.6	1.9–56.6	

*Compared with the remaining cases of neonatal *Cronobacter* infections reported in 2000-2008, respectively

**At birth

[#] Bayesian information criteria (Schwarz)

risk factors of gestational age at birth and parentage not from the EU for the outcome of meningitis. Neonates with meningitis not originating from North America have the highest risk for lethal outcome (model no. 9).

Significant logistic regression models based on the data of neonatal *Cronobacter* meningitis cases in 2000–2008 have been summarised in Table 3. Among the reported cases of *Cronobacter* meningitis, parentage from North America (model no. 12), and parentage from the USA (model no. 13) is associated with a lower probability of death, respectively. The gestational age of cases of neonatal *Cronobacter* meningitis from South America and other

Table 3 Risk factors for death in neonatal *Cronobacter* meningitis in 2000–2008

Model		Model quality		Variables		Results					Interpretation*
No.	Logistic	Likelihood	BIC[#]	Dependent	Effect	z-score	CI_z (95%)	p	OR	CI (95%)	
11	Univariate	0.0007	35.0	Death	EU	n.s.			n.s.		Not possible
12	Univariate	0.0013	36.2	Death	North America	−2.8	−4.9–(−1.0)	0.004	0.06	0.01–0.4	Lower probability of death with parentage from North America
13	Univariate	0.0051	38.8	Death	USA	−2.3	−4.2–(−0.7)	0.0095	0.10	0.02–0.6	Lower probability of death with parentage from USA

*Compared with the remaining cases of neonatal *Cronobacter* meningitis in 2000–2008

[#] Bayesian information criteria (Schwarz)

continents (Asia, Australia and Oceania) does not differ from the gestational age at birth of the remaining cases of neonatal *Cronobacter* meningitis. For illustrating previous modelling, the corresponding aggregated case numbers and fatality rates of invasive neonatal *Cronobacter* infections have been stratified by continents as shown in Table 4.

Reporting of *Cronobacter*-contaminated powdered infant formula in Europe

RASFF alerts concerning *Cronobacter* in PIF are summarised in Table 5. During the reporting period 2002–2008, *Cronobacter* infection and colonisation had been associated with three of the 11 reported contaminated PIF products. Two of the three products associated with diseases have been intended as dietary products for special medical purposes, i.e. one product of PIF for premature neonates and one product of hypoallergenic PIF, respectively.

Cronobacter infections in infants not related with powdered formulae

Between 2000 and 2008, 11 cases of invasive *Cronobacter* infections in neonates and infants not fed with powdered infant or follow-up formula have been reported (Table 6). Nine of these 11 cases are health care-related infections. Four of five *Cronobacter* infections occurred in infants treated in intensive medical units. Further cases of *Cronobacter* infections in infants with other environmental sources of infections, e.g. drinking water installations [14, 32] and intensive medical interventions [12] have been described.

Discussion

The lethality of neonatal *Cronobacter* infections, especially of neonatal *Cronobacter* meningitis, remains at a high level. So far, reliable rates of incidence, neurological complications and lethality of neonatal *Cronobacter* infections could not be reported due to missing or different reporting criteria. Most of the available data have derived from case and outbreak descriptions. Some data of sporadic cases have been communicated by passive reporting (systems) of clinical or laboratory data. Further submerged information have been retrieved actively by organised calls for data [33] or sporadical personal requests. After the occurrence of clustered cases, passive reporting systems have been established, e.g. for invasive *Cronobacter* infections in infants up to 12 months of age in the USA [8] and for *Cronobacter* meningitis in New Zealand [34]. In Brazil and Hungary, *Cronobacter* infections are mandatorily notifiable diseases [14]. Cases of bacteraemia (and meningitis) with the related age (groups) have been reported

Table 4 Case fatality rates of neonatal *Cronobacter* infections stratified by continents

Continent	All			Meningitis			Sepsis			NEC		
Europe	36.7%	(11/30)	$P<0.0005$	100%	(6/6)		11–20%[#]	(1/5)[#]		23–25%[#]	(5/20)[#]	
North America	15.4%	(4/26)	$P<0.05$	26%	(4/19)		0%	(0/6)		0%	(0/1)	
Other*	27.3%	(3/11)	n.s.	50%	(3/6)		0%	(0/5)		–	(0/0)	
All	26.9%	(18/67)		41.9%	(13/31)	$P<0.0001$	3–6%[#]	(1/16)[#]	n.s.	19.0%[#]	(5/21)[#]	$P<0.05$

Based on the aggregated data set

*Asia, Australia, South America, Oceania

[#] One fatal case with simultaneous NEC and septicaemia

Table 5 Notification of *Cronobacter* spp. in the European Rapid Alert System for Food and Feed (RASFF)

