Risk factors for healthcare-associated infection in pediatric intensive care units: a systematic review

Fatores de risco para infecções associadas aos cuidados de saúde em unidades de terapia intensiva pediátrica: uma revisão sistemática

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Abstract

A systematic review of observational studies on risk factors for healthcare-associated infection in pediatric Intensive Care Units (ICU) was carried out. Studies indexed in MEDLINE, LILACS, Cochrane, BDENF, CAPES databases published in English, French, Spanish or Portuguese between 1987 and 2006 were included and cross references added. Key words for search were "cross infection" and "Pediatric Intensive Care Units" with others sub-terms included. 11 studies were selected from 419 originally found: four studies had healthcare-associated infection as the main outcome without a specific site; three articles identified factors associated with lower respiratory tract infection (pneumonia or tracheitis); three articles were concerned with laboratory-confirmed bloodstream infection; and a single retrospective study analyzed urinary tract infection. The production of evidence on risk factors Paediatric ICU has not kept up the same pace of that on adult – there are few studies with adequate design and statistical analysis. The methodological diversity of the studies did not allow for a summarized measurement of risk factors.

Cross Infection; Pediatric Intensive Care Units; Delivery of Health Care

Introduction

Substantial progress has been made in the surveillance of healthcare-associated infections (HAI), previously known as hospital infections. The identification of risk factors enables the development of preventive strategies [1,2]. Although the National Nosocomial Infection Surveillance System (NNIS) was established in 1970 in the United States, it was not until 1987 that Jarvis and colleagues published a study using data from the NNIS, stressing the higher incidence of healthcare-associated infection in children and adolescents as well as differences in the site and microorganisms involved [3]. Another ten years went by before the Centers for Disease Control and Prevention (CDC), in cooperation with the National Association of Children's Hospitals and Related Institutions (NACHRI), established the Pediatric Prevention Network (PPN) with the aim of determining the characteristics of hospital infection as well as developing and testing intervention strategies for reducing the occurrence of these events [4].

The incidence or prevalence rates of healthcare-associated infections in pediatric Intensive Care Units (ICU) and their sites vary considerably in both individual and multicentric studies, but most authors have progressively adopted the standardized methodology of the NNIS [5,6,7]. Although indicators differed according to the type of adult ICU (cardiothoracic, surgical, medical,

oncology, etc.), the NNIS system did not establish a classification for different types of pediatric ICU. Similarly, information reported on surgical patients in pediatric ICUs used to be combined with data on patients in adult ICUs in this surveillance system [8]. In the NNIS system, data were collected using standardized protocols that relied upon selected procedures such as urinary catheter, central line and ventilator utilization. Despite the advances made with this approach, these studies do not allow the establishment of associations other than those with the selected risk procedures.

Studies carried out to establish predictive models for healthcare-associated infection have investigated risk factors, both intrinsic and extrinsic, either separately or in combination. Intrinsic factors generally include age, gender, nutritional status, underlying disease and severity of the illness. To assess disease severity and to predict the risk of death, scores such as the *Paediatric Risk of Mortality* (PRISM), or its modified PRISM III version, and the *Paediatric Index of Mortality* (PIM) or its PIM II modification have been used [9,10,11,12,13,14,15]. Extrinsic factors such as aspects of treatment, available structure and the quality of care have been studied as well [16]. These include common invasive procedures (mechanical ventilation, central venous catheter, urinary catheter), the use of medication (antimicrobial agents, immunosuppressors, gastric acid blockers), parenteral nutrition and blood products, for example [14,15].

A large number of studies have demonstrated associations between different risk factors and healthcare-associated infection in adult ICU. Such studies have been carried out with a certain degree of standardization, which allowed systematic and non-systematic literature reviews to support the production of guidelines [17,18,19,20,21,22,23,24]. However it is inadequate to simply extrapolate data on adult ICU to paediatric ICU, as children are not little adults [25]. Pediatric ICUs are unique entities and require specific prevention and control strategies based on the results of studies carried out locally.

Healthcare-associated infections in paediatric ICUs result in substantial illness, mortality and high costs and requires specific prevention measures. This justifies the present systematic literature review, the aim of which is to describe the variables studied and those identified as risk factors for healthcare-associated infection in pediatric ICUs.

Material and methods

A protocol for the systematic review was designed based on the recommendations of the *Meta-analysis of Observational Studies in Epidemiology* (MOOSE) study group [26] and the definitions, outcomes and study eligibility criteria were defined a priori.

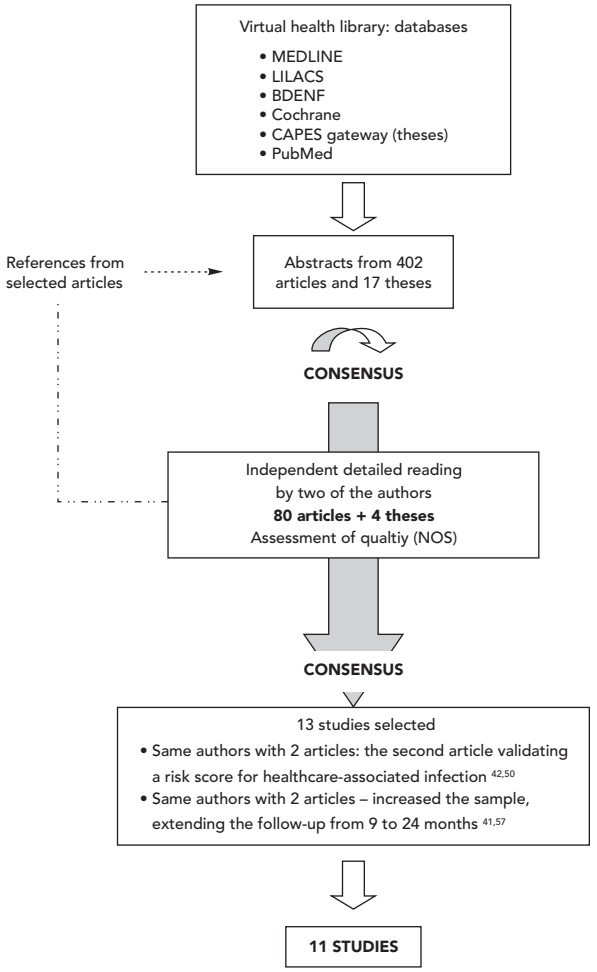
Observational cohort or case-control studies published between 1987 and 2006 in English, French, Spanish or Portuguese investigating healthcare-associated infection as an outcome in children or adolescents (from one month to 12 years old) in paediatric ICUs were included. Healthcare-associated infection and its specific infection sites were defined by the CDC criteria. There are specific criteria only for children ≤ 12 months [5,6,7].

