Systematic review of invasive *Acinetobacter* infections in children

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INTRODUCTION: Clinicians are generally familiar with *Acinetobacter* as an etiological agent for serious nosocomial infections in intensive care units. However, there are no previous reviews of the full spectrum of invasive infections in children.
METHODS: A systematic review of the literature was completed up to December 2008 for reports of invasive *Acinetobacter* infections in children.
RESULTS: There were 101 studies that met the inclusion criteria including 18 possible outbreaks, 33 case series and 49 case reports. Suspected outbreaks were concentrated in neonatal intensive care units (16 of 18 outbreaks) and involved bacteremia or meningitis. Proof of isolate clonality or identification of the source of the outbreak was seldom established. Case series were primarily of children younger than five years of age presenting with bacteremia (sometimes multiresistant), meningitis, endocarditis or endophthalmitis, with many community-acquired infections being reported from India. Case reports consisted of unique presentations of disease or the use of novel therapies. Attributable mortality in the outbreaks and case series combined was 68 of 469 (14.5%).
DISCUSSION: Invasive *Acinetobacter* infections in children usually manifest as bacteremia, meningitis or both, but can result in a wide variety of clinical presentations. Outbreaks are primarily a problem in newborns with underlying medical conditions. Most reports of community-acquired infections are from tropical countries. The study of the mechanism of colonization and infection of children in intensive care units and of neonates in tropical countries may provide some insight into prevention of invasive infections.

Key Words: Acinetobacter *infections; Bacteremia; Disease outbreak; Meningitis*

Une analyse systématique des infections envahissantes à *Acinetobacter* chez les enfants

INTRODUCTION : D'ordinaire, les cliniciens connaissent l'*Acinetobacter* comme agent étiologique de graves infections nosocomiales dans les unités de soins intensifs. Cependant, il n'existe pas d'analyse de tout le spectre des infections envahissantes chez les enfants.
MÉTHODOLOGIE : Les chercheurs ont procédé à une analyse systématique des publications jusqu'en décembre 2008 afin d'extraire les déclarations d'infections envahissantes à *Acinetobacter* chez les enfants.
RÉSULTATS : Cent une études respectaient les critères d'inclusion, y compris 18 éclosions éventuelles, 33 séries de cas et 49 rapports de cas. Les éclosions présumées étaient concentrées dans des unités de soins intensifs néonatals (16 sur 18) et mettaient en cause des bactériémies ou des méningites. On établissait rarement la preuve de la clonalité des isolats ou la source des éclosions. Les séries de cas se composaient surtout d'enfants de moins de cinq ans ayant une bactériémie (parfois multirésistante), une méningite, une endocardite ou une endophtalmie, de nombreuses infections non nosocomiales provenant de l'Inde. Les rapports de cas portaient sur des présentations uniques de la maladie ou sur le recours à des thérapies novatrices. Les décès attribués aux éclosions et aux séries de cas totalisaient 68 cas sur 469 (14,5 %).
EXPOSÉ : Les infections envahissantes à *Acinetobacter* chez les enfants se manifestent généralement sous forme de bactériémie, de méningite ou de ces deux maladies, mais elles peuvent s'associer à de nombreuses présentations cliniques. Les éclosions sont surtout problématiques chez les nouveau-nés ayant des problèmes de santé sous-jacents. La plupart des rapports d'infections non nosocomiales proviennent de pays tropicaux. L'étude du mécanisme de colonisation et d'infection des enfants aux unités de soins intensifs et des nouveau-nés de pays tropicaux pourrait donner un aperçu de la prévention des infections envahissantes

The *Acinetobacter* genus is a group of immotile, aerobic, non-fermenting Gram-negative coccobacilli found in soil and fresh water (1). *Acinetobacter* species have become an important culprit in nosocomial infection (1) and, in recent years, have displayed increasing resistance to a broad range of antimicrobials (2-4). The purpose of the present study was to perform a systematic review of the literature on *Acinetobacter* invasive infection in pediatric patients to describe the epidemiology and outcome of reported cases. This may aid clinicians in outlining the prognosis for children with invasive infections and guide them when they suspect an outbreak due to *Acinetobacter* species.

