Review Article

Gram-negative infections in pediatric and neonatal intensive care units of Latin America

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Abstract

In order to review the epidemiology of Gram-negative infections in the pediatric and neonatal intensive care units (PICUs and NICUs) of Latin America a systematic search of PubMed and targeted search of SciELO was performed to identify relevant articles published since 2005.

Independent cohort data indicated that overall infection rates were higher in Latin American PICUs and NICUs versus developed countries (range, 5%–37% vs 6%–15%, respectively). Approximately one third of Latin American patients with an acquired PICU or NICU infection died, and crude mortality was higher among extremely low-birth-weight infants and those with an infection caused by Gram-negative bacteria. In studies reporting > 100 isolates, the frequency of Gram-negative pathogens varied from 31% (Colombia) to 63% (Mexico), with *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* the predominant pathogens in almost all countries, and *Acinetobacter* spp. and *Serratia* spp. isolated sporadically. The activity of quinolones and third-generation cephalosporins against *P. aeruginosa*, *Acinetobacter* spp., and Enterobacteria was seriously compromised, coincident with a high prevalence of circulating extended-spectrum β-lactamases. Furthermore, we identified two observational studies conducted in Chile and Brazil reporting infections by *P. aeruginosa* and *Acinetobacter baumannii* in PICUs, demonstrating resistance to carbapenems, and two outbreaks of carbapenem-resistant *K. pneumoniae* in Colombia and Brazil.

The endemicity of multidrug-resistant Gram-negative infections in Latin American PICUs and NICUs is punctuated by intermittent clonal outbreaks. The problem may be alleviated by ensuring ICUs are less crowded, increasing staffing levels of better-trained health care personnel, and implementing antimicrobial stewardship and surveillance programs.

Key words: Pediatric intensive care unit; neonatal intensive care unit; nosocomial infection; Latin America; Gram-negative infection.

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Introduction

Gram-negative bacilli represent a leading cause of serious infections. Chemotherapeutic options available to clinicians for treatment of invasive Gram-negative infections have been compromised by the rapid emergence of antimicrobial-resistance mechanisms [1-3]. Of particular concern is the capacity of Gram-negative bacilli to accumulate co-resistance and cross-resistance mechanisms to commonly used antimicrobial drug classes, which has culminated in the circulation of multidrug-resistant strains [1]. The enhanced complexity of the patient, with a consequent increase in the duration of the hospital stay and greater need for intravascular devices, has increased the risks for hospital-acquired infections (HAIs).

In developed countries, bloodstream infections (BSIs) and respiratory infections are the most frequent HAIs in pediatric intensive care units (PICUs), and are almost always associated with use of an invasive device [4,5]. Depending on the infection site, Gram-negative bacilli are the causative organism in 24% to ≥ 58% of cases reported for PICUs and neonatal intensive care units (NICUs) [3,5,6]. It is not unexpected that the probability of encountering a multidrug-resistant Gram-negative pathogen is far higher in the ICU than in other patient-care areas [3], and also far higher in ICUs in developing than developed countries [7]. Based on information published about Latin America, it has been observed that the frequency of multiresistant Gram-negative pathogens in both community- and hospital-acquired varies by region and type of medical service [7].

The aim of this review is to document the epidemiology and burden of Gram-negative infections

in the PICU and NICU population in Latin America, using primary data from published studies and policy decisions from secondary review articles.

Methodology

To review the published clinical data relating to all pediatric Gram-negative HAIs in Latin American ICUs, a systematic search of the biomedical literature was conducted in line with the tenets of PRISMA guidance [8]. MEDLINE (via PubMed) was searched limited by the dates 1 January 2005 to 3 July 2013 for articles using the following terms and Boolean logic: (pediatric OR paediatric OR neonat* OR children OR newborn OR nursery) AND ("intensive care unit" or ICU or hospital OR nosocomial OR "patient care area") AND ("Gram-negative infection" OR "Gram-negative pathogen" OR bacilli OR *Acinetobacter* OR *Klebsiella* OR *Pseudomonas* OR *Escherichia*) AND ("Latin America" OR "South America" OR "Central America" OR Mexico OR Guatemala OR Honduras OR Nicaragua OR "Costa Rica" OR Cuba OR "Dominican Republic" OR Panama OR Colombia OR Venezuela OR Guyana OR Suriname OR "French Guiana" OR Brazil OR Ecuador OR Peru OR Bolivia OR Paraguay OR Uruguay OR Chile OR Argentina). A separate search in the title/abstract of published articles was conducted for "infection control AND antimicrobial stewardship," which was delimited by the dates and geographical search terms stated above.

