ORIGINAL ARTICLE

Healthcare-Associated Infections in Pediatric and Neonatal Intensive Care Units: Impact of Underlying Risk Factors and Antimicrobial Resistance on 30-Day Case-Fatality in Italy and Brazil

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OBJECTIVES. To describe trends in the epidemiology of healthcare-associated Infections (HAIs) in pediatric/neonatal intensive care units (ICUs) and to evaluate risk factors and impact of multidrug resistance in children admitted to ICUs.

DESIGN. Multicenter, retrospective, cohort study with a nested case-control study conducted from January 1, 2010, through December 31, 2014.

SETTING. Three tertiary care pediatric hospitals in Italy and Brazil with a total of 103 ICU beds.

PATIENTS. Inclusion criteria were admission to ICU during the study period, age at onset less than 18 years, and microbiologically confirmed HAI.

RESULTS. A total of 538 HAIs in 454 children were included; 93.3% of patients had comorbidities. Bloodstream infections were the leading pattern (45.4%). The cumulative incidence of HAI was 3.6/100 ICU admissions and the crude 30-day fatality rate was 5.7/1,000 admissions. The most frequently isolated pathogens were Enterobacteriaceae, followed by *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Forty-four percent of isolates were multidrug-resistant (MDR). Two multivariate logistic regressions were performed. Factors independently associated with an MDR-HAI were country, previous antibiotics, transplantation, major surgery, and colonization by an MDR strain. Factors independently associated with 30-day case fatality were country, previous transplantation, fungal infection, bloodstream infection, lower respiratory tract infection, and infection caused by MDR strains.

CONCLUSIONS. Infection control and prevention can limit the spread of MDR strains and improve outcomes. Targeted surveillance programs collecting neonatal and pediatric HAI/bloodstream infection data and outcomes would allow global benchmarking. The next step is to identify methods to monitor key HAIs and integrate these into affordable intervention programs.

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Healthcare-associated infections (HAIs) are one of the most frequent adverse events affecting children admitted to intensive care units (ICUs).[1,2] Exposure to invasive devices and procedures, immune suppression, and underlying conditions are considered as main determinants of patients' increased susceptibility.[3,4] The impact of multidrug-resistant (MDR) organisms in pediatrics is increasing globally.[5–7] It is assumed that infections caused by MDR bacteria will have a worse prognosis because of the delay in the administration of appropriate therapy. However, it is difficult to estimate the clinical impact of MDR-HAI in children.

Previous literature has shown conflicting results about the impact of different underlying risk factors on the clinical outcome of patients with HAI admitted to ICUs. There is no clear independent correlation between antimicrobial resistance and patients' mortality.[8–11]

Clarifying the relationship between patient risk factors and pediatric HAI mortality could allow improved targeting of interventions on the patients most at risk of adverse outcome. The aims of this study were to describe trends in the epidemiology of HAIs in Italian and Brazilian pediatric ICUs over a 5-year period and to evaluate patient risk factors and the clinical impact of MDR-HAI in children admitted to ICUs.

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METHODS

Study Design and Setting

We conducted a multicenter, retrospective, cohort study with a nested case-control study in 1 pediatric hospital in Italy and 2 in Brazil. These countries were chosen because of the high rates of antimicrobial resistance identified. The Bambino Gesù Children's Hospital (Rome, Italy) is a 607-bed pediatric tertiary care center with 5 ICUs: 1 neonatal, 3 pediatric, and 1 cardiac (47 ICU beds). The Prontobaby Hospital da Criança (Rio de Janeiro, Brazil) is a 135-bed private service including neonatal ICU and pediatric ICU (45 ICU beds). The Centro Pediátrico da Lagoa (Rio de Janeiro, Brazil) is a 39-bed private service including an 11-bed pediatric ICU.

The study was conducted from January 1, 2010, through December 31, 2014. During this period, ongoing prospective surveillance of HAIs was performed in all the participating ICUs. Patients with a microbiologically confirmed diagnosis of HAI were retrieved from this data source. Inclusion criteria were admission to ICU during the study period, age at onset less than 18 years, and diagnosis of microbiologically confirmed HAI. Polymicrobial infections were included if criteria for HAI were fulfilled. Episodes with a positive isolate from the same patient for the same pathogen within 4 weeks of the first one were excluded.

Definitions

The study was conducted using Centers for Disease Control and Prevention HAI case definitions, with only those infections presenting and identified more than 48 hours after admission to ICU considered as ICU-acquired and included.[12]

The multidrug resistance of the isolates was defined according to Magiorakos et al.[13] Coagulase-negative staphylococci were considered as MDR if resistant to 3 or more different antibiotic classes, including oxacillin, aminoglycosides, trimethoprim-sulfamethoxazole, clindamycin, and quinolones.[14] Isolates that did not meet MDR definition were classified as susceptible. Patients with polymicrobial infection with mixed MDR and non-MDR isolates were classified as MDR. *Cases* were defined as patients with HAI due to MDR isolates. *Controls* were defined as patients with HAIs caused by non-MDR.

Microbiologic Methods

In Italy, isolation and identification of microorganisms were made with accredited routine laboratory methods (Vitek 128 2, bioMérieux; or Phoenix, BD Diagnostics). The Clinical and Laboratory Standards Institute criteria were used for antibiotic susceptibility testing from 2010 to 2011 whereas from 2012 the European Committee on Antimicrobial Susceptibility Testing breakpoints have been introduced in the hospital's practice.

In Brazil, isolation of microbiological species was done by semiquantitative process (Auto-Scan 4; Siemens). Antibiotic susceptibility testing was performed by disk diffusion in accordance with Clinical and Laboratory Standards Institute recommendations until 2013 and with European Committee on Antimicrobial Susceptibility Testing from 2014.

Prior colonization with MDR strains was assessed by stool culture/rectal swab.

Data Source and Statistical Analysis

We considered the cohort of patients admitted to the ICU to estimate