Current Infectious Disease Reports (2018) 20: 48
https://doi.org/10.1007/s11908-018-0654-5

PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Acinetobacter Infections in Neonates

Raffaele Zarrilli[1] · Maria Bagattini[1] · Eliana Pia Esposito[1] · Maria Triassi[1]

Published online: 10 October 2018

Abstract

Purpose of Review MDR-Gram-negative bacteria are a great concern in the neonatal population, with a worldwide rise in the reported incidence and with very limited therapeutic options. *Acinetobacter baumannii* is responsible for many infections in neonates and outbreaks in neonatal intensive care unit (NICU); also, outbreaks caused by other *Acinetobacter* species have been reported. The aim of this review is to document the epidemiology of *Acinetobacter* spp. infections in neonates and risk factors for acquisition of *Acinetobacter* spp. in the NICU using data from published studies.

Recent Findings *Acinetobacter* spp. infections are increasing in neonates in NICU. Outbreak caused by multidrug resistant (MDR) or extensively drug resistant (XDR) *A. baumannii* but also outbreak caused by susceptible *A. soli* and *A. septicus* sp. nov., were reported in neonates. *Acinetobacter* spp. were responsible for bloodstream infections and respiratory tract infections in neonates. Risk factors for *A. baumannii* acquisition in neonates were low birthweight, length of NICU stay, umbilical catheterization, central-venous catheterization, assisted ventilation, and prior antibiotic use.

Summary This review highlights the importance of surveillance of risk factors for healthcare-associated infections in NICU to control MDR and XDR *A. baumannii* infections in neonates.

Keywords *Acinetobacter* · Neonatal intensive care unit · Outbreak · Antimicrobial resistance · Infection · Risk factor analysis

Introduction

Acinetobacter spp. are glucose non-fermentative Gram-negative bacteria that have emerged in recent years as a major cause of healthcare-associated infections and hospital outbreaks, especially in intensive care unit patients [1, 2]. *A. baumannii* and to a lesser extent *A. nosocomialis*, *A. pittii*, *A. seifertii*, and *A. dijkshoorniae* are the most clinically relevant species [1–4]. They are genetically and phenotypically similar to the environmental species *A. calcoaceticus* and are therefore grouped into the *A. calcoaceticus-A. baumannii* (Acb) complex [1, 3, 4]. *A. baumannii* isolates responsible for epidemics are frequently multidrug resistant (MDR) or extensively drug resistant (XDR) according to Magiorakos et al. [5], the majority of them being resistant to carbapenems and showing intermediate resistance to tigecycline, but usually retaining susceptibility to colistin [6]. Resistance to antimicrobials and disinfectants [1, 6], along with elevated resistance to desiccation and high biofilm-forming capacity on abiotic surfaces [7] may favor the spread and persistence in the hospital environment of epidemic *Acinetobacter* spp. strains. Mounting evidence suggests that *Acinetobacter* spp., in particular *A. baumannii*, may cause severe healthcare-associated infections in neonates and hospital outbreaks in neonatal intensive care unit (NICU) [8, 9, 10••,11•, 12–14, 15•, 16, 17••, 18, 19•, 20–22, 23•]. A previous review by Hu and Robinson analyzed only invasive *Acinetobacter* infections in children younger than 5 years of age from 1982 to 2008 [24]. In the current review, we summarize the recent literature on *Acinetobacter* spp. infections in neonates and discuss risk factors responsible for acquisition of *A. baumannii* in NICU.