The titles and abstracts of all references obtained in the search were screened by the authors. We selected and used data from all original research articles that reported information on the following: (1) the incidence, clinical presentation, and mortality rates of invasive Gram-negative infections in Latin American PICUs and/or NICUs; (2) antimicrobial resistance rates among the causative pathogens; (3) presence of circulating extended-spectrum ß-lactamases (ESBLs) and carbapenemases; and (4) nosocomial infection-control strategies. To maximize the likelihood of some level of generalizability within reporting centers, we arbitrarily excluded articles that reported on < 40 cases or < 40 clinical isolates (with the exception of outbreak data). Only infection-control articles reporting outcome data pertaining to infection risk, transmission, surveillance, and drug use were selected for review. We also reviewed articles that focused on management of individual cases and outbreaks, although this evaluation was not intended to be comprehensive, but rather provide a stand-alone summary of Gram-negative bacterial molecular epidemiology in Latin American PICUs and/or NICUs.

Results

Selected studies

The literature searches yielded a total of 158 extremely diverse microbiological articles, of which 112 articles were dismissed based on information contained within their abstracts (Figure 1). Most articles were rejected at this stage because the epidemiology of invasive Gram-negative infections in Latin American PICUs and/or NICUs was not reported. Full-text articles were retrieved for 46 abstracts and further reviewed for eligibility by both authors, after which 12 articles met our inclusion criteria and were appropriate for in-depth assessment (Table 1)

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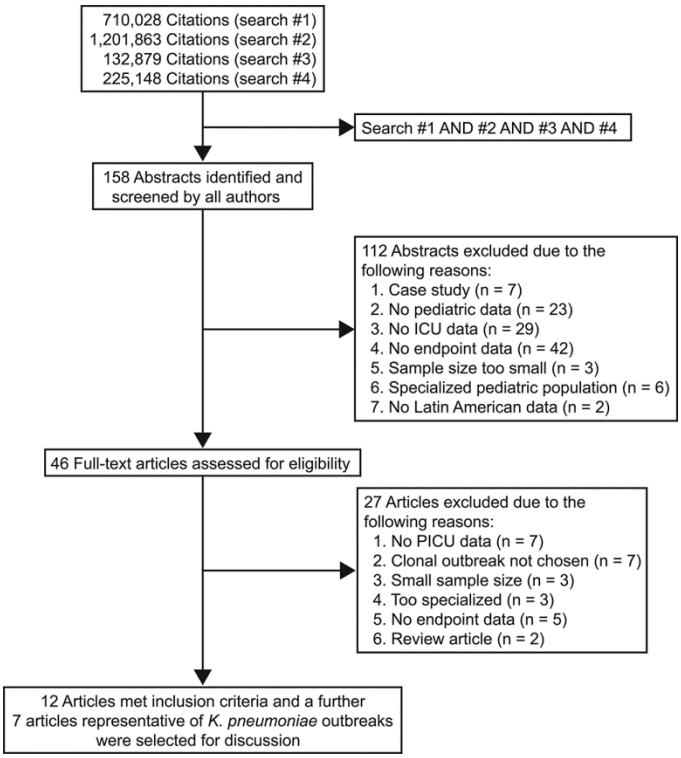
Figure 1. Flow chart of included studies. Search #1 = pediatric OR paediatric OR neonat* OR children OR newborn OR nursery; Search #2 = "intensive care unit" or ICU or hospital OR nosocomial OR "patient care area"; Search #3 = "Gram-negative infection" OR "Gram-negative pathogen" OR bacilli OR *Acinetobacter* OR *Klebsiella* OR *Pseudomonas* OR *Escherichia*; Search #4 = "Latin America" OR "South America" OR "Central America" OR Mexico OR Guatemala OR Honduras OR Nicaragua OR "Costa Rica" OR Cuba OR "Dominican Republic" OR Panama OR Colombia OR Venezuela OR Guyana OR Suriname OR "French Guiana" OR Brazil OR Ecuador OR Peru OR Bolivia OR Paraguay OR Uruguay OR Chile OR Argentina.