As part of the search strategy, we conducted searches on MEDLINE, LILACS, Cochrane and BDENF (Nursing) databases through the Virtual Health Library (http://www.bireme.br/php/index.php). This was complemented by searches on PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez), as well as the CAPES gateway, which provides access to Masters' Dissertations and doctoral theses produced in Brazil (http://servicos.capes.gov.br/capesdw/). The Medical Subject Headings (MeSH) terms "*cross infection*" and "*intensive care units, paediatric*" were used. The term "*cross infection*" encompasses the following sub-terms: "*infection, cross*"; "*cross infections*"; "*infections, cross*"; "*infections, hospital*"; "*hospital infection*"; "*infection, hospital*"; "*hospital infections*"; "*infections, nosocomial*"; "*infection, nosocomial*"; "*nosocomial infection*" and "*nosocomial infections*". The term "*intensive care units, paediatric*" includes pediatric ICU. Equivalent terms were also searched in the other languages, according to their indexing notes. The following limits were used: humans, english, french, spanish, portuguese, infant: 1-23 months; preschool child; 2-5 years, child; 6-12 years. Reference lists of the articles selected for detailed reading were also hand searched (Figure 1).

After combining the results of all searches and excluding repeated references, abstracts from 402 articles and 17 theses were initially identified to be independently assessed by two of the authors (M. J. G. M. and M. F. P. M. A.) for eligibility for detailed reading. At this stage, intervention studies, studies with inadequate exposure or outcome definitions, and studies on healthcare-associated infection of a viral etiology were excluded. Abstracts for which there was no agreement as to the inclusion were analyzed jointly and the decision was made by consensus. Thus, 84 (80 articles and four theses) were ob-

Figure 1

Flowchart of study selection process in the systematic review of risk factors for healthcare-associated infection in pediatric intensive care units.



tained for detailed reading by the same two authors independently [27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110].

The same authors independently assessed the full papers on the basis of *a priori* eligibility criteria. Reasons for exclusion at this stage included studies that simultaneously analyzed children and adults [32], those with no multivariate analysis or with no presentation of association measures [33,34,35], those in which the outcome was death due to healthcare-associated infection [36] or that reported healthcare-associated infection in paediatric patients analyzing "stay in the pediatric ICU" was one of the risk factors [37,38]. Thirteen papers were selected after consensus, but two of these studies were subsequently excluded, either because the results of the study had already been published on the same population and assessed the same outcome, differing only in sample size [41], or because the authors performed a randomization of the cases for a validation study of the risk of healthcare-associated infection based on a previously published article [42].

Data from the final 11 selected studies were extracted into a pre-defined, Microsoft Excel v. 8.0

(Microsoft Corp., USA) spreadsheet, with the following parameters from each study: design, duration, setting, sample size, age range, main healthcare-associated infection indicators, results of univariate analysis and final model of the multivariate analysis.

Studies were assessed for quality using the "Newcastle-Ottawa Scale" [111] for cohort studies, which includes evaluation of selection (representativeness of exposed subjects, selection of non-exposed subjects, assessment of exposure and outcome not present at the beginning of the study), comparability and outcome (assessment, sufficient follow-up for the outcome to occur and percentage of losses). This scale is recommended by the Cochrane Non-Randomized Studies Methods Working Group available at the electronic address (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

Although the authors intended to construct a summarized measurement of the association between risk factors and healthcare-associated infection, this was not possible due to the diversity of outcomes and the manner in which the risk factors were defined or categorized.

Results

Description and quality of studies

The 11 selected studies included 10 papers published in peer-reviewed journals and one dissertation. Age range was heterogeneous and it was unclear whether some studies included newborns. The upper age limit found was 18 years. In these studies, the main outcomes were hospital infection in any site [50,51,52,54], laboratory-confirmed bloodstream infection [55,56,57], lower respiratory tract infection [58,59,60] and urinary tract infection [49]. All but one article [49] achieved the maximum score of the Newcastle-Ottawa Scale for cohort studies. Table 1 presents the characteristics of the selected studies.

Healthcare-associated infection as outcome

Four selected studies had healthcare-associated infection without a specific site as the main outcome [50,51,52,54]. These reported an incidence of healthcare-associated infection episodes ranging from 10 to 33%. The healthcare-associated infection incidence density (not reported in the study by Singh-Naz et al. [50]) ranged from 20.0 to 51.7 per 1,000 patients/days.

Among the intrinsic variables (displayed in Table 2) neither gender nor underlying disease remained associated to healthcare-associated infection in the final model in any of the four studies. Regarding disease severity as assessed by PRISM, Singh-Naz et al. [50] and El-Nawawy et al. [52] found a significant association to healthcare-associated infection (the latter used the PRISM III). Singh-Naz et al. [50] considered the mean PRISM score of the patients for the analysis, whereas Gilio et al. [51], who categorized the scores into four-unit intervals, found no significant association. Being a patient in the post-operative period was a risk factor in the analysis of Singh-Naz et al. [50] and Figueiredo [54]. This variable was not significant in the final model of Gilio et al. [51] and was not studied by El-Nawawy et al. [52].