This article is part of the Topical Collection on *Pediatric Infectious Diseases*

✉ Raffaele Zarrilli
rafzarri@unina.it

[1] Department of Public Health, University of Naples 'Federico II', Via Pansini 5, 80131 Naples, Italy

Characteristics of Neonatal *Acinetobacter* spp. Cases

We conducted a PubMed search for English language articles between 2007 and June 2018 on *Acinetobacter* infections in neonates. In addition, we searched for articles containing the

following terms, i.e., *Acinetobacter* spp. infections, *Acinetobacter baumannii* infections, and *Acinetobacter* infections in neonatal intensive care unit (NICU). We selected and used data from all original research articles that reported information on the following: design of the study, study period, country, number of cases and/or infections, microbial etiology, infection-control strategies, and risk factors for *Acinetobacter* spp. acquisition in neonates. Sixteen articles met our inclusion criteria and were appropriate for in-depth assessment (Table 1). The studies were very different with respect to time of occurrence and geographical location, reporting data from 2004 to 2017 and from 12 different countries. All 16 studies took place in inpatient hospital setting, specifically in neonatal intensive care units.

The majority of the studies described epidemics due to *Acinetobacter* spp. colonization/infections from neonates in NICUs and were classified as outbreak investigations [8, 9, 12–14, 16, 18, 23•]. Five studies were organized as case-control studies [10••, 15•, 17••, 21, 22] and three as case series studies [11•, 19•, 20].

A. baumannii was identified in the majority of the studies [8, 9, 10••, 11•, 14, 15•, 16, 17••, 18, 19•, 20–22, 23•], but identification at the species level using a genotypic method was confirmed in few of them [11•, 15•, 17••, 21, 23•]. Phenotypic identification of *Acinetobacter* isolates to the species level using biochemical methods has proven to be insufficient and need to be confirmed by a genotypic method or by MALDI-TOF [1, 3, 4]. Because of this, identification as *A. baumannii* of bacterial isolates from neonates was reliable when a genotypic method was used to confirm it [11•, 15•, 17••, 21, 23•]. Instead, isolation of non-*baumannii Acinetobacter* species from neonates was reported and confirmed by a genotypic method in few other studies [12, 13, 15•]. In particular, non-*baumannii Acinetobacter* species belonging to the Acb complex such as *A. calcoaceticus* and *A. nosocomialis* [15•] or outside the Acb complex such as *A. lwoffi*, *A. junni*, *A. variabilis*, *A. haemolyticus*, and *Acinetobacter* 14TU isolates were identified by ARDRA [15•]; *A. septicus* sp. nov. and *A. soli* isolates were identified by *rpoB* gene sequence analysis [13], or *rpoB* and *gyrB* gene sequence analysis [12], respectively.

The isolation of MDR *A. baumanni* was described in the majority of the selected studies [8, 9, 10••, 14, 15••, 16, 18, 19•, 21, 23•], the isolation of XDR *A. baumannii* in two other studies [17••, 22]. In accordance with previous data from the literature [6], resistance to carbapenems emerged in 10% [10••, 11•], 50% [15•], 70% [23•], or all *A. baumanni* isolates from neonates [8, 14, 16, 17••, 18, 19•, 21, 22]. On the other hand, susceptibility to colistin was found in all *A. baumannii* isolates from neonates [8, 9, 10••, 11•, 14, 15•, 16, 17••, 18, 19•, 21, 22, 23•]. Non-*baumannii Acinetobacter* spp. isolates from neonates were either susceptible to all antimicrobial tested, such as *A. soli* [12], susceptible to all antimicrobials but resistant to ceftazidime and cefotaxime, such as *A. septicus* sp.

Table 1 Characteristics of neonatal *Acinetobacter* spp. cases

Study period	Country	Number of cases	Number of infections	Deaths	Microbial etiology	Study design	Reference
2004	Taiwan	9	2	0	*A. baumannii*[a]	Outbreak investigation	[8]
2004	USA	7	4	4	*A. baumannii*[a]	Outbreak investigation	[9]
2004–2005	Palestine	40	40	15	*A. baumannii*[a]	Case-control	[10••]
2004–2014	Taiwan	40	40	2	*A. baumannii*	Case series	[11•]
2005	Brazil	5	5	1	*A. soli*	Outbreak investigation	[12]
2006	Turkey	5	5	2	*A. septicus* sp. nov.	Outbreak investigation	[13]
2006–2007	Tunis	36	31	10	*A. baumannii*[a]	Outbreak investigation	[14]
2007–2014	India	68	68	–	*Acinetobacter* spp.	Case-control	[15•]
2008–2009	USA	6	6	0	*A. baumannii*[a]	Outbreak investigation	[16]
2010–2011	Italy	22	6	1	*A. baumannii*	Case-control	[17••]
2011	Greece	8	10[b]	1	*A. baumannii*[a]	Outbreak investigation	[18]
2012–2013	Taiwan	59	67[b]	12	*A. baumannii*[a]	Case series	[19•]
2012–2015	Jordan	18	18	13	*A. baumannii*[a]	Case series	[20]
2013–2015	Brazil	21	4	–	*A. baumannii*	Case-control	[21]
2014–2015	Turkey	41	41	24	*A. baumannii*[a]	Case-control	[22]
2016–2017	Fiji	34[c]	34 [c]	23 [c]	*A. baumannii*	Outbreak investigation	[23•]