Latin American PICUs and NICUs

Reference	Study location	Study design	Study period	No. of patients	No. of isolates	Anatomical collection site (Infection types)
All children						
Pérez-González et al. 2007 [9]	San Luis Potosi, Mexico	Prospective	1991–2005	29,273 (NICU, n = 5,041; PICU, n = 733)	868	Blood (BSI)
Carvalho et al. 2005 [14]	1 PICU in Santa Casa de São Paulo, Brazil	Prospective	2002–2003	100	133*	Respiratory tract (VAP)
Becerra et al. 2010 [16]	1 PICU in Instituto Nacional de Salud del Niño of Lima, Peru	Prospective	2006–2007	414	67	Blood, urine, and respiratory tract (CLABSI, CAUTI, and VAP)
Silva et al. 2011 [20]	Chile	Prospective	2009	NR	126	Blood and urine (BSI and UTI)
Porto et al. 2012 [18]	1 PICU in Hospital das Clinicas of the Universidade Federal de Uberlandia, State of Minas Gerais, Brazil	Prospective case-control	2009–2010	172	60	Blood, urine, and respiratory tract (CLABSI, CAUTI, VAP, and sepsis)
Neonates only						
Couto et al. 2007 [10]	6 NICUs in Belo Horizonte, Brazil	Prospective†	1993–2002	6,243	1197‡	Entire body including non-sterile sites (all infection types)
Efird et al. 2005 [11]; Rojas et al. 2005 [12]	8 NICUs (2 public and 6 private hospitals) in Colombia	Prospective§	2001	1,504	127	Blood, urine, CSF, and other sterile sites (BSI, UTI, meningitis, other)
Cifuentes et al. 2005 [13]	University Hospital in Bogotá, Colombia	Prospective	2002	2,331	1097	Blood, urine, catheters, CSF, other (BSI, UTI, catheter-associated infections, meningitis, other)
Amaya et al. 2010 [15]	Hospital Oscar Danilo Rosales, León, Nicaragua	Prospective	2005	135	46	Blood (BSI)
De Brito et al. 2010 [17]	Uberlandia University Hospital, Brazil	Prospective	2006–2008	318	73	Blood (CLABSI)
Pereira et al. 2009 [19]	Servidores do Estado Hospital, Rio de Janeiro, Brazil	Retrospective	2001–2004	203	87	Blood (sepsis)

BSI = bloodstream infection, CAUTI = catheter-associated urinary tract infection, CLABSI = central line-associated BSI, CSF = cerebrospinal fluid, NICU = neonatal intensive care unit, NR = not reported, PICU = pediatric intensive care unit, VAP = ventilator-associated pneumonia.

* From 3 sequential collections.

† Open-cohort enrolling consecutive patients.

‡ From blood.

§ Consecutive or every 1 in 2 or 3 patients.

Table 2. Summary of observational studies reporting acquired infection and mortality rates in Latin American PICUs and NICUs

Reference	Country	Study period	No. of patients	Patients infected/ admission (%)	Incidence rate (infections/100 patients, n)	Incidence density	Mortality rate
All children							
Pérez-González et al. 2007 [9]	Mexico	1991–2005	29,273		3.5 in NICU* 3.3 in PICU*	NR	NR
Carvalho et al. 2005 [14]	Brazil	2002–2003	100	24	NR	NR	NR
Becerra et al. 2010 [16]	Peru	2006–2007	414	20	BSI, 20 VAP, 9 UTI, 4	BSI, 18/1,000 device-days VAP, 8/1,000 device-days UTI, 5/1,000 device-days	38% in infected patients vs. 20% in noninfected patients ($P < 0.001$), yielding a crude excess mortality of 18%.
Porto et al. 2012 [18]	Brazil	2009–2010	172	16	NR	BSI, 18/1,000 device-days VAP 18/1,000 device-days UTI, 7/1,000 device-days	8% for entire NICU population
Neonates only							
Couto et al. 2007 [10]	Brazil	1993–2002	6243†	37	58	Overall: 30/1,000 patient-days; BSI: 14/1,000 patient-days CLABSI: 3/1,000 device-days Pneumonia: 2/1,000 patient-days VAP: 4/1,000 device-days	NR
Efird et al.2005 [11]	Colombia	2001	1504†	5	8	6/1,000 patient-days	NR
De Brito et al. 2010 [17]	Brazil	2006–2008	318‡	NR	NR	CLABSI, 13/1,000 device days‡ CLABSI, 2.1/1,000 device days§	14%
Pereira et al. 2009 [19]	Brazil	2001–2004	203†	35‖	NR	NR	Crude rate associated with sepsis was 30%

BSI = bloodstream infection, CLABSI = central line-associated BSI, NICU = neonatal intensive care unit, NR = not reported, PICU = pediatric intensive care unit, VAP = ventilator-associated pneumonia, UTI = urinary tract infection.
* 2005 Values interpreted from a graph.
† Neonates only.
‡ No laboratory confirmation of central venous catheter colonization.
§ Causative pathogen identified on catheter tip.
‖ Sepsis in very low-birth-weight babies.