Among the extrinsic factors, the time from pediatric ICU admission to the development of healthcare-associated infection was found to be significantly associated to healthcare-associated infection in the studies by Singh-Naz et al. [50] and Gilio et al. [51]. El-Nawawy et al. [52], on the other hand, found that healthcare-associated infection was associated to a longer mean length of hospitalization in the pediatric ICU.

The ratio of invasive procedures, defined as the relation between the total utilization time in days of each procedure (central venous catheter, urinary catheter and respirator) and length of stay in the pediatric ICU until healthcare-associated infection diagnosis, was associated to healthcare-associated infection in the studies by Singh-Naz et al. [50] and Gilio et al. [51]. In contrast, El-Nawawy et al. [52] and Figueiredo [54] did not find a significant association between invasive procedures and HAI.

Parenteral nutrition was a risk factor for HAI in the studies by Singh-Naz et al. [50], Gilio et al. [51] and Figueiredo [54]. This variable was not studied by El-Nawawy et al. [52].

Antimicrobial therapy and its duration were analyzed by Singh-Naz et al. [50] and Gilio et al. [51] and only in the former a significant association was found. Being admitted to the pediatric ICU being referred from wards other than the emergency room was a risk factor observed by El-Nawawy et al. [52] but was not studied by others.

Bloodstream infection as outcome

Three studies assessed risk factors for bloodstream infection – Laboratory-confirmed bloodstream infection (BSI-LCBI) [55,56,57], two of them included only patients with central venous access [55,56]. The BSI-LCBI rate (Table 1) ranged from 4.2 to 9.98%. Table 3 displays the set of variables associated to the outcome. Amongst intrinsic factors, underlying disease and age showed no statistical significance, whereas genetic syndrome remained in the model by Elward et al. [57].

Table 1

Characteristics of the studies included in the systematic review of observational studies on healthcare-associated infection (HAI) in pediatric Intensive Care Units, published between 1987 and 2006.

Study	Year	Outcome	Method				HAI indicators		
			Design	Year begun *, duration and setting	Number of participants	Age	Accumulated incidence		Incidence density #
							HAI rate ** (n)	PHAI rate *** (n)	HAI/1,000 patients-day
Singh-Naz et al. [50]	1996	HAI	Prospective cohort	1992, 12 months/USA	945	Mean in years with HAI = 0.6 and without HAI = 3.5	10.2 (96)	7.93 (75)	-
Gilio et al. [51]	2000	HAI	Prospective cohort	1994, 25 months/Brazil	500	28 days to 192 months	13.0 (65)	9.2 (46)	31.7
Figueiredo [54]	2002	HAI	Ambi-directional cohort	1997, 45 months/Brazil	425	28 days to 36 months	33.4 (142)	33.4 (142)	51.7
El-Nawawy et al. [52]	2006	HAI	Prospective cohort	2003, 12 months/Egypt	216	1 to 46 months	29.6 (64)	23.14 (50)	40.0
Odetola et al. [55]	2003	CRBSI ##	Retrospective cohort	1997, 30 months/USA	1,043	0 to 18 years (median 4.1 years)	4.2 (44)		By type of catheter/1,000 CVC - days ECLS = 22.1; RRT = 13.3; tunneled = 5.2; other ### = 3.3 By number of intravascular accesses ≥ 3 accesses = 20.1; 2 accesses = 12.1; 1 access = 4.0
Almuneef et al. [56]	2006	CRBSI	Prospective cohort	2000, 19 months/Saudi Arabia	501	Mean 2.6±3.4 years	9.98 (50)	9.18 (46)	20.06/1,000 CVC day
Elward et al. [57]	2006	BSI	Prospective cohort	1999, 24 months/USA	2,310	Includes < 28 days; 0 to 18 years (median 3.26 years)	5.36 (124)	3.76 (87)	9.00/1,000 CVC day
Fayon et al. [58]	1997	BNP	Prospective cohort	1991, 13 months/Canada	960	Mean 64.5±65.8 months	1.2 (12)	1.2 (12)	Mean BNP and BNT = 6.5/1,000 days of mechanical ventilation
		BNT					1.8 (17)	1.8 (17)	
Elward et al. [59]	2002	VAP	Prospective cohort	1999, 10 months/USA	625	Mean 5.5±5.9 years; median 2.9 years	5.4 (34)	4.8 (30)	11.6/1,000 ventilator-day

(continues)

Elward et al. [57] studied the use of central venous access as an extrinsic risk factor for bloodstream infection, whereas this variable was an inclusion criterion in the studies by Odetola et al. [55] and Almuneef et al. [56]. The use of multiple catheters and parenteral nutrition were found to be significant risk factors for Almuneef et al. [56]. Only Elward et al. [57] assessed the number of packed red blood cell transfusions and they found that a high number was a significant risk factor. Hemodialysis was studied either separately [57] or associated to blood filtration and no significant association was found with BSI [55]. Odetola et al. [55] were the only authors to examine extracorporeal circulation and determined it to be a risk factor for BSI.

Table 1 (continued)

Study	Year	Outcome	Method				HAI indicators		
			Design	Year begun *, duration and setting	Number of participants	Age	Accumulated incidence		Incidence density #
							HAI rate ** (n)	PHAI rate *** (n)	HAI/1,000 patients-day
Almuneef et al. [60]	2004	VAP	Prospective cohort	2000, 30 months/Saudi Arabia	361	1 month to 12 years; median 6 months	10.24 (37)	10.24 (37)	8.87/1,000 ventilator-day
Matlow et al. [49]	2003	UTI	Retrospective longitudinal	1997, 20 months/Canada	2,832	Unreported	0.95 (27)	0.95 (25)	Unreported

CVC: central venous catheter; ECLS: extracorporeal life support; RRT: renal replacement therapy (dialysis or blood filtration); BSI: bloodstream infection; BNP: bacterial nosocomial pneumonia (corresponding to Nosocomial Infection Surveillance System 2004; PNEU: pneumonia, PNU2: with isolation of etiologic agent); BNT: bacterial nosocomial tracheitis (corresponding to Nosocomial Infection Surveillance System 2004, LRI-BRON: lower respiratory tract infection – bronchitis, tracheobronchitis, tracheitis without evidence of pneumonia); VAP: ventilator associated pneumonia (pneumonia associated to ventilation or ventilator); UTI: urinary tract infection.

