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ORIGINAL ARTICLE

Healthcare associated infections by multidrug resistant organisms in paediatric intensive care: Analysis of four years

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Abstract

The objective of this study was to report healthcare associated infections (HAI) in paediatric intensive care units, caused by multidrug resistant bacteria, and what measures can be taken to control them. A retrospective descriptive study of all HAI in three paediatric intensive care units and one neonatal intensive care unit of Prontobaby Hospital da Criança, Rio de Janeiro, Brazil was performed.

Between 2009 and 2012 we had 36,883 patients-days which 10,442 were from NICU and 26,441 from the PICUs. We reported 482 healthcare-related infections (109 from NICU and 373 from PICU). Gram negative bacteria were the most prevalent group, also in NICU (22.9%) as in PICU (35.9%). The rates of multiresistant Gram positive bacteria (MRSA and CoNS multiresistant) of HAI in the PICUs and NICU were 22% (22/100) and 13.6% (3/22) respectively. The rates of multiresistant Gram negative bacteria (ESBL group, *Pseudomonas aeruginosa* resistant to carbapenem, *Acinetobacter* sp multiresistant, *Burkholderia cepaciae* and *Stenotrophomonas maltophilia)* in PICUs and NICU were 49.3% (66/134) and 56% (14/25) respectively. Ventilator-associated pneumonia was the most common type of infection (incidence density rate of 7.0 per 1000 VM-days) in PICU. A bundle of measures (training of team assistance, oral chlorexidine to all intubated children and use of bacteriological filters in expiration phase) was implemented in the two years of study and reduced the number of VAP to 2.2 per 1000 VM-days in the two last years.

In conclusion, we found higher rates of multiresistant Gram negative bacteria also in PICU as NICU and a bundle of measures to control VAP in PICU was a well done intervention.

Keywords: Cross infection and prevention and control; ICU, paediatric; Multiple drug resistance, antibacterial

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Introduction

Healthcare associated infections (HAI) are a global preoccupation in intensive care units. Prevalence of infections in paediatric intensive care units (PICU) ranges from 6 to 12% in paediatric intensive care units and 10 to 25% in neonatal intensive care unit (NICU) in different countries.[1] Several countries around the world has surveillance system of healthcare associated infections including paediatric patients, but focus are based specifically on infections related to invasive devices and real number of global infections is not known[2,3]

Bloodstream infections related or not to central venous catheter are described as a most common hospital acquired-infection.[1,4] Others prevalent infections in PICU and NICU are ventilator associated pneumonias, urinary tract infections, gastrointestinal infection, surgical site infections and cutaneous infections. Many healthcare associated infections occur as outbreaks related to common source, as healthcare workers or contaminated medical devices.[5,6]

Knowledge about common microorganism that causes HAI is important to define a better approach to patient, considering judicious use of antibiotics. In bloodstream infections, Coagulase negative *Staphylococcus, Staphylococcus aureus, Enterobacter* spp, *Klebsiella pneumoniae* and *Candida* spp are frequently reported.[7,8] Gram-negative bacteria as *Pseudomonas* spp, *Serratia* spp, *Escherichia coli* and *Acinetobacter* spp and S. *aureus* are related to pneumonia associated to mechanical ventilation (VAP).[9,10,11] Enteric Gram-negative bacteria including *Enterobacter* spp, *Proteus* spp, *E. coli* and Fungi as *Candida* spp, are reported as common agents of urinary tract infection related to vesical catheter.[12,13,14]

Multidrug resistant bacteria (MDR) are found in almost all PICU and NICU and its importance is growing around the world. Anderson *et al.*,[15] found that 23% of *Enterobacter* spp, in colonisation or infection in PICU, are extend spectrum beta-lactamase producers. Hufnagel *et al.* found 33% of neonates of a NICU colonised by *Entercoccus* spp.[16]

The aim of this study was to report principal healthcare associated infections in intensive care units of children caused by multidrug resistant bacteria, among four years of follow-up and measures to control them.

Material and Methods

We performed a retrospective descriptive study of all hospital acquired-infections in three paediatric intensive care units (30 beds) and one intensive neonatal care unit (15 beds) of Prontobaby Hospital da Criança.