Table 3. Proportion of health care-acquired Gram-negative bacterial isolates nonsusceptible to third-generation cephalosporins, quinolones, and carbapenems in Latin American PICUs and NICUs

Pathogen	Antimicrobial drug class	Study (population)		
		Couto et al. 2007 [10] (neonates)	Silva et al. 2011 [20] (all children)	Cifuentes et al. 2005 [13]* (neonates)
E. coli	Third-generation cephalosporin	19%; n = 104 isolates	–	40%; n = 14 isolates
	Quinolone	–	–	0%; n = 14 isolates
	Carbapenem	–	–	0%; n = 14 isolates
K. pneumoniae	Third-generation cephalosporin	64%; n = 290 isolates	–	75%†; n = 27 isolates
	Quinolone	–	–	5%†; n = 27 isolates
	Carbapenem	–	0%; n = 61 isolates	4%†; n = 27 isolates
P. aeruginosa	Third-generation cephalosporin	24%; n = 71 isolates	23%; n = 65 isolates	–
	Quinolone	6%; n = 66 isolates	9%; n = 65 isolates	–
	Carbapenem	0%; n = 75 isolates	18% for imipenem; n = 65 isolates 22% for meropenem; n = 65 isolates	–
Serratia marcescens	Third-generation cephalosporin	19%; n = 21 isolates	–	–

* Blood cultures only.
† *Klebsiella* spp.

These were 11 observational and one case-control study citations describing acquired infection and mortality rates, as well as epidemiology of Gram-negative infections, in Latin American PICUs and NICUs [9-20]. The studies varied widely with respect to location, time period, patient population, design, and data reporting, which prevented inter-study comparisons. Ten of the 12 studies were performed in South America, with five conducted in Brazil. Seven of the 12 studies focused on the neonatal population exclusively [10-13,15,17,19], six of which were conducted in the NICU [10-12,15,17,19]. Blood was the most common collection site for pathogens. Only one study dealt with Gram-negative infections exclusively [19].

Clinical epidemiology

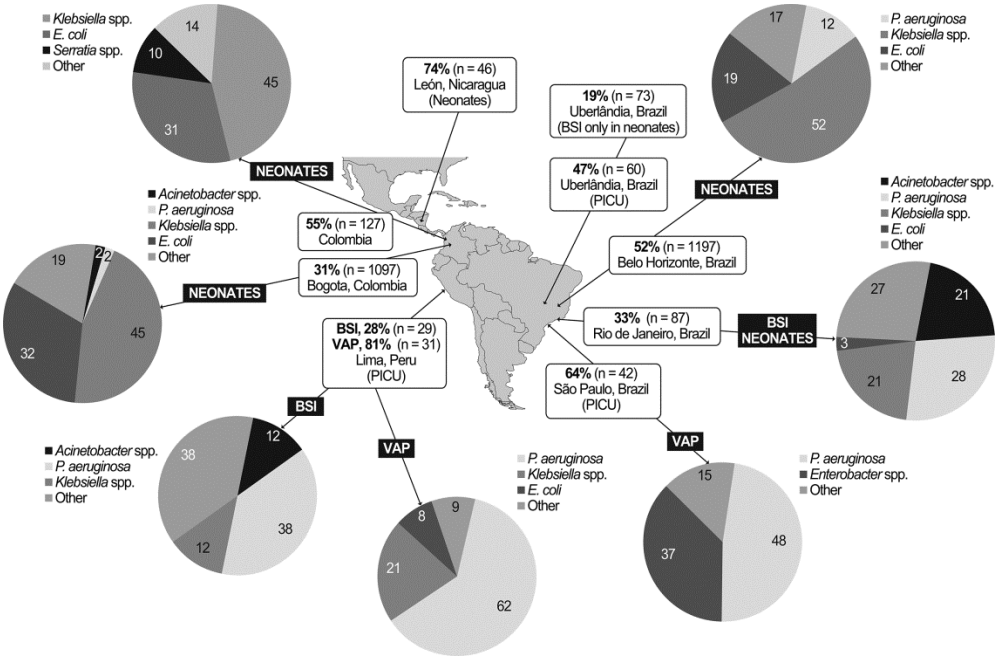
Eight of the 12 studies reported data regarding acquired infection and mortality rates (Table 2) [9-11,14,16-19]. The infection rate (35% to 37% vs ≤ 24%) and incidence rate (58% vs ≤ 20%) was highest in studies enrolling significant proportions of extremely low-birth-weight infants, as evidenced by data from a 10-year prospective follow-up study and a 3-year retrospective study, both of which were conducted in Brazil [10,19]. These findings were supported by data from the largest and longest study, conducted in Mexico, which revealed that incident rates in NICUs and PICUs (3.5 and 3.3 cases per 100 discharges, respectively) were approximately two-fold higher than in other pediatric care areas [9]. However, it should be noted that incidence rates of all BSI in NICUs and PICUs decreased markedly over the last 3 years of this study, from 2002 to 2005 [9].