METHODS

Inclusion criteria
All studies that provided information on the clinical course of one or more cases of *Acinetobacter* infection isolated from a normally sterile site in children up to 18 years of age were included in the present review (studies till December 2008). There was no date or foreign language restrictions. Translation was only available for French language articles; otherwise data were mainly derived from an English abstract if provided. Reports that described colonization, pneumonia or soft tissue infections were excluded, unless the organism was also grown from blood cultures or from a normally sterile site. Studies that involved both children and adults were included if the clinical information on pediatric patients could be ascertained.

Classification of studies
Studies were classified into one of three categories: outbreaks, case series or case reports. Studies describing nosocomial *Acinetobacter* infections or colonization (with a minimum of one case of invasive disease) that were believed by the study

TABLE 1
Characteristics of pediatric *Acinetobacter* outbreaks with at least one case of invasive infection

Ref	Year	Country	Cases of invasive infection, n	Setting	Bacteremia, n	Meningitis, n	Deaths from any cause, n	Deaths from *Acinetobacter*, n	Species
5	2008	Turkey	5	NICU	5	NR	NR	2	*A septicus*
6	2007	Taiwan	1	NICU	1	NR	0	0	*A baumannii*
7	2006	Venezuela	16	NICU	16	2	NR	NR	*A* RUH 1139
8	2005	Brazil	11	NICU	11	NR	3	3	*A baumannii*
9	2003	India	36	NICU	36	9	13	NR	*A baumannii*
10	2003	Israel	9	NICU	9	2	3	NR	*A baumannii*
11	2002	Taiwan	9	NICU	9	NR	3	0	*A baumannii*
12	2001	South Africa	7	PICU/NICU	5	NR	NR	NR	*A calcoaceticus*
13	2000	Germany	3	Pediatric oncology ward	3	0	NR	NR	*A junii*
14	1999	Netherlands	6	NICU	6	NR	NR	0	*A junii*
15	1999	South Africa	4	NICU	4	NR	1	1	Not specified
16	1998	Bahamas	8	NICU	8	0	6	3	*A baumannii*
17	1993	Israel	9	NICU	9	0	4	4	Not specified
18	1991	Chile	21	NICU	21	NR	NR	NR	*A calcoaceticus*
19	1990	Germany	6	NICU	6	NR	0	0	*A calcoaceticus*
20	1989	United Kingdom	7	NICU	7	NR	0	0	*A lwoffi*
21	1983	United Kingdom	2	Burn unit	2	NR	2	NR	*A calcoaceticus*
22	1982	United Kingdom	4	NICU	NR	4	NR	0	*A calcoaceticus*

All species belong to the Acinetobacter *genus. NICU Neonatal intensive care unit; NR Not reported; PICU Pediatric intensive care unit; Ref Reference*

authors to be epidemiologically linked were classified as outbreaks. Studies describing two or more cases (including at least one child) that were not believed to have a common source were classified as a case series. The remaining studies, generally individual reports of interesting manifestations of *Acinetobacter* infection, were classified as case reports.

Search strategy

The English and foreign-language literature on *Acinetobacter* species was searched using MEDLINE, EMBASE, PUBMED, and SCOPUS databases in December 2008. For MEDLINE, all subject headings were checked off when terms were mapped. The study was limited to "all children, 0-18 years". For EMBASE, all subject headings were checked off when terms were mapped. The study was limited to "infant", "child", "preschool child", "school child" and "adolescent". For PUBMED, the study was limited to "all child: 0 to 18 years". For SCOPUS, an advanced search was conducted with "*Acinetobacter* AND infant* or child* or newborn* or neonate* or neonatal or preschool* or adolescent* or teen*or toddlers*".