Population

The hospital is a private healthcare service located at Rio de Janeiro city, Brazil and patients were admitted from others healthcare units or by own emergency room or from wards of the hospital.

The hospital didn't have obstetric service and neonates are referred from others services. All the units are located at the same floor of the hospital, but in different sectors.

Hospital acquired infections surveillance

In Brazil, surveillance of HAI in hospitals with 10 or more beds of intensive care units is compulsory by a federal law.[17] In this study, surveillance was performed daily by a nurse or a physician, both with post-graduation in paediatric infectious diseases and members of Infection Committee Control (ICC) of the institution.

Healthcare associated infection prevention measures

The ICC performed the following measures to prevent HAI, during the period of the study: practical routine training with multidisciplinary team ("in service training") about infection prevention, electronic surveillance of patients colonised by MDR organisms, annual review of written routines, daily discuss with PICU and NICU staff about antibiotics and mensal meetings of ICC with presentation of prevalent agents of HAI and principal sites of infections.

Definition of nosocomial infections

We utilised Center for Disease Control (CDC) and National Healthcare Safety Network (NHSN) criteria for HAI definitions in children.[18]

All children that stay for more than 24 hours are included at this study and all children that stay less than 24 hour was excluded. Principal sites of invasive devices (related to central venous catheter, pneumonia related to mechanical ventilation and urinary tract infections related to urinary catheter) were measured.

Definition of multidrug-resistant bacteria (MDR)

We also used CDC criteria for MDR organism in healthcare settings.[19] We also defined Coagulase negative staphylococcus (CoNS) as resistant if isolates were resistant to four or more different antibiotics classes including: oxacillin, aminoglycosides, trimethoprim sulfamethoxazole, clindamycin and quinolones.[20]

Microbiological isolation

Isolation of microbiological species was performed by laboratory of microbiology of institution according medical staff solicitation. Bacteria were isolated by semi-quantitative process (Auto-Scan 4- SIEMENS). Manual antibiogram was done when necessary by disk-diffusion according CLSI recommendations.[21]

Analysis of data

The rate of infections associated with invasive devices was measured monthly by incidence density (number of infections associated with a specific device / number of device-days X 1000). For infections associated with devices, at least 50 device-days per month were considered. If the number of device days was less than 50 in one month, we add number of device days of subsequent months, until we reached 50 device-days.

Microorganisms found and implicated in infections associated with health care were tabulated and analysed individually. Analysis of demographic variables was carried out descriptively.

The infections were analysed by the Program EPI INFO 6.0- CDC Atlanta-USA. We used Satterhwaite test to compare means and $\chi 2$ test to compare proportions. We considered a value of statistical significance when the p value less than 0.05.

Results

Between January 1ST 2009 and December 31st 2012 we had 36,883 patients-days which 10,442 were from NICU and 26,441 from the three PICU. In this period we registered 482 healthcare-related infections (109 from NICU and 373 from PICU). Table I show the causative organism of HAI, in three PICU and one NICU of Prontobaby.

Table I. Causative organism of HAI in three PICU and one NICU of Prontobaby (2009-2012)

Agents	PICU N (%)	NICU N (%)	Total N (%)
Gram negative bacteria	134 (35.9)	25 (22.9)	159 (33)
Gram positive bacteria	100 (26.8)	22 (20.2)	122 (25.3)
No agent identified	77 (20.7)	44 (40.4)	121 (25.1)
Fungi	52 (13.9)	44 (40.4)	65 (13.4)
Mixed	6 (1.7)	4 (3.7)	10 (2)
Virus	4 (1)	2 (1.8)	6 (1.2)
Virus	**373 (100)**	**109 (100)**	**482 (100)**

The overall rates of multiresistant Gram positive bacteria (MRSA and multiresistant CoNS) of HAI in the PICUs and NICU were 22% (22/100) and 13.6% (3/22) respectively. The rates of all multiresistant Gram negative bacteria (ESBL group, *P. aeruginosa* resistant to carbapenem, multiresistant *Acinetobacter* spp, *B. cepaciae and S. maltophilia*) in PICUs and NICU were 49.3% (66/134) and 56% (14/25) respectively. Table II shows the profile of principal multiresistant bacteria in PICUs and NICU.