[a] Identification of *Acinetobacter* isolates to the species level was not confirmed by any genotypic method

[b] The numbers include cases with more than one infection

[c] Only cases of neonates in the NICU were included in the table

-, not reported

nov. [13], or MDR *Acinetobacter* spp. isolates, 50% of whom resistant to carbapenems [15•].

Acinetobacter spp. isolates from neonates were responsible for bloodstream infections [9, 10••, 11•, 12, 13, 15•, 20, 22, 23••], respiratory tract infections [14, 17••], bloodstream infections, and respiratory tract infections [8, 16, 18, 19•]. Mortality of neonates with *Acinetobacter* spp. infections ranged from 0 [8, 16] to 72% [20]. Elevated mortality was reported in bloodstream infections caused by MDR or XDR *A. baumannii* [20, 22, 23•]. The majority of the studies did not report *Acinetobacter* spp.—attributable mortality.

Genotyping analysis of *Acinetobacter* spp. isolates using PFGE [8, 9, 12–14, 16, 17••, 18, 19•, 21, 22] or whole genome sequencing [23•] demonstrated clonal-relationship and cross-transmission among patients in the same NICUs. Also, MLST analysis assigned *A. baumannii* isolates from neonates in different NICUs to international clonal lineage clonal lineage I in one study [21] and to international clonal lineage II in three studies [11•, 17••, 23•]. This finding is in accordance with previous data from the literature, showing the worldwide occurrence of *A. baumannii* international clones II and to a lesser extent international clone I in the hospital setting [2].

Infection control measures were performed during *A. baumannii* outbreaks in NICUs, which included environmental microbiological investigations, surveillance swabs from the nasopharynx and rectum of neonates, implementation of contact isolation precautions, cohorting of *A. baumannii* colonized and infected neonates, and environmental cleaning [8, 9, 14, 16, 17••, 18, 19•, 21, 22]. Environmental cultures identified source/reservoir of *A. baumannii* on ventilation tubes [8]; incubators [14]; monitors and humidifiers [17••]; EKG monitor, incubator, and operating table [19•]; and patient bed, locker, and formula preparation dish [22]. Daily audits by infection control team were conducted to alert the clinical staff during the outbreak [16, 18, 23•]. In one case, the ward was temporarily closed to external admissions during the outbreak [17••].

Antimicrobial therapy with colistin in neonates with MDR or XDR *A. baumannii* infections was reported by several studies [16, 17••, 18, 19•, 20–22, 23•], but only one of these studies specified the route of administration and dosing of the drug, i.e., intravenous colistin at a dose of 5 mg/kg/day [17••]. The potential nephrotoxicity and the emergence of colistin resistance, which are the major issues of colistin treatment [6], have not been reported yet in *A. baumannii* infections in neonates.