* Year of start of study;

** HAI rate: number of episodes of HAI/100;

*** PHAI rate: rate of patients with HAI (number of patients with HAI/100);

Incidence density: number of HAIs/1,000 patients-days of exposure;

CRBSI: catheter-related bloodstream infection – as reported in Odetola et al. [55] and Almuneef et al. [56], corresponding to NNISS (National Nosocomial Infection Surveillance System) 2004, CABSI: catheter-associated bloodstream infection – in the presence of central venous catheter;

Others – umbilical venous catheter, PICC (peripherally-inserted central catheter).

The duration of arterial catheter use was a risk factor for BSI in the study by Elward et al. [57] whereas the duration of central catheter use remained in the final model in the Odetola et al. [55] study. Almuneef et al. [56] did not study these variables. Changing the catheter with a guidewire represented a nearly five-fold greater risk for BSI in the study by Almuneef et al. [56] but this was not assessed in the other two studies.

Lower airway infection as outcome

Three studies assessed risk factors for lower airway infection [58,59,60]. The incidence of healthcare-related pneumonia was 1.2%, 5.4% and 10.2%, respectively (Table 1). The latter two studies assessed ventilator associated pneumonia (VAP). Fayon et al. [58] also studied bacterial tracheitis, which had a cumulative incidence of 1.8%, with an incidence density for grouped bacterial nosocomial tracheitis and bacterial pneumonia of 6.5 per 1,000 days on a ventilator. VAP rates were 11.6 and 8.87 per 1,000 days of ventilation in the studies by Elward et al. [59] and Almuneef et al. [60], respectively.

Factors related to underlying diseases were associated to bacterial tracheitis [58] (Table 4). With regard to bacterial pneumonia, the same study found an immunodeficiency status to be significant. Genetic syndrome was found to be a risk factor in the study by Elward et al. [59] for VAP. No intrinsic factors were significant in the study by Almuneef et al. [60].

Regarding extrinsic factors, Fayon et al. [58] found that the use of immunosuppressor drugs or neuromuscular blockers had a 4-fold and 11-fold greater risk for healthcare-associated pneumonia, respectively. In the study by Elward et al. [59], transporting the patient out of the pediatric ICU was a risk factor for VAP. Almuneef et al. [60] found risks for VAP with prior antibiotic therapy, continuous enteral nutrition and bronchoscopy.

Urinary tract infection as outcome

In a retrospective study, Matlow et al. [49] identified 25 patients who developed 27 episodes of urinary tract infection among 2,832 admissions over 20 months (0.95 per 100 admissions). Heart surgery was identified as a significant adjusted risk factor (odds ratio, OR = 2.67; 95% confidence interval, 95%CI: 1.13-6.32).

Discussion

Systematic reviews of observational studies have limitations that have been well described in the literature. However, such reviews are justified when there is interest in attempting to summarize association measurements between risk factors and illness outcomes that, for ethical rea-

Table 2

Intrinsic and extrinsic risk factors for healthcare-associated infection (HAI) in pediatric Intensive Care Units (ICU) identified in the articles selected in the systematic review of observational studies published between 1987 and 2006.

Study	Year	Associated variables in univariate analysis	Multivariate analysis	OR adjusted	95%CI	p value
Singh-Naz et al. [50]	1996	Intrinsic factors	Intrinsic factors			
		Age	PRISM *	1.6	1.5-1.78	0.0022
		Weight	Post-operative	2.6	1.215-6.0	0.0224
		Immunity status ** (median of sum of criteria)				
		PRISM upon admission (mean)				
		Extrinsic factors	Extrinsic factors			
		Ratio of invasive procedures	Ratio of invasive procedures ***	2.36	1.6-3.5	0.001
		Use of H_2 blocker	Antimicrobial therapy	5.21	2.0-13.6	0.0007
		Parenteral nutrition	Parenteral nutrition	22.1	7.1-68.8	0.0001
		Length of stay in ICU prior to HAI	Length of stay in ICU prior to HAI #	4.3	3.8-4.8	0.0001
		Use of antimicrobial agents (none, < 10 days and ≥ 10 days)	Post-operative and parenteral nutrition ##	0.3	0.1-0.9	0.0261
			PRISM and antimicrobial therapy ###	0.7	0.6-0.7	0.011
			Parenteral nutrition and length of stay in ICU prior to HAI §	0.2	0.2-0.3	0.0001
Gilio et al. [51]	2000	Intrinsic factors	Intrinsic factors			
		Underlining condition (sepsis and others, excluding cardiovascular surgery, multi-traumatism, central nervous system disease, respiratory disease)	PRISM §§	1.047	0.891-1.230	0.5744
			Post-operative	1.030	0.508-2.089	0.9920
			Extrinsic factors			
			Ratio of invasive procedures §§§	1.609	1.104-2.345	0.0132
			Antimicrobial therapy	1.003	0.563-1.786	0.9930
			Parenteral nutrition	2.467	1.048-5.811	0.0388
			Length of stay in ICU prior to HAI	1.705	1.313-2.214	0.0001
El-Nawawy et al. [52]	2006	Intrinsic factors	Intrinsic factors			
		PRISM III (mean ± SD)	Patient sent from emergency ward	0.269	0.178-0.406	
		Underlining condition (pneumonia, meningitis)	PRISM III	1.073	1.041-1.105	
		Extrinsic factors	Extrinsic factors			
		Length of stay ‡	Length of stay > 7 days	1.537	1.423-1.659	
		Ward of origin (emergency or other)				

(continues)

Table 2 (continued)

Study	Year	Associated variables in univariate analysis	Multivariate analysis	OR adjusted	95%CI	p value
Figueiredo [54] ‡‡	2002	Intrinsic factors	Intrinsic factors			
		Age	Age	1.27	1.06-1.54	0.01
		Post-operative period	Nutritional state (weight z score < -2)	1.07	0.74-1.53	0.71
		Previous hospital infection	Previous hospital infection	0.71	0.50-1.01	0.05
			Post-operative	2.08	1.31-3.29	0.0000
		Extrinsic factors	Extrinsic factors			
		Parenteral nutrition	Parenteral nutrition	1.62	1.09-2.42	0.02
		Invasive procedures	Invasive procedure ‡‡‡	1.08	0.73-1.60	0.63
		Duration of previous antibiotic use – from admission to hospital to first HAI in the pediatric ICU				
		Previous antibiotics – number used from admission to hospital to first HAI in the pediatric ICU				

PRISM: Pediatric Risk of Mortality; SD: standart deviation.