Table II. Profile of principal multiresistant bacteria of HAI in PICUs and NICU of Prontobaby, 2009-2012

	PICU (resistant/total of isolated) (%)	NICU (resistant/total of isolated) (%)	P value
Gram positive bacteria			
• *S. aureus*	3/3 (100)	11/14 (78.6)	0.43
• CoNS	0/18 (0)	11/79 (13.9)	0.20
Gram negative bacteria			
• ESBL producers*	10/17 (58.8)	32/67 (47.8)	0.30
• *Pseudomonas aeruginosa*	0/3 (0)	23/51 (45)	0.35
• *Acinetobacter* spp	0/1 (0)	5/10 (50)	0.33

**Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp, *Serratia* spp, and *Proteus* spp

Nosocomial infections related to invasive devices

We also measure HAI related to central venous catheter (Central line associated bloodstream infection – CLABSI), pneumonia related to mechanical ventilation (VAP) and urinary tract infection related to urinary catheter (CAUTI). In table III, we show principal agents according to invasive devices.

Devise days measured in PICU were: 6,810 ventilator days (density of incidence of VAP of 7.0 per 1,000 ventilator-days, 13,157 CVC-days (density of incidence of CLABSI of 3.5 per 1,000 CVC days) and 4,439 urinary catheter days (density of incidence of CAUTI of 6.3 per 1,000 urinary catheter-days).

Table III. Number of HAI by different agents related to invasive devices in three PICU of Prontobaby (2009-2012)

Agents	CLABSI	VAP	CAUTI
Fungi	12	5	19
Gram positive bacteria	18	7	1
Gram negative bacteria	12	30	8
Mixed	0	3	0
No agent	4	3	0
Total	**46**	**48**	**28**

Organisms causing infections related to invasive devices in PICU

The causative organisms for BSI were: 34% CoNS, 14% Candida sp, 12% *Pseudomonas aeruginosa* and 40% for others organisms. *Pseudomonas aeruginosa* (32.7%), *Klebsiella pneumoniae* (10.9%), CoNS (9%) and *Candida* spp (5.5%) were more commonly found in VAP. In urinary tract infections, principal agents were Fungi and Gram negative bacteria. *Candida albicans* was the most prevalent type of fungi and *Klebsiella pneumoniae* represented 50% of the isolated Gram negative bacteria.

There were 40 VAP infection in 2009 and 2010 against 8 in 2011 and 2012 ($P < 0.01$). Density of incidence of VAP considering these years were 12.4 in the first period versus 2.2 per 1000 ventilator-days in the second period. Because the number of VAP was higher than the median of CDC/NHSN reports, in December of 2010, we implemented a bundle of measures to prevent and reduce VAP, including additional training of staff, use of oral chlorexidine gluconate 0.12% and bacteriological filters in expiration phase to all patients during mechanical ventilation period.

We didn't find a significant statistical difference in CVC and UTI infections rates during the four years of study (data not showed). No specific measures were done to reduce infections related to these devices.

In NICU, patients were separated according the birth-weight: (<750g: 14 patients-days, 751g to 1000g: 230 patients-days, 1001g to 1500g: 631 patients-days, 1501g to 2500g: 2,389 patients-days and >2500g: 7,178 patients-days). Devices associated HAI were also measured according to birth-weight:

- <750g: no HAI associated to invasive device;
- 751g-1000g: no HAI associated to invasive device;
- 1001g-1500g: one CLABSI (373 CVC days with 2.6 density of incidence of BSI related to CVC);
- 1501g-2500g: two CLABSI (1337 CVC days with a 1.5 density of incidence of BSI related to CVC), two VAP (444 ventilator-days with a 4.5 density of incidence of VAP);
- >2500g: 1 CLABSI (2232 CVC days with a 0.4 density of incidence of BSI related to CVC) and five VAP (1015 ventilator-days with a 4.9 density of incidence of VAP).