Risk Factors for *Acinetobacter* spp. Acquisition in NICUs

Risk factors for *Acinetobacter* spp. acquisition and/or colonization/infection of neonates in NICUs were analyzed in five case-control studies [10••, 15•, 17••, 21, 22] and three case series studies [11•, 19•, 20]. Prematurity or low birthweight (< 1500 g) were identified as risk factors of *A. baumannii* acquisition at univariate analysis in four case-control studies [10••, 17••, 21, 22] and length of NICU stay/days of hospitalization in two case-control studies [10••, 17••] (Table 2). The uses of the following devices were risk factors of *A. baumannii* acquisition: (i) umbilical catheter at univariate [17••, 22] and multivariate analysis [22]; central-venous catheter at univariate [10••, 17••, 21, 22] and multivariate analysis [10••, 17••]; assisted ventilation at univariate [10••, 17••, 22] and multivariate analysis [10••, 17••] (Table 2). In addition, the antibiotic use prior to *A. baumannii* isolation was risk factors of *A. baumannii* acquisition at univariate [10••, 21] and multivariate analysis [10••] (Table 2). Moreover, incidence of NDM-1-harboring *Acinetobacter* spp. in late-onset sepsis cases was significantly higher than that in early onset sepsis cases [15•].

Similarly, a case series of 40 neonates having *A. baumannii* bacteremia showed that 95% of them were premature, with very low birth weight (70% < 1500 g) prolonged intubation, usage of percutaneous central venous catheter (65%) and long-term usage of total parenteral nutrition (95%) [11•]. Prior use of imipenem and use of high frequency oscillation ventilation (HFOV) were statistically significant risk factors for acquisition of infections caused by imipenem-resistant *A. baumannii* [11•]. Another retrospective case series study on 59 neonates in a NICU in Taiwan showed that the mortality rate due to MDR *A. baumannii* sepsis was 20.34% [19•]. The risk factors for mortality due to MDR *A. baumannii* infection were

Table 2 Risk factors for *A. baumannii* acquisition in NICU

Patients' variables	Univariate analysis [a]	Multivariate analysis [a]
Length of NICU stay/days of hospitalization	[10••, 17••]	
Birthweight < 1500 g/prematurity	[10••, 17••, 21, 22]	
Use of UC	[17••, 22]	[22]
Use of CVC	[10••, 17••, 21, 22]	[10••, 17••]
Use of AV	[10••, 17••, 22]	[10••, 17••]
Prior antibiotic use	[10••, 21]	[10••]

[a] Case-control studies in which risk factors showed p values ≤ 0.05 (considered statistically significant)

UC, umbilical catheter; *CVC*, central venous catheter; *AV*, assisted ventilation

A. baumannii infection within 7 days of admission to the NICU, use of umbilical vein catheters, absolute neutrophil count < 1500/mm3, platelet count < 100,000/mm^3, and a delay in initiating adequate antibiotic treatment [19•]. Multivariate analysis revealed that prompt antibiotic therapy with colistin significantly decreased the risk of mortality [19•]. The result logistic regression analysis of another case series study was not considered because the study analyzed risk factors for sepsis due to *A. baumannii* and KPC producing bacteria compared with those caused by other microorganisms [20].