Year	Powdered infant formula (PIF)		Detection of *Cronobacter* spp. in:		RASFF no.
	Origin	Distribution	PIF (quant.)	Infants (qual.)*	
2002	Germany	Belgium	4/100 g	1	190/2002
2004	Netherlands	France, Algeria, Italy	1–10 CFU/100 g	9	658/2004
2006	Denmark	Cyprus	pos./sample	n.k.	699/2006
2007	Germany	Bulgaria, Germany	pos./25 g	n.k.	383/2007
2007	Germany	Bulgaria, Germany, Latvia	pos./10 g	n.k.	391/2007
2007	Switzerland	Spain, Switzerland	pos./10 g	1	452/2007
2007	Netherlands	Germany, Luxembourg, Austria, Spain, Slovenia	3 CFU/100 g	n.k.	470, 471/2007
2007	Germany	Austria, Czech Republic, Slovakia, Croatia, Slovenia	3.6 CFU/100 g	n.k.	472/2007
2007	Germany	Austria, Germany, Spain, Croatia, Slovenia	pos./10 g	n.k.	618/2007
2007	Uganda	Great Britain	pos./1 g	n.k.	BOG/2007
2007	Germany	Germany	pos./25 g	n.k.	CBU/2007

*Number of associated cases

n.k. = not known

Adapted from Table 2 in Friedemann (2008) [16]

in England and Wales [35]. In Canada, adverse symptoms associated with the consumption of infant formulae should be reported to local food inspection agencies [36]. National epidemiological bulletins have reported current *Cronobacter* infections, e.g. in the Netherlands [37] and in France [7], as well as surveys of *Cronobacter* infections [38]. In the Norwegian national register for nosocomial infections, *Cronobacter* spp. is registered as a causative agent [39]. Laboratory data-based *Cronobacter* infections have been reported, e.g. from England, Wales and Northern Ireland [40] and the Philippines [14]. In most countries, foodborne diseases or outbreaks should be reported to local authorities. In notifications of the European RASFF about contaminated PIF, three associated cases (Table 1) have been known. "Affected persons associated with the dangerous subject" is a notification parameter of the RASFF. Even in 2009, notifications of contaminated infant formulae have appeared [41]. Via the European EWRS, outbreaks will be communicated to the competent public health authorities [42].

The main source of neonatal *Cronobacter* infections, contaminated PIF, has been ascertained in various outbreaks [7, 9, 43, 44] and single cases [4, 45]. The environment in PIF processing facilities has to be regarded as potentially contaminated. Manufacturers of powdered formulae for infants and young children should control the microbiological hazards in the raw materials during the

Table 6 *Cronobacter* infections in infants not fed with powdered infant formula (PIF) published in 2000–2008

Infection	Nosocomial	Age at onset (days)	Birth weight (g)	Medical condition**	Feeding**	Country	Source
Bacteraemia	Yes	12	1,091	NICU	Parenteral, breast milk, RTF premature infant formula	USA	[15]
Meningitis*	No	14	2,650	/	Breast milk	Brazil	[22]
Bacteraemia	Yes	60	/	PICU	Breast fed	India	[21]
Bacteraemia	Yes	5	1,715	NICU	Parenteral	Spain	[56]
Meningitis	No	20	3,300	Icterus	Breast fed	Korea	[13]°
Bacteraemia*	Yes	60	/	PICU	Unknown	Spain	[11]
Bacteraemia	Yes	60	/	/	Breast fed	India	[14]
Bacteraemia (four cases)	Yes	/	/	/	Parenteral	Brazil	[14]

*Fatal cases

**Pre-infection

°Personal communication

RTF = ready-to-feed

whole processing chain and of the final products according to international recommendations and European legislation [31, 46, 47]. Atypical *Cronobacter* infections like conjunctivitis and urinary tract infections are unlikely to be directly related with contaminated PIF. The hospital environment, e.g. water outlets, medical equipment, surfaces and interpersonal contacts, may act as sources of infection, since *Cronobacter* spp. has been isolated from, e.g. incubators for newborn infants [48], the stethoscope of a physician [49], the sinks of a maternity ward, as well as from contaminated infusion [32] and blood culture bottles [49].

The present statistical analyses are based on spontaneously published case reports and on additionally actively reported data of neonatal *Cronobacter* infections in response to the call for data. Consequently, interpretations of statistical models refer to this database. Bowen and Braden found similar results of a higher gestational age and birth weight in cases of *Cronobacter* meningitis in comparison to *Cronobacter* bacteraemia in infants, respectively [28]. Continental differences in case numbers and fatality rates in neonatal *Cronobacter* meningitis are noticeable. They may depend on different health care-related, therapeutic and infection control procedures, on seasonal and climatic differences, as well as genetic aspects of cases. The kind and the direction of a possible publication and reporting bias, e.g. concerning the number of related cases, kind of outcome, location of acquisition, case reporting and data recruitment strategies, and case numbers from less developed countries, should be considered. Other feasible causes like differences in the microbiological agent have not been indicated. While the virulence factors among the *Cronobacter* genus remains to be described, each species has to be considered as virulent. The generality of present conclusions should be confirmed by models of comprehensive data, which are, so far, not available. For a reliable risk assessment, a consistent reporting system for *Cronobacter* infections in neonates and infants should be established.

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