Mortality specifically attributed to nosocomial infections acquired in PICUs and NICUs was not routinely reported. Nevertheless, enough crude mortality data were collected in critically ill children with and without a nosocomial infection to indicate that 30% to 38% of patients in PICUs and NICUs who acquire an infection will die (Table 2) [16,19]. Notably, the crude mortality rate associated with sepsis was higher among very-low-birth-weight infants who had contracted a Gram-negative infection than among counterparts who had contracted a Gram-positive infection (45% vs 13%, $p < 0.05$) [19]. Mortality was highest among very-low-birth-weight infants with *Pseudomonas aeruginosa* sepsis (six of eight infants died; $p < 0.05$) [19].

Frequency and distribution of Gram-negative infections

Frequency of Gram-negative infection ranged from 14 of 73 (BSI) isolates (in Uberlandia, Brazil) to 25 of 31 ventilator-associated pneumonia (VAP) isolates (in Lima, Peru) taking into account all PICU and NICU infections (Figure 2) [10,11,13-16,18,19]. When studies reporting < 100 clinical isolates were excluded,

Figure 2. Frequency and species of Gram-negative pathogens isolated from pediatric and neonatal intensive care units (PICUs and NICUs) in Latin America [10,11,13-16,18,19]. The distribution of Gram-negative pathogens was not available for all studies reporting incidence rates. BSI = bloodstream infections, VAP = ventilator-associated pneumonia



this range narrowed to 31% and 55% (both in Colombia). There was no obvious trend to indicate that Gram-negative bacteria were isolated more or less often in a specific pediatric or neonatal population or body compartment.

Klebsiella spp., *Escherichia coli*, and *P. aeruginosa* were the most frequently isolated Gram-negative bacteria in pediatric and neonatal populations (Figure 2). *Klebsiella* spp. were isolated in 21% to 52% of Gram-negative neonatal infections, and 12% to 21% of BSIs. *E. coli* was responsible for 3% to 32% of Gram-negative neonatal infections. The frequency of *P. aeruginosa* infection in the larger NICU studies varied widely from 2% (in Bogotá, Colombia) to 28% (in Rio de Janeiro, Brazil). In addition, two small studies reported that half of 30 and 27 VAP isolates from PICUs in Lima, Peru, and São Paulo, Brazil, respectively, belonged to this species. Hospital-acquired meningitis/ventriculitis occurred with an incidence range of 0.7% to 3% (in two NICUs in Colombia and one NICU in Belo Horizonte, Brazil) [10,11,13], but the proportion of meningitis/ventriculitis due to Gram-negative bacteria was only reported by one of the Colombian studies (three of eight cases) [13].

Phenotypes

Only six of the 12 studies reported some level of antimicrobial susceptibility data, clearly indicating that there has been a paucity of surveillance studies examining the phenotypes of Gram-negative bacteria causing HAIs in Latin American PICUs and NICUs [10,13-16,20]. In one of only two comprehensive studies, network surveillance conducted throughout Chile in 2009 revealed that 77% of *P. aeruginosa* strains collected from children were susceptible to third-generation cephalosporins (Table 3) [20]. All strains of *Klebsiella pneumoniae*, and approximately 80% of *P. aeruginosa* strains, were susceptible to carbapenems [20]. The susceptibility of *E. coli* and *P. aeruginosa* strains to third-generation cephalosporins was assessed in a 10-year prospective surveillance of HAIs in six NICUs in Belo Horizonte, Brazil (Table 3) [10]. Nearly two thirds (64%) of *K. pneumoniae* isolates were resistant to ceftriaxone, cefotaxime, or ceftazidime [10]. Resistance of *P. aeruginosa* to quinolones (ciprofloxacin or ofloxacin) was extremely low and all strains were susceptible to carbapenems [10].