For the above four database searches, "*Acinetobacter*" was used as the first search term. The nomenclature for *Acinetobacter* species has changed over the decades, and all other known terms for any species of the bacteria were also searched with the four databases – these were *Mima polymorpha, Herellea vaginicola,* B5W, *Bacterium anitratum, Achromobacter haemolyticus* var. *glucidolytica, Achromobacter conjunctivae, Moraxella glucidolytica, Achromobacter anitratus, Neisseria winogradskyi, Micrococcus calcoaceticus, Diplococcus mucosus, Achromobacter citroalcaligenes, Achromobacter haemolyticus* var. *alcaligenes, Alcaligenes metalcaligenes, Achromobacter lwoffii, Moraxella lwoffii* and *Alcaligenes hemolysis.*

Data extraction

Data extraction was performed by both authors. Relevant clinical information on the course of *Acinetobacter* infection was collected.

RESULTS

There were 101 studies that met the inclusion criteria including 18 outbreaks, 33 case series, and 49 case reports. There were 28 studies up to 1970, 13 from 1971 to 1990, and 70 from 1991 to 2008.

Outbreaks

Eighteen of the studies (5-22) described outbreaks, beginning in 1982 (Table 1). The frequency of outbreak reports has been increasing, with nine of the 18 outbreaks reported within the past 10 years. Outbreaks were reported from Europe (seven studies), Asia (three studies), South America (three studies), Africa (two studies), the Middle East (two studies) and the Carribbean (one study).

Fifteen of the 18 outbreaks occurred in neonatal intensive care units (NICUs) with another occurring in a combined NICU and pediatric intensive care unit (PICU). There was an outbreak reported from a burn unit (21) and from a pediatric oncology ward (13). The number of cases of invasive *Acinetobacter* infection varied from one to 36 per outbreak (median: seven cases), with colonized patients also being reported in many outbreaks.

A variety of *Acinetobacter* species were implicated in the outbreaks: *Acinetobacter baumannii* (six studies), *Acinetobacter calcoaceticus* (five studies), *Acinetobacter junii* (two studies), *Acinetobacter lwoffii* (one study) and unspecified species (two studies). Two studies described cases with novel strains of *Acinetobacter,* including *Acinetobacter septicus* (5) and *Acinetobacter* RUH 1139 strain (7). In most studies, the authors assumed an outbreak based solely on an increased number of children with *Acinetobacter* colonization or infection in a medical unit over a period of weeks to months. Typing of isolates was described in only one study (11), identifying six of nine strains in bacteremic neonates as identical.

The source of the outbreak was proven only in one study in which an *Acinetobacter* RUH 1139 strain caused bacteremia infections in 16 neonates and was isolated from the total parenteral nutrition solution (7). Many studies described isolation of

Acinetobacter from environmental sources, air conditioners, aerators, dressings, suction catheters or the hands of health care workers; however, typing was never performed to confirm whether the patient and environmental strains were identical.

The vast majority of patients in the outbreaks had *Acinetobacter* bloodstream infections. Of the 18 studies, 17 described at least one bacteremic patient. The other study (22) did not report blood culture results in four preterm infants with *Acinetobacter* meningitis. Meningitis was the second most common infection after bacteremia, with four of the 18 studies describing patients with *Acinetobacter* meningitis with or without bacteremia. There were no other sites of proven invasive infection described in the outbreak studies.

Fourteen of the 18 studies provided information on patient outcome, with all these studies involving only neonates. For the 11 studies that reported deaths attributable to *Acinetobacter*, mortality varied from 0% to 44%; 13 of 70 neonates (19%) died.

Case series

Thirty-three of the studies (23-56) were case series dating back to 1953 (Table 2). As with the outbreaks, the number of case series reported also seems to be increasing, with 15 of 33 (45%) occurring within the past 10 years. Case series were concentrated in India (seven studies [21%]), Slovakia (four studies [12%]) and the United States (four studies [12%]).