* Score was estimated based on 14 physiological parameters during the first 24 hours since admission to the pediatric ICU;

** Assessed upon admission: no risk in immune function (absence of the criteria to follow), minor risk (total lymphocytes < 1,500/mm^3, albumin < 2g% or corticoid use), moderate risk (neutrophil count < 500/mm^3, AIDS diagnosis), major risk (no granulocyte, bone marrow transplant or anti-neoplasm chemotherapy less than 6 months prior to admission). Maximum state of dysfunction as criterion for major risk;

*** Ratio of invasive procedures = [central venous catheter – days] + [urinary catheter -days] + [mechanical ventilation – days]/Length of stay until day of HAI diagnosis;

Singh-Naz et al. [73] – an increase of five days in length of stay was associated to a four-fold greater risk of developing HAI (OR = 4.3; 95%CI: 3.8-4,8); Gilio et al. [51] categorized variable in five-day intervals;

Yes for both variables;

> 0 but < 10 days of antimicrobial therapy and a four-point increase on the PRISM score;

§ Yes for parenteral nutrition and a five-day increase in length of stay;

§§ Singh-Naz et al. [73] – an increase of four points of the PRISM score was associated to a 1.5-fold greater risk of developing HAI (OR = 1.6; 95%CI: 1.5-1.7); Gilio et al. [51] categorized variable in 4-point intervals;

§§§ An increase of 1 unit;

‡ Mean duration of hospitalization;

‡‡ Dependent variable – time elapsed until first HAI episode;

‡‡‡ Categorized the number of invasive procedures (2 or less and more than 2).

sons, cannot be analyzed in clinical trials [111,112]. Although the importance of critically appraising articles is well recognized, there is no consensus on valid indicators for the quality of observational studies [113]. In the analysis of quality proposed by the Newcastle-Ottawa Scale, studies can obtain the maximum score even when presenting a number of sources of heterogeneity and bias.

Factors related to external validity should be pointed out: one of the pediatric ICUs only offered care to children and dependents of military personnel [56,60]; and one of the Brazilian studies was carried out in a private hospital, the patients of which are not representative of the general community [51].

Regarding the records of exposure and the detection of outcomes, there was a degree of homogeneity in the NNIS/CDC definitions and procedures for healthcare-associated infection. The opposite occurred for the categorization of exposure levels (intervals of PRISM scores; length of stay in the pediatric ICU or catheter use). Multidisciplinary pediatric ICUs were described as clinical-surgical pediatric ICUs, or the post-operative status was included as the underlying condition in the methodology. Age range was also heterogeneous, and it was unclear whether some studies included newborns and whether the upper age limit was 12 or 18 years. Occupational conditions, turnover and number

Table 3

Intrinsic and extrinsic risk factors for bloodstream infection according to authors of the articles selected in the systematic review on "risk factors for healthcare-associated infection (HAI) in pediatric Intensive Care Units (ICU)".

Study	Year	Outcome	Associated variables in the univariate analysis	Multivariate analysis	OR adjusted	95%CI	p value
Elward et al. [57]	2006	BSI *	Intrinsic factors	Intrinsic factors			
			Age - median or < 30 days, 30 days to 1 year, 1 to 12 years, >12 years	Genetic syndrome	4.7	1.8-12	0.001
			PRISM III – median				
			Underlying condition: stunted growth, congenital heart disease				
			Extrinsic factors	Extrinsic factors			
			Use of invasive procedures: central venous catheter, multiple central accesses, arterial catheter	High number of packed red blood cell transfusions	1.2	1.1-1.4	< 0.001
			Surgery or procedure: dialysis, transplant and heart surgery	Long duration of arterial catheter use – days	5.7	3.4-9.8	< 0.001
			Transfusion: packed red blood cell transfusions (mean)				
			Locale where procedure was performed: pediatric ICU				
			Medications: prednisone, inotropic, immunossupressor and H_2. blocker				
			Parenteral nutrition				
			Transport outside of pediatric ICU				
			Transference from other unit				
Odetola et al. [55]	2003	CRBSI **	Extrinsic factors	Intrinsic factors			
			Type of catheter (for renal replacement therapy ***, catheter for ECLS)	Age (in years)	1.030	0.973-1.090	0.304
			Number of accesses (2 and ≥3)				
				Extrinsic factors			
				Tunneled catheter	1.061	0.397-2.835	0.905
				Duration of catheter use	1.110	1.070-1.151	< 0.001
				Parenteral nutrition	1.180	0.498-2.797	0.707
				Mechanical ventilation	1.212	0.448-3.280	0.705
				Catheter for renal replacement therapy	2.330	0.914-5.940	0.77
				ECLS	2.753	1.013-7.487	0.047

(continues)

Table 3 (continued)

Study	Year	Outcome	Associated variables in the univariate analysis	Multivariate analysis	OR adjusted	95%CI	p value
Almuneef et al. [56]	2006	CRBSI #	Intrinsic factors	Extrinsic factors			
			Age (mean and older then 2 years)	Parenteral nutrition through catheter	8.69	3.518-21.484	< 0.0001
			Underlying condition (oncohematologic)	Change of catheter with guidewire	4.56	1.110-18.776	0.04
				Multiple central lines ##	9.19	3.767-22.43	< 0.0001
			Extrinsic factors				
			Site of central venous catheter (jugular and femoral)				
			Locale where insertion of central venous catheter was performed (surgery ward, pediatric ICU or other)				

BSI: bloodstream infection; PRISM: Paediatric Risk of Mortality; CRBSI: catheter-related bloodstream infection; ECLS: extracorporeal life support; CRBSI: catheter-related bloodstream infection.