Findings from a number of small but geographically and temporally diverse observational studies in pediatric patients revealed that multidrug-resistant strains of Gram-negative bacteria are harming public health [14-16]. In the northern part of the continent, 16 of 20 isolates of Gram-negative bacteria causing septicemia in newborns in Leon, Nicaragua, were ESBL-producers, harboring genes encoding for TEM and CTX-M [15]. In the western part of the continent, multidrug-resistant strains of *P. aeruginosa* and *K. pneumoniae* were detected in a small surveillance study conducted at the PICU of the Instituto Nacional de Salud del Niño of Lima, Peru, during 2006 and 2007 [16]. Of the 16 *Pseudomonas* spp. strains isolated from endotracheal aspirates, 12 were resistant to meropenem, 13 were resistant to ceftazidime, and 14 were resistant to amikacin [16]. ESBL was produced by one of three *E. coli* strains and five of ten *Klebsiella* spp. strains, but none of these strains were resistant to meropenem. Finally, in a PICU of Santa Casa de São Paulo, Brazil, during 2002 and 2003, of ten VAP cultures, two were ß-lactamase–producing *Klebsiella* spp. and one was a *P. aeruginosa* culture resistant to carbenicillin [14].

Outbreaks

The true epidemiology and burden of multidrug-resistant Gram-negative infections in PICUs of Latin America have not been fully captured by surveillance studies, as evidenced by the plethora of independent single- and multicenter studies describing sporadic outbreaks of recalcitrant infections. Figure 3 illustrates that PICUs and NICUs of Central America, Venezuela, and Brazil have been inundated by lethal outbreaks of multidrug-resistant strains of *K. pneumoniae*, which harbored genes for ESBL enzymes and carbapenemases [21-27]. These outbreaks were, in part, propagated by breaches in infection-control procedures, including inappropriate intravenous solution use, inadequate hand hygiene and contact precautions, and failure to screen the local environment and equipment as sources of contamination [21-23]. The capacity for virtually all ESBL-producing strains of *K. pneumoniae* to form biofilms underscores the need to sterilize and replace equipment appropriately [28].

Cross-transmission via the hands of health care workers was also the likely source of an outbreak of *E. coli* in NICUs in Mexico City during 2008 [29]. Twelve *E. coli* strains were isolated from blood, urine, or indwelling catheter samples from five preterm infants within a 3-day period. Pulsed-field gel electrophoresis revealed two profiles: one (pattern A) was identified as the outbreak's cause and an outcome of cross-infection, whereas the other profile (pattern

B) had the same serotype (O20:H9) but was not genetically the same. Pattern A was resistant to aminoglycosides, ampicillin/sulbactam, third-generation cephalosporins, and fluoroquinolones, but susceptible to other β-lactam antibacterial agents and trimethoprim/sulfamethoxazole. Isolates in pattern B were resistant to piperacillin, ampicillin, and trimethoprim/sulfamethoxazole, but susceptible to amikacin, carboxypenicillin, and β-lactam antibacterial agents.

In Venezuela (Mérida), a humidifier located in the high-risk NICU was the source of 20 *Acinetobacter baumannii* strains exhibiting high levels of resistance to commonly used antimicrobial agents. All of the strains produced TEM-1 enzymes, and two strains produced OXA-58 enzymes (the first report in Venezuela) [30]. In addition to the evolution of established Gram-negative bacteria into multidrug-resistant pathogens, there is always the potential for less well-known species to emerge as public health threats. For example, during 2005 in a Brazilian NICU (Rio de Janeiro), *Acinetobacter soli* was the cause of BSIs in five neonates, resulting in the death of one [31]. *A. soli* had previously only been detected in forest soil. Since four of the five neonates were receiving antibiotics to which the bacterial isolate was susceptible, it was considered likely that a contaminated intravenous solution was the source of the outbreak [31].