The number of children per case series ranged from one to 138 (median: nine cases). For 12 of the 33 studies (36%), all cases were from the same setting: five studies were from an NICU (15%), two were from neurosurgery wards (6%), one was from a PICU (3%), one was from a general pediatric ward (3%) and three (all from India) described only community-acquired infections (9%). A study (26) from Philadelphia (USA) investigating risk factors for bacteremia with *Acinetobacter* found that almost 50% of infections were acquired at home in children with central venous catheters, many of whom had malignancies.

In terms of types of infection, five of the 33 (15%) studies included cases of neonatal (younger than one month of age) meningitis, 10 (30%) included cases of pediatric (older than one month of age) meningitis and four (12%) included cases of post-surgical meningitis. Fifteen of the 33 (45%) studies reported cases of bacteremia with no meningitis, one reported cases of endophthalmitis and one reported cases of endocarditis (Table 2). Four of the case series were published primarily because they reported infection with strains of multidrug-resistant *Acinetobacter* infection, with all being published since 2004 (23,24,27,28).

There was no information regarding the ages of the patients in six of the 33 case series, but 24 of the remaining 27 case series reported on patients five years of age and younger. For the 21 studies in which sex was reported, there were 334 males (54.6%) and 278 females (45.4%). For the 20 studies that reported deaths directly attributable to *Acinetobacter* infection, mortality varied from 0% to 83%; 55 of 397 children (13.9%) died.

Twenty-eight of the 33 case series provided information on the strain(s) of *Acinetobacter* responsible for causing infection, with nine reporting multiple strains. The strains implicated included the following: *A lwoffii* (15 studies), *A baumannii* (13 studies), *A calcoaceticus* (nine studies), *A hemolyticus* (one study), *A junii* (one study), genomospecies 3 (one study), genomospecies 14 (one study) and unidentified species (four studies). It should be noted that in seven of the studies, *A lwoffii*

species was reported as the former name *M polymorpha* and, in four of the studies, *A calcoaceticus* was reported as the former names *D mucosus* or *B anitratus*.

Case reports

There were 49 case reports of invasive pediatric *Acinetobacter* infection dating back to 1950. Unlike the outbreaks or the case series, a relatively smaller fraction of the case reports were reported recently, with only 12 from the past 10 years. The geographical distribution of the case reports also differs from the outbreaks and case series in that only 12 of the 44 that provided the location were from developing countries.

Case reports described unusual presentations including multiple nodules in the spleen and lung mimicking fungal infection in a child with leukemia (57), a mediastinal mass in a child with chronic granulomatous disease (58), skin abscesses in a neonate (59), osteomyelitis of a phalanx following a hamster bite (60), gangrene of the toes in an infant (61,62) and corneal perforation with iris prolapse in a child (63). Novel aspects of therapy from the case reports included responses to parenteral colistin (64-66), netilmicin (65), tigecycline (67) and intrathecal polymyxin (68).

DISCUSSION

A systematic literature review of pediatric *Acinetobacter* infection yielded 18 descriptions of possible outbreaks, 33 case series and 49 case reports from around the globe dating back to 1950. Early publications were case reports of primarily meningitis, followed by case series of infections that occurred in specific settings (such as intensive care units, burn units or oncology wards). The first possible outbreak from a United Kingdom NICU was reported in 1982 (22). None of the outbreaks occurred in North America, but a NICU outbreak was reported from New York (USA) in 2009 after the literature search was completed (69).

One of the striking features of the outbreaks was that the vast majority (89%) occurred in NICUs, suggesting that neonates with a complicated course are at particular risk of *Acinetobacter* infection. However, it is important to realize that outbreaks may be easier to recognize in a NICU because infection control surveillance is more likely in this setting, with patients often staying in a NICU until discharge; consequently, almost all nosocomial infections are detected. In settings with no surveillance, linked cases may not be noted if different physicians are caring for the patient. Evidence for an outbreak was simply based on clustering of cases in the majority of studies; therefore, it is very difficult to determine whether they were truly outbreaks. The source of infection was definitely proven in only one study (7); therefore, it was difficult to make specific recommendations to prevent such outbreaks in the future. In fact, one study (12) reported that although all isolates were *A calcoaceticus*, susceptibility patterns varied, which would make one question if this truly was an outbreak.