* Elward et al. [59], primary infection that began after 48 or more hours of internment in the pediatric ICU, with the isolation of bacterium or fungus in the blood culture and that were not present in incubation prior to hospital admission. Coagulase-negative *Staphylococcus* was only considered as an etiological agent if blood culture was positive at least twice on separate occasions;

** Odetola et al. [55], primary bloodstream infection in patient with vascular access at least 48 hours prior to the establishment of the infection;

*** In the Odetola et al. [55] study refers to catheter with double or triple lumen for dialysis or blood filtration;

Almuneef et al. [56], bacteremia or fungemia in patient with intravascular catheter, with at least one positive blood culture obtained in peripheral vein with clinical manifestation of infection and no apparent source of bacteremia other than the catheter. Coagulase-negative Staphylococcus was only considered as an etiological agent if blood culture was positive at least twice on separate occasions;

In the Almuneef et al. [56] study refers to the use of other central venous catheters in comparison to a single central venous catheter.

of patients admitted in the pediatric ICUs also varied.

Structural factors, such as area and distribution of beds, availability of isolation beds, number of sinks or dispensers of products for hand hygiene and ratio of patients to healthcare workers, were not part of the analysis of the studies selected, nor were factors related to care processes and compliance to infection control protocols.

Among the four studies that analyzed healthcare-associated infection regardless of site of infection, only the Figueiredo study [54] found age to be a risk factor. The other authors did not discuss the association of age to healthcare-associated infection. The heterogeneity of the populations studied, especially in relation to age, hinders a comparison of the results. The currently accepted paradigm that the frequency of healthcare-associated infection in pediatrics is inversely proportional to age (more common among children under 12 [3,30] or 24 months [28,114]) needs to be clarified, despite its biological plausibility: immunological immaturity could account for the higher incidence of healthcare-associated infection among younger patients [115].

Many pediatric ICUs were clinical-surgical and catered for a large variety of conditions, making it difficult to establish associations between risk and underlying disease or severity of the condition. The post-operative period per se was a risk factor for healthcare-associated infection [50,54]. Severity, as assessed by the PRISM score, was significant in four studies, but differences in the scores employed (PRISM has 14 clinical and laboratory parameters, whereas PRISM III has 17) and in the manner of categorizing the variable did not allow for summarizing how the measurement is associated with healthcare-associated infection.

Among extrinsic factors, the length of stay in the pediatric ICU was found to be the only risk factor for healthcare-associated infection in three studies [50,51,52]. Pediatric ICU stay reflects the severity of the condition, requiring greater care, but also expresses a measure of time in which the patient is potentially exposed to diverse sources of infection. Thus, NNIS recommendations focus

Table 4

Intrinsic and extrinsic risk factors for healthcare-related pneumonia and traqueitis and pneumonia associated to the respirator according to authors of the articles selected in the systematic review on "risk factors for healthcare-associated infection in pediatric Intensive Care Units (ICU)".

Study	Year	Outcome	Variables associated in the univariate analysis	Multivariate analysis	OR adjusted	95%CI	p value
Fayon et al. [58]	1997	BNP *	Intrinsic factors	Intrinsic factors			
			PRISM upon admission and worse score upon evolution	Age ≤ two months	6.1	4.0-8.2	0.02
			Underlying condition: multiple organ failures or failure of one of the systems, such as respiratory, cardiovascular, neurological, hematological or renal failure; SARA, immunodeficiency	Male gender	1.7	-	NS
				Immunodeficiency **	6.9	4.1-9.7	0.06
			Extrinsic factors	Extrinsic factors			
			Mechanical ventilation	Neuromuscular block	11.4	9.5-13.3	0.02
			Enteral nutrition	Immunossupressor drugs ***	4.8	2.7-6.9	0.04
			Drugs: immunossupressor, blocker neuromuscular, ranitidine, sucralfate				
		BNT *	Intrinsic factors	Intrinsic factors			
			Gender	Age ≤ 28 months	3.1	1.1-5.1	0.10
			Age – mean in months	Male gender	2.4	0-4.8	NS
			PRISM upon admission and worse score upon evolution	Respiratory failure	8.4	6.5-10.3	0.001
			Worse score on Glasgow Coma Scale	Head trauma	12.5	9.8-15.2	0.01
			Underlying condition: organ failure – multiple organ failures or respiratory failure – cranial trauma				
			Extrinsic factors				
			Procedures: intubation, mechanical ventilation				
			Neuromuscular blocker				
Elward et al. [59]	2002	VAP #	Intrinsic factors	Intrinsic factors			
			PRISM upon admission ≥ 10	Genetic syndrome	2.37	1.03-5.46	0.043
			Underlying condition: burns, genetic syndrome, bloodstream infection				
			Extrinsic factors	Extrinsic factors			
			Procedures: reintubation, tracheostomy, bronchoscopy, toracocentesis, central venous catheter.	Transport out of pediatric ICU ##	8.90	3.82-20.7	0.0001
			Drugs: Histamine-2 receptor blocker, steroids	Reintubation ###	2.71	1.18-6.21	0.011
			Parenteral nutrition	Transfusion prior to infection	-	-	0.884
			Transfusion of blood products				
			Transport outside of pediatric ICU				

(continues)

Table 4 (continued)

Study	Year	Outcome	Variables associated in the univariate analysis	Multivariate analysis	OR adjusted	95%CI	p value
Almuneef et al. [60]	2004	VAP §	Extrinsic factors	Extrinsic factors			
			Accidental extubation or reintubation	Reintubation or accidental extubation ###	1.62	0.776-3.370	0.1992
			Bronchoscopy	Witnessed aspiration	2.17	0.588-8.010	0.2446
			Continuous enteral nutrition	Previous antibiotic therapy	2.45	1.112-5.405	0.0262
			Previous antibiotic therapy	Continuous enteral nutrition	2.29	1.093-4.798	0.0042
			Witnessed aspiration	Bronchoscopy	5.04	1.665-15.266	0.0008

BNP: bacterial nosocomial pneumonia; BNT: bacterial nosocomial tracheitis; PRISM: Paediatric Risk of Mortality; VAP: ventilator associated pneumonia.