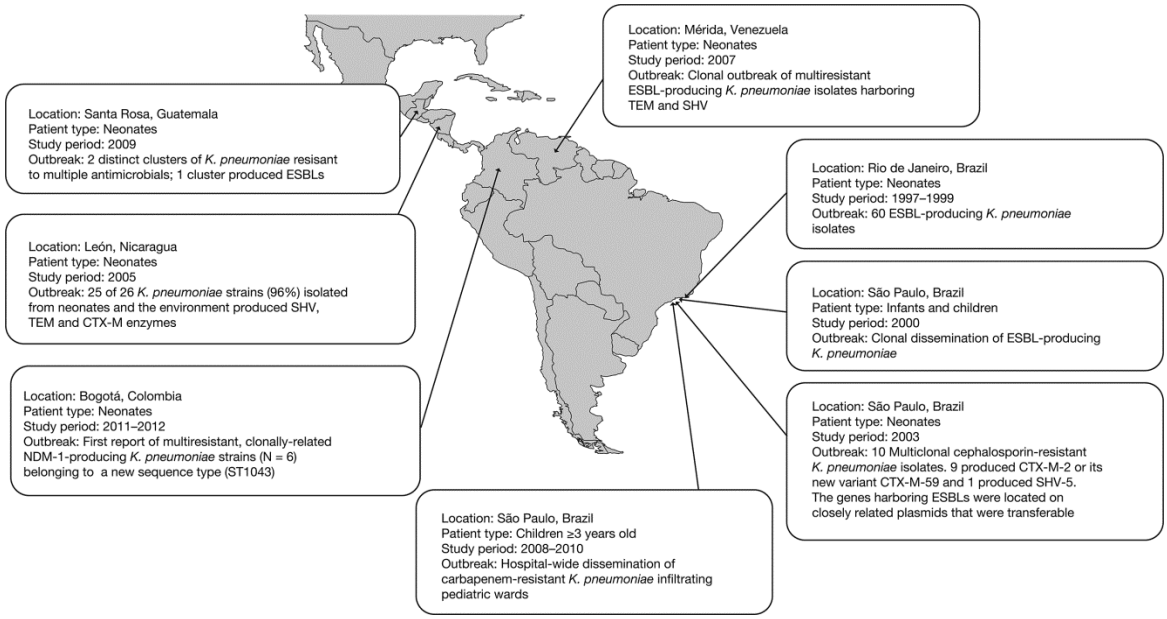
Infection control

The primary issues in preventing HAIs in PICUs and NICUs are: (1) risk-factor identification and management, and (2) awareness of the sources of infectious agents and transmission routes. Murni *et al.* [32] performed a systematic review of nosocomial infections in the developing world that included two studies in Latin America. The authors concluded that there were few studies evaluating infection-control measures in developing countries.

Specific risk factors associated with the development of BSIs are prematurity and low birth weight, age < 1 year, admission into ICU, underlying disease, prior surgery, hemodialysis, duration of hospital stay, elevated Pediatric Risk of Mortality (PRISM) score, use of central venous catheters, and parenteral nutrition [6,33-37]. Not surprisingly, some of these risk factors also place the patient at risk for death. In addition to nosocomial infection, a systematic review of the literature identified other risk factors associated with mortality: leukemia; lymphopenia; neutropenia; corticosteroid therapy; multiple organ failure; previous antimicrobial therapy; catheter use duration; candidemia; cancer; bacteremia; invasive procedures; mechanical ventilation; transport out of the PICU; methicillin-resistant *Staphylococcus aureus*, *P. aeruginosa*, and *Burkholderia cepacia* infections; and Acute Physiology and Chronic Health Evaluation (APACHE) II scores > 15 [38].

A few Latin American studies have assessed the

Figure 3. Main features of *K. pneumoniae* outbreaks in Latin American pediatric and neonatal intensive care units [21-27]. ESBL = extended-spectrum β-lactamase, NDM-1 = New Delhi metallo-β-lactamase, PICU = pediatric intensive care unit.



risk-factor profile of Gram-negative infections among children in the ICU setting [12,14,15,39]. Cyanosis was the only independent risk factor for acquisition of a Gram-negative bacterial septicemia in León, Nicaragua [15], whereas HAIs in eight Colombian NICUs were associated with use of postnatal steroids and histamine 2 receptor blockers [12]. In São Paulo, Brazil, there was a significant increase in the incidence of positive *Pseudomonas* spp. cultures collected from the respiratory tract of children on ventilator support [14]. Three sequential tracheal aspirates were obtained from each child (within 6 hours of intubation and 48 and 96 hours after the first sample); incidence of positive cultures, 6%, 12%, and 22%, respectively (relative risk, 2.1; 95% confidence interval, 1.4–3.1). This finding suggests that endotracheal intubation compromises the barriers between the environment and the tracheal mucosa of patients, allowing progressive colonization by ubiquitous *Pseudomonas* spp. with respect to time. Over a 5-month period during 2008 in Recife, Brazil, use of third-generation cephalosporins and stay in PICU ≥ 7 days were risk factors for colonization by ESBL-producing *Klebsiella* spp. in children [39].

Among all of these factors, the only ones that can be adjusted to minimize infection and mortality rates are the direct contact and intervention of health care staff with patients. After high rates of BSIs were acknowledged by staff at a 292-bed tertiary care children's hospital in Arkansas, USA, the stepwise introduction of maximal barrier precautions, transition to antibiotic-impregnated central venous catheters, annual hand-washing campaigns, and changing of skin disinfectant from povidone-iodine to chlorhexidine resulted in a 75% relative risk reduction in the BSI rate (from 10/1,000 central venous catheter-days in 1997 to 3.0/1,000 central venous catheter-days in 2005) [40]. Other multidimensional infection-control strategies developed by the International Nosocomial Infection Control Consortium and World Health Organization involving education and performance feedback, and use of sequential checklists that remind health care personnel to take part in prevention bundles, have reduced HAI rates in developing countries, including those of Latin America [41-44]. Furthermore, proper hand hygiene appears to be an effective strategy to prevent transmission of pathogens causing outbreaks in PICUs and NICUs of Latin America [29]. Hospital leadership of a multidisciplinary team, as well as ongoing data collection, interpretation, and dissemination subsequent to the introduction of specific evidence-based interventions, is required to implement these infection-control programs successfully.