Among the 33 case series, it is interesting to note that a significant number were from India (eight studies), with four of these case series including community-acquired cases. It is possible that *Acinetobacter* is more predominant in the normal flora of this population or in warm humid climates and, therefore, causes more community-acquired infections.

Bacteremia and meningitis were the most common presentations of pediatric *Acinetobacter* infection, with dissemination to other sites being rare. There were five case reports (69-74) and

TABLE 2
Characteristics of pediatric *Acinetobacter* case series involving at least one child with invasive infection

Ref	Year	Country	Cases of invasive infection, n	Age range	Setting	Primary infection	Deaths from *Acinetobacter,* n	Species
23	2008	Iran	40	<28 days	NICU	Bacteremia	NR	*A baumannii*
24	2007	Taiwan	52	3 years to 27 years, mean: 6 years	Wards, PICU, NICU	Bacteremia	NR	NR
25	2007	Slovak Republic	25	NR	Children's hospital general wards, ICUs	Meningitis	5	*A baumannii*
26	2007	United States	92	IQR: 1.8 to 13.2	Children's hospital general wards, ICUs, outpatients	Bacteremia	4	*A baumannii, A lwoffii, A calcoaceticus,* unidentified species
27	2006	Greece	26	Mean: 7.6 years	PICU	Bacteremia	NR	*A baumannii*
28	2006	India	23	NR	7 community acquired, 16 hospital acquired	Bacteremia	NR	*A baumannii, A lwoffii*
29	2006	India	42	34 were <12 h old	9 community acquired, 33 hospital acquired	Bacteremia and meningitis	NR	*A baumannii, A lwoffii*
30	2005	Greece	2	14 years, 16 years	NR	Meningitis	0	*A baumannii*
31	2004	India	78	NR	NR	Bacteremia	NR	*A baumannii, A lwoffii*
32	2003	Morocco	20	<28 days old	NICU	Bacteremia and meningitis	NR	NR
33	2003	India	4	7 years, 14 years, 14 years, 18 years	NR	Endophthalmitis	0	*A calcoaceticus*
34,35	2001	Slovak Republic	48	0 to 12 years	Multiple wards across 8 teaching hospitals	Bacteremia	6	*A baumannii*
36	2000	Slovak Republic	10	1 to 36 months	NR	Meningitis	4	*A calcoaceticus*
37	2000	Taiwan	3	3 years, 3 years and 6 years	NR	Bacteremia	2	*A lwoffii*
38	2000	Slovak Republic	14	1 to 36 months	3 pediatric hospitals	Meningitis	0	*A baumannii*
39	1999	Taiwan	1	17 years	Neurosurgery ward	Meningitis	0	Unidentified species
40	1998	India	79	NR	55 nursery, 24 community acquired	Bacteremia	NR	NR
41	1998	Bangladesh	138	82% were 5 years or younger	Community and hospital acquired	Bacteremia	22	*A baumannii, A lwoffii, A hemolyticus*
42	1995	Netherlands	6	1, 3, 8, 13, 20 and 29 days	NICU	Bacteremia	5	*A baumannii, A lwoffii, A junii,* genomospecies 3, genomospecies 14, unidentified species
43	1993	India	26	NR	NICU	Bacteremia	NR	NR
44	1993	Israel	3	2 months, 3 months, 1 year	Neurosurgery ward	Meningitis	0	*A baumannii*
45	1991	Nigeria	2	NR	NR	Endocarditis	NR	NR
46	1989	Japan	19	4 to 22 days	NICU	Bacteremia	NR	*A calcoaceticus*
47	1986	United States	29	NR	Oncology ward	Bacteremia	0	*A lwoffii, A calcoaceticus,* unidentified species
48	1973	Israel	2	2 years, 3 years	NR	Bacteremia	NR	*A lwoffii*
49	1969	India	2	2 years, 2 years	NR	Meningitis	NR	*A lwoffii*
50	1965	United States	2	23 months, 6 years	Community acquired	Meningitis	1	*A lwoffii*
51	1965	United States	2	4 years, 16 years	Community acquired	Meningitis	1	*A lwoffii*
52	1965	India	2	4 years, 18 years	Community acquired	Meningitis	0	*A lwoffii*
53	1965	Uganda	5	1 month, 1 year, 1 year, 6 years, 7 years	NR	Bacteremia and meningitis	0	*A lwoffii, A calcoaceticus*
54	1961	Puerto Rico	7	4 days to 2 years	NR	Bacteremia and meningitis	3	*A lwoffii, A calcoaceticus*
55	1957	Canada	2	4 days, 6 days	NR	Meningitis	1	*A calcoaceticus*
56	1953	Unknown	2	11 days, 21 days	NR	Meningitis	0	*A calcoaceticus*