* Fayon et al. [58] consensus among 3 "blinded" experts (2 intensivists and 1 bacteriologist), using Centers for Disease Control and Prevention criteria and analyzing evocative signs and symptoms (purulent secretions, fever, new consolidation on thorax radiography, etc.) In intubated patients, tracheal aspirations were collected through a tracheal probe or tracheostomy and immediately sent to the laboratory for gram determination and culture. The patient was considered colonized in the presence of normal flora of the upper tract or if more than two different bacteria were identified in small quantities in the secretions without any formation of pus (<25 polymorphonuclears per field);

** Congenital (ex: adenosine desaminase deficiency) or acquired (ex: AIDS);

*** Barbiturates in high dose (≥ 30mg/kg/day), cyclosporine, azathioprine and corticosteroids;

Elward et al. [59] – patient on mechanical ventilation for at least 48 hours, presenting new infiltration on the thorax radiography 48 hours or more after initiating mechanical ventilation. Additionally, the patient must have 2 or more of the following: fever > 38°C, leukocytosis (> 12,000) and the appearance of purulent sputum (> 25 leukocytes per field in the GRAM). Associated organisms were designated as those recovered from the tracheal aspiration or bronchoalveolar lavage in patients with respirator-associated pneumonia;

Moving the patient out of the pediatric ICU for surgery or imaging exams;

Reported in the study by Almuneef et al. [83]; the study by Elward et al. [59] only mentions reintubation;

§ Almuneef et al. [83] – patient on mechanical ventilation for at least 48 hours, presenting new or progressive infiltrate, consolidation, cavitation or pleural effusion on the thorax radiography. Additionally, the patient must have: appearance of purulent sputum or change in the appearance of phlegm; microorganism isolated in the blood culture not related to other source of infection; isolation of pathogens of specimen obtained from tracheal aspiration, bronchoalveolar lavage or protected pulmonary brushing or biopsy; or histopathologic with evidence of pneumonia in pulmonary biopsy.

primarily on time reduction in the use of invasive procedures. The diversity of the categorization of the variable "length of stay in the pediatric ICU" renders the summarization of the association measure unfeasible. It was also not possible to summarize the association measures between healthcare-associated infection and the invasive procedure ratio [50,51] or the use of parenteral nutrition [50,51,54] due to the unavailability of tabled data in the articles.

One of the characteristics of healthcare-associated infection in the pediatric ICU is that BSI is the most frequent type of infection [6]. As in adults, BSI in the pediatric ICU is nearly always associated with the use of a central venous catheter [27,30,61]. Except in specialized ICUs for burn victims or newborns weighing less than 1,000g, the NHSN (which replaced the NNIS) reports that it is in the clinical-surgical pediatric ICU that BSI associated to a central venous catheter which has the highest incidences [8].

Regarding BSI-LCBI, the incidence density observed in the present review was as high or higher than NHSN references for clinical-surgical pediatric ICU [56,57]. This indicator currently includes only BSI associated to a central venous catheter with bacteriological confirmation, whereas, previously, clinical sepsis was included [8]. Without reporting an overall rate, Odetola et al. [55] analyzed an increasing incidence density according to the number of intravascular accesses and characteristics of the catheter type or use, finding rates that ranged from 4.0 to 22.1/1,000 catheter-days.

Regarding risk factors for BSI in the pediatric ICU, the use of an arterial or venous catheter, devices with multiple lumens, changing the catheter with a guidewire, central vein parenteral nutrition, extracorporeal circulation and packed red cell transfusions are risk factors that are potentially modifiable through educative measures. In turn, a genetic syndrome may be a marker of

immune defects that impede the defense of the host against microorganisms. However, it should be stressed that in the three studies that analyzed BSI in the pediatric ICU, no common risk factors were found [55,57].

In the prevention of infection associated to a central venous catheter, the "package" of interventions proposed in a campaign by American hospitals to save 100,000 lives addressed five components: hand hygiene, maximal sterile barrier, skin antisepsis with chlorhexidine, the choice of the subclavian vein as the preferred insertion site for non-tunneled catheters and daily checks with immediate removal if central access is no longer necessary [116]. Based on these recommendations, Lee & Johston [117] published a systematic review seeking the best evidence for handling central venous catheters and the prevention of bloodstream infections associated to catheters in the pediatric population and concluded that the quality and diversity of the articles in relation to the outcome did not allow the establishment of clear guidelines, such as those existing for adults.

The present systematic review, together with that by Lee & Johnston [117] and other narrative reviews, stress the fact that most of the current knowledge on bloodstream infection related to central venous catheters has principally emerged from data collected in adult ICUs [118,119]. The interventions currently recommended regarding the use of central venous catheters are the same from the 100,000 lives campaign [120]. Although the pediatric ICUs have high rates of BSI associated to central venous catheters, the mean percentage of use (approximately 50%) of this procedure is among the lowest when considering the different types of ICU [8,121]. Thus, recommendations regarding the identification of factors other than the frequency of central access per se seem to be particularly necessary.

Pneumonia is among the three main types of infection in the pediatric ICU and, as in adults, is more frequent among patients on mechanical ventilation [4,27,30,31,61]. The diagnosis of VAP, however, is challenging and may explain the differences in the diverse studies concerning the occurrence of this event as well as possible risk factors. Taking into account the difficulty in diagnosing nosocomial pneumonia or tracheitis, Fayon et al. [58] used a consensus between three researchers, two intensivists and one microbiologist. Agreement was good for pneumonia and weak for tracheitis. Recent criteria aimed at improving the specificity of this diagnosis were stipulated by the NNIS for both adults and children [122], but need to be validated with regard to pediatric patients.