Given the epidemic of multidrug-resistant strains of Gram-negative bacteria circulating within the hospital setting of Latin America, staff microbiologists must be aware that infectious agents can colonize and spread from any surface or device [45] and be colonized in new patients upon admission to the ICU [39]. It is hoped that high-throughput molecular biology techniques will enable detection and monitoring of viable pathogens within PICUs and NICUs [45].

Misuse of antimicrobial agents is the other main risk factor that can be modified in order to mitigate colonization of Gram-negative bacteria and onset of multidrug-resistant infections [39]. Antimicrobial stewardship programs provide instructions on appropriate antimicrobial use and administering the correct dose via the correct route of administration, as well as the optimum duration of therapy [46]. These initiatives have real potential to reduce the prevalence of bacterial resistance, with associated reductions in morbidity, mortality, and costs [46].

Discussion

Compared to developed countries, there are higher infection rates in PICUs and NICUs of Latin America. Observational data collected from developed countries of Europe and North America suggest that between 6% and 15% of children admitted to a PICU develop health care-associated infections [4,47], which have an attributable mortality of approximated 8% to 11% [5,47,48]. Our literature review indicated that only one study reported an infection rate (5%) below the range reported in developed countries, whereas all of the other studies reported higher infections rates, ranging between 16% and 37% (Table 2). Moreover, mortality in PICUs and NICUs is high. The literature that we analyzed did not report attributable mortality rates. Although there were no directly comparable data pertaining to outcomes in extremely low-birth-weight infants in Latin American NICUs, we did find that this vulnerable patient population fared much worse than older children housed in PICUs, especially when infection was caused by a Gram-negative pathogen.

Microbiologically, there were large differences in the *frequency* of Gram-negative infections across Latin American PICUs and NICUs — but not in the *type* of species isolated. Positive cultures for *Klebsiella* spp., *P. aeruginosa*, *and E. coli* were commonplace, whereas the incidence of infections by *Acinetobacter* spp. was sporadic. We were particularly concerned

about the high frequency of *Pseudomonas* spp. and *Acinetobacter* spp., given their propensity to colonize almost any habitat and their capacity to acquire antimicrobial-resistance mechanisms, as well as their high virulence. The weight of evidence in this review suggested that the susceptibility of both of these species to quinolones and third-generation cephalosporins was low, and the susceptibility of enterobacteria in general to these antimicrobial drug classes was moderate at best. The predominant resistance mechanisms used by these pathogens appeared to be ESBL production, which is a problem because this phenotype often harbors aminoglycoside-, tetracycline-, sulfonamide-, or fluoroquinolone-resistance genes located on the same mobile genetic elements [49]. Clinicians have the option to treat infections caused by multidrug-resistant strains with carbapenems, bearing in mind that this intervention may be a risk factor for emergence of carbapenem-resistant strains [50]. Indeed, we identified an observational study conducted in Chile reporting infections by *P. aeruginosa* in PICUs that demonstrated resistance to carbapenems [20], and two outbreaks of carbapenem-resistant *K. pneumoniae* (in Colombia and Brazil) [26,27].

The limitations of this review should be acknowledged when considering the results. There was a complete lack of published data available for some countries in Latin America as well as bias in data reported from different studies (e.g., methodology of data reporting, collection, and analysis). In general, data collected from single-center studies are more likely to report elevated resistance rates than network studies. Additionally, we did not include information reported only in local conferences or in local databases. There is a clear need to publish in the scientific literature information collected by nosocomial infection control surveillance teams of the most important pediatric hospitals in each Latin American country.

Conclusions

Despite a lack of representation from some countries, our review of the literature indicates that there is an endemicity of multidrug-resistant Gram-negative infections in Latin American PICUs and NICUs complicated by sporadic episodes of clonal outbreaks continent-wide. The main factors predisposing to this problem are crowded PICUs and NICUs coupled with disproportionately low levels of nurses and other professional health care staff. Staff members caring for critically ill patients in Latin American PICUs and NICUs do not always receive appropriate training, especially on infection control. The situation will likely deteriorate unless specific measures are adopted in all PICUs and NICUs in Latin America — specifically, hand hygiene, antimicrobial stewardship, and multi-level, real-time, surveillance programs.

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