All species belong to the Acinetobacter *genus. ICU Intensive care unit; IQR Interquartile range; NICU Neonatal ICU; NR Not reported; PICU Pediatric ICU; Ref Reference*

one case series that described endocarditis (45). There was one case series with four patients with endophthalmitis (33). There were only three cases reports of well-documented pulmonary involvement with isolation of *Acinetobacter* from pleural fluid (75), pulmonary lymph node (58) and lung at autopsy (76). However, it is important to recognize that ventilator-associated pneumonia *Acinetobacter* may also be common in children, but such cases would have been excluded from the current study because *Acinetobacter* is typically isolated from pulmonary secretions in the absence of a tissue diagnosis. *Acinetobacter* grew from superficial abscesses in two cases (59,77) and from an intra-abdominal abscess in one case (78), but was otherwise not implicated in abscess formation. This distribution of infections suggests that *Acinetobacter* is more likely to be part of skin rather than respiratory or gastrointestinal flora.

Acinetobacter taxonomy has changed markedly over time. As of 2008, there were 31 genomic species of which 17 had valid species names (79). It remains controversial whether *A calcoaceticus* and *A baumannii* should be regarded as the same species because they are difficult to differentiate. *A calcoaceticus* appears to be more common from environmental sources and *A baumannii* from human sources (79). To clarify some of the terms used in older literature, *A anitratus* is actually a subtype of *A calcoaceticus* and is more accurately written as *A calcoaceticus* var *anitratus*. *Mima polymorpha* is an older name for *A lwoffii*, while *B anitratum*, *D mucosus*, *M glucidolytica* and *H vaginicola* are all *A calcoaceticus*. A wide variety of species have been described as etiological agents of invasive disease, with *A baumannii* traditionally being considered to be of greatest clinical significance, although *A lwoffii* and *A calcoaceticus* were commonly implicated in the published pediatric literature.

The outcome of infection with multiresistant or panresistant *Acinetobacter* in children remains unclear because it is probable that authors are more likely to publish cases of success than of failure. There are few published cases (64-66) in which the only reasonable therapeutic option was colistin. Fortunately, it appears that ill children develop less nephrotoxicity from colistin than adults (80).

The primary limitation of the present study is that infections reported in the literature may not mirror the relative incidence, spectrum and severity of infection, especially in developed countries or nonacademic centres where clinicians may not have the opportunity to report unusual infections or outbreaks. Pediatric cases that were reported as part of adult series may have been missed. Identification and speciation of *Acinetobacter* is complex, and may not always be accurately reported.

CONCLUSION

Reported invasive *Acinetobacter* infections in children generally manifest as bacteremia or meningitis. Ventilator-associated pneumonia may also be a common presentation, but this could not be ascertained from the current study. Infections that have been reported from developed countries are usually nosocomial, with community-acquired infections often being reported from India. Outbreaks appear to most likely occur in NICUs, with the source usually remaining unknown. A large multicentre, prospective study concentrating on NICUs and PICUs would be beneficial to further characterize risk factors for and current outcome of invasive infection with this organism. A study of colonization of normal newborns in tropical countries would also be of value.

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