The heterogeneity of the three studies on risk factors for lower airway infection impeded the summarization of the measures found [58,59,60]. The outcomes were different: tracheitis and pneumonia, in which endotracheal intubation was one of the risk factors [58]; and ventilator-associated pneumonia, in which being on a ventilator was a criterion for inclusion [59,60]. The studies analyzing VAP found different independent risk factors and no risk factors that were common to both studies [59,60].

In a systematic review of intervention studies based on risk factors for VAP, the authors graded the prevention recommendations according to the quality of the studies, but none was based on a pediatric population [123]. Recommendations were extrapolated for children and adolescents: elevation of the head between 30 and 45 degrees, daily verification of sedation and the possibility of extubation, prophylaxis for peptic ulcers and deep venous thrombosis [116].

Urinary tract infection is the main cause of healthcare-associated infection in adults, but is scarcely studied in the pediatric ICU, despite being considered the third most frequent type of infection. Only two of the 84 studies in the present review discussed risk factors for urinary tract infection and one of these failed to present multivariate analysis [62]. The study by Matlow et al. [49] presents several methodological difficulties for being a retrospective study, including the impossibility of calculating the incidence density in relation to catheter use in the exposed and non-exposed populations, which is the main risk factor reported in the literature. Despite the relatively lesser use of urinary catheters in children in the pediatric ICU (mean use ratio of approximately 0.30), the rate of infection remains high, with a median value of 2.8 per 1,000 urinary catheters-days [8], indicating the presence of risk factors likely associated to urinary catheter use. EPIC 2 (Evidence based Practice in Infection Control) recommendations for the prevention of infection associated to the use of short-term urinary catheters only applied to adults and children over the age of one, and a number of reviews cited were of studies on adult patients [24].

Children have anatomical and functional peculiarities, different underlying conditions and are submitted to different surgical procedures than adults. This justifies the conducting of specific studies on pediatric patients [59]. An important step toward determining specificities and improving the comparison of healthcare-associated infection surveillance in the pediatric ICU was the definition of different types of pediatric ICU considered in the new system adopted by the NHSN [8,124]. A number of reviews have sought

to establish a consensus among the different medical societies and governmental surveillance agencies for the standardization of definitions regarding the types of infection – sepsis, pneumonia and urinary tract infection [125,126,127].

The present systematic review demonstrates the scarcity of studies on risk factors for healthcare-associated infection in children hospitalized in pediatric intensive care units. The following were risk factors for a first episode of healthcare-associated infection: post-operative period, greater severity upon admission based on the PRISM or PRISM III, invasive procedures, the use of antimicrobial agents, parenteral nutrition, remaining more days or more than seven days in the pediatric ICU. However, being sent from the emergency ward is a protective factor. Risk factors identified for BSI-LCBI were: age, genetic syndrome, use of packed red cells, long duration of catheter use, parenteral nutrition through a catheter, change of catheter with a guidewire, multiple central lines and extracorporeal circulation. The development of bacterial pneumonia were associated to the following risk factors: young age, immunodeficiency, neuromuscular blocker and immunosupressor drugs; for tracheitis: age ≤ 28 months, respiratory failure, head trauma; for VAP: genetic syndrome, transport outside of the pediatric ICU, reintubation, bronchoscopy and continuous enteral nutrition.

Risk factors for healthcare-associated infection in PICUs stem from the dynamics of healthcare in child or adolescent units and are specific to these populations.

This systematic review demonstrated that the production of evidence on risk factors in paediatric ICUs has not kept up the same pace of that on adult ICUs. There are few studies on the subject with adequate design and statistical analysis. Furthermore, the methodological diversity of the studies requires a systematic analysis of the scientific evidence produced on this topic. Efforts should be made to obtain data on risk factors utilizing standardized prospective protocols to measure these different factors. Recommendations drafted from evidence produced in pediatric ICUs would be more adequate for contributing to control strategies of these adverse healthcare events, thereby ensuring the safety of children who require intensive care.

Resumo

Realizou-se revisão sistemática de estudos observacionais sobre fatores de risco para infecção relacionada aos cuidados de saúde em Unidades de Terapia Intensiva (UTI) pediátrica. Foram incluídos estudos em inglês, francês, espanhol ou português indexados no MEDLINE, LILACS, Cochrane Library, BDENF, CAPES, entre 1987 e 2006. As palavras-chave foram "Infecção Hospitalar" e "Unidades de Terapia Intensiva Pediátricas", com diferentes formas de escrever. Onze artigos foram selecionados a partir de 419 resumos encontrados: quatro tinham como desfecho infecção em qualquer topografia; três eram sobre infecções de vias aéreas inferiores; três estudaram infecção da corrente sanguínea confirmada laboratorialmente e um analisou infecção do trato urinário. A produção de evidências na UTI pediátrica não vem acompanhando o ritmo dos estudos em adultos – existem poucos estudos com desenhos e análise estatística adequados. A diversidade metodológica não permitiu a realização de medição sumarizada dos fatores de risco.

Infecção Hospitalar; Unidades de Terapia Intensiva Pediátrica; Assistência à Saúde

Contributors

M. J. G. Mello accessed the databases; read the selected summaries and complete articles; carried out the data extraction; analyzed the quality of the chosen articles and wrote the article. M. F. P. M. Albuquerque read the selected summaries and complete articles; participated in the data extraction; and helped in the write up. H. R. Lacerda participated in the design of the protocol for data extraction; analyzed the results of the selected articles; and helped in the write up. W. V. Souza analyzed the quality of the chosen articles, according to the "Newcastle-Ottawa Scale" protocol; analyzed the heterogeneity of the results and the possibility of summarizing the measures for associations found in the studies. J. B. Correia participated in the preparation of the protocol for data extraction and the article write up. M. C. A. Britto participated in the preparation of the protocol for data extraction and the article write up.

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