Discussion:

In different PICUs around the world, HAI represent a great problem because of increased mortality, morbidity and costs of hospital stays.[1,22,23] Surveillance of HAI in PICU and NICU is necessary to determine prevalent pathogens and define strategies to use the best antibiotic classes. It is important to known that each unit have its own specific flora and it is necessary to be careful when extrapolating data to others PICUs. For example, in our study the principal HAI was pneumonia associated to mechanical ventilation followed by bloodstream infection and urinary tract infection. These results are different of others studies performed in Brazil and others countries in which BSI was the principal type of nosocomial infection.[22-25]

We believe that is not right to compare rates of HAI in different institutions because of different profiles of patients. Institutions need to establish parameters to decrease rates, considering prevalent types of HAI. Despite these observations, our CLABSI rates in PICUs were lower compared with a surveillance system of São Paulo State, Brasil.[26] Similar study performed in Brazil, in a single PICU of a teaching hospital, found BSI rates of 18.2 per 1000 device-days, 17.8 for VAP and 7.0 to CAUTI.[23] Becerra *et al.*, studying HAI in a PICU of Peru reported rates of 18.1, 7.9 and 5.1 per 1000 devices–days for CLABSI, VAP and CAUTI respectively.[27]

We found CoNS, *Candida* spp and *P. aeruginosa* as prevalent agents of CLABSI that was comparable with previous studies.[4,8] Pereira *et al.* studying BSI in 16 different paediatrics hospitals in Brazil found that Gram-negative organisms caused 49% of infections and Gram-positive 42.6%.[28] In this report the most common pathogens were CoNS (21.3%), *Klebsiella* spp (15.7%) and *S. aureus* (10.6%). In the same study, meticillin resistance was detected in 27% of *S. aureus* isolated and 21,5% of *Pseudomonas aeruginosa* were carbapanemases producers. In our study, we found higher levels of resistance in isolates of *S. aureus* implicated in HAI, both in PICU and in NICU.

For VAP, the three more common agents in our study, were *P. aeruginosa, K. pneumoniae* and CoNS that was similar to previous reports.[10] During the follow up of patients we found a higher rate of VAP as the major cause of a specific type of HAI. These results are different from others studies in which BSI are the principal cause of HAI.

The excessive number of VAP in PICUs (not in NICU) motivate a specific action by ICC to reduce rates of VAP. Oral chlorexidine is a well known effective measure recommended to reduce VAP in adults. In children, several reports showed conflicting results.[29,30] We also instituted bacteriological filters in expiration phase, also reported as a measure strongly recommended in adults to reduce VAP. It was not possible to define

which measure reduces VAP in this study, in the two subsequent years after their institution. We believe that a combined effect contributed to reduce VAP.

In NICU, the majority of neonates were more than 2500g of weight because the hospital didn't have an obstetric service. All the newborns were referred from others units. As the PICU, the principal type of HAI related to invasive device in NICU, was VAP.

In our study we found a higher number of urinary tract infections caused by fungi. In adults, according to several reports and guidelines is difficult to make a true diagnosis because colonisation of genito-urinary tract is a common finding. In children, there's no consensus about the correct diagnosis, manly in newborns. In our units, patients are critically ill children, with many invasive devices, longer stay and use of broad spectrum antibiotic, which is possible to lead to fungal infection. Recent reports from USA and China showed that UTI caused by fungi isn't an uncommon finding.[31,32]

In this paper, we found higher levels of resistant Gram negative bacteria that caused HAI, manly ESBL and carbapenemase producers. In PICU, it's a problem because we have fewer options of newer antibiotic to treat infections due to MDR agents.[33] Tygecycline, a newer agent with broad spectrum is recommended only to children older than eight years of age.[34] Others new agents which are recommended, such as daptomycin, doripenem, ertapenem, still have little experience to be used with confidence in children.

Infection Control Committee is fundamental in PICU and NICU to prevent and control HAI. Knowledge about levels of resistance of Gram positive and negative bacteria in ICUs is necessary to help prescribe correct antibiotics to children. In our case, in case of suspect of HAI, use of broad spectrum antibiotics is strongly necessary, to save the children's life. In conclusion, VAP was the most important HAI detected in intensive care units of children in a developing country. Specific measures, such as oral chlorexidine 0.12% and use of bacteriological filters in expiration phase, were successful measures to reduce VAP rates. The efficacy of these procedures needs to be evaluated in future studies.

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