Conclusions

MDR and XDR *A. baumannii* and MDR non-*baumannii Acinetobacter* spp. are increasingly isolated from neonates in NICUs and are responsible for bloodstream infections and respiratory tract infections. Outbreaks in the NICUs are frequently caused by *A. baumannii* isolates belonging to highly successful international clonal lineages I and II, which spread in adult intensive care units and in the hospital setting worldwide also. Low birthweight, the use of assisted ventilation and vascular devices and prior antibiotic use are risk factors for MDR *A. baumannii* acquisition in neonates in the NICU. Therapy with last resource antimicrobial agent colistin is currently used against MDR *A. baumannii* infections in neonates. Future research should focus on strategies to reduce the transmission of MDR *Acinetobacter* spp. among neonates in the NICU and to validate the therapeutic and infection control strategies for management of MDR *Acinetobacter* spp. infections in neonates. This highlights the importance of international guidelines for the prevention of MDR microorganisms in neonates in the NICU.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Durante-Mangoni E, Zarrilli R. Global spread of drug-resistant *Acinetobacter baumannii*: molecular epidemiology and management of antimicrobial resistance. Future Microbiol. 2011;6(4):407–22. https://doi.org/10.2217/fmb.11.23.
2. Zarrilli R, Pournaras S, Giannouli M, Tsakris A. Global evolution of multidrug-resistant *Acinetobacter baumannii* clonal lineages. Int J Antimicrob Agents. 2013;41(1):11–9. https://doi.org/10.1016/j.ijantimicag.2012.09.008.
3. Dijkshoorn L, Nemec A, Seifert H. An increasing threat in hospitals: multidrug resistant *Acinetobacter baumannii*. Nat Rev Microbiol. 2007;5(12):939–51.
4. Marí-Almirall M, Cosgaya C, Higgins PG, Van Assche A, Telli M, Huys G, et al. MALDI-TOF/MS identification of species from the *Acinetobacter baumannii* (Ab) group revisited: inclusion of the novel *A. seifertii* and *A. dijkshoorniae* species. Clin Microbiol Infect. 2017;23(3):210.e1–9. https://doi.org/10.1016/j.cmi.2016.11.020.
5. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268–81. https://doi.org/10.1111/j.1469-0691.2011.03570.x.
6. Durante-Mangoni E, Utili R, Zarrilli R. Combination therapy in severe *Acinetobacter baumannii* infections: an update on the evidence to date. Future Microbiol. 2014;9(6):773–89. https://doi.org/10.2217/fmb.14.34.
7. Giannouli M, Antunes LC, Marchetti V, Triassi M, Visca P, Zarrilli R. Virulence-related traits of epidemic *Acinetobacter baumannii* strains belonging to the international clonal lineages I-III and to the emerging genotypes ST25 and ST78. BMC Infect Dis. 2013;13:282. https://doi.org/10.1186/1471-2334-13-282.
8. Chan PC, Huang LM, Lin HC, Chang LY, Chen ML, Lu CY, et al. Control of an outbreak of pandrug-resistant *Acinetobacter baumannii* colonization and infection in a neonatal intensive care unit. Infect Control Hosp Epidemiol. 2007;28(4):423–9.
9. Simmonds A, Munoz J, Aguero-Rosenfeld M, Carbonaro C, Montecalvo M, Clones B, et al. Outbreak of *Acinetobacter* infection in extremely low birth weight neonates. Pediatr Infect Dis J. 2009;28(3):210–4. https://doi.org/10.1097/INF.0b013e31818cb0aa.
10.•• Al Jarousha AM, El Jadba AHN, Al Afifi AS, El Qouqa IA. Nosocomial multidrug-resistant *Acinetobacter baumannii* in the neonatal intensive care unit in Gaza City, Palestine. Int J Infect Dis. 2009;13(5):623–8. https://doi.org/10.1016/j.ijid.2008.08.029 **This case-control study identifies for the first time risk factors for *A. baumannii* acquisition in NICU.**
11.• Lee HY, Hsu SY, Hsu JF, Chen CL, Wang YH, Chiu CH. Risk factors and molecular epidemiology of *Acinetobacter baumannii* bacteremia in neonates. J Microbiol Immunol Infect. 2018;51(3):367–76. https://doi.org/10.1016/j.jmii.2017.07.013 **This is a large case series study on *A. baumannii* bacteremia in neonates.**
12. Pellegrino FL, Vieira VV, Baio PV, dos Santos RM, dos Santos AL, Santos NG, et al. *Acinetobacter soli* as a cause of bloodstream infection in a neonatal intensive care unit. J Clin Microbiol. 2011;49(6):2283–5. https://doi.org/10.1128/JCM.00326-11.
13. Kilic A, Li H, Mellmann A, Basustaoglu AC, Kul M, Senses Z, et al. Acinetobacter septicus sp. nov. association with a nosocomial outbreak of bacteremia in a neonatal intensive care unit. J Clin Microbiol. 2008;46(3):902–8.
14. Touati A, Achour W, Cherif A, Hmida HB, Afif FB, Jabnoun S, et al. Outbreak of *Acinetobacter baumannii* in a neonatal intensive care unit: antimicrobial susceptibility and genotyping analysis. Ann Epidemiol. 2009;19(6):372–8. https://doi.org/10.1016/j.annepidem.2009.03.010.
15.• Chatterjee S, Datta S, Roy S, Ramanan L, Saha A, Viswanathan R, et al. Carbapenem resistance in *Acinetobacter baumannii* and other *Acinetobacter* spp. causing neonatal sepsis: focus on NDM-1 and its linkage to ISAba125. Front Microbiol. 2016;7:1126. https://doi.

org/10.3389/fmicb.2016.01126 **This study characterizes at molecular level MDR *non-baumannii Acinetobacter* isolates.**

16. McGrath EJ, Chopra T, Abdel-Haq N, Preney K, Koo W, Asmar BI, et al. An outbreak of carbapenem-resistant *Acinetobacter baumannii* infection in a neonatal intensive care unit: investigation and control. Infect Control Hosp Epidemiol. 2011;32(1):34–41. https://doi.org/10.1086/657669.
17.•• Zarrilli R, Di Popolo A, Bagattini M, Giannouli M, Martino D, Barchitta M, et al. Clonal spread and patient risk factors for acquisition of extensively drug-resistant *Acinetobacter baumannii* in a neonatal intensive care unit in Italy. J Hosp Infect. 2012;82(4):260–5. https://doi.org/10.1016/j.jhin.2012.08.018 **This case-control study genotypes *A. baumannii* isolates, analyzes risk factors for *A. baumannii* acquisition and describes infection control measures for the containment of the outbreak.**
18. Tsiatsiou O, Iosifidis E, Katragkou A, Dimou V, Sarafidis K, Karampatakis T, et al. Successful management of an outbreak due to carbapenem-resistant *Acinetobacter baumannii* in a neonatal intensive care unit. Eur J Pediatr. 2015;174(1):65–74. https://doi.org/10.1007/s00431-014-2365-8.
19.• Wei HM, Hsu YL, Lin HC, Hsieh TH, Yen TY, Lin HC, et al. Multidrug-resistant *Acinetobacter baumannii* infection among neonates in a neonatal intensive care unit at a medical center in central Taiwan. J Microbiol Immunol Infect. 2015;48(5):531–9. https://doi.org/10.1016/j.jmii.2014.08.025 **This is a large case series study on *A. baumannii* bloodstream infections and respiratory infections in neonates.**
20. Yusef D, Shalakhti T, Awad S, Algharaibeh H, Khasawneh W. Clinical characteristics and epidemiology of sepsis in the neonatal intensive care unit in the era of multi-drug resistant organisms: a retrospective review. Pediatr Neonatol. 2018;59(1):35–41. https://doi.org/10.1016/j.pedneo.2017.06.001.
21. Maciel WG, da Silva KE, Croda J, Cayô R, Ramos AC, de Sales RO, et al. Clonal spread of carbapenem-resistant *Acinetobacter baumannii* in a neonatal intensive care unit. J Hosp Infect. 2018;98(3):300–4. https://doi.org/10.1016/j.jhin.2017.10.015.
22. Ulu-Kilic A, Gundogdu A, Cevahir F, Kilic H, Gunes T, Alp E. An outbreak of bloodstream infection due to extensively resistant *Acinetobacter baumannii* among neonates. Am J Infect Control. 2018;46(2):154–8. https://doi.org/10.1016/j.ajic.2017.08.007.
23.• Zimmerman P A, Lyman M, Andersson P. *Acinetobacter baumannii* outbreak in NICU at the Colonial War Memorial Hospital Suva, Fiji, December 2016–July 2017. Ministry of Health and Medical Services of Fiji-September 2017. Available at: http://www.health.gov.fj/wp-content/uploads/2017/09/ACINETOBACTER-BAUMANNII-JULY-2017.pdf. **This is an outbreak investigation in which *A. baumannii* isolates were genotyped by whole genome sequencing.**
24. Hu J, Robinson JL. Systematic review of invasive *Acinetobacter* infections in children. Can J Infect Dis Med Microbiol. 2010;21(2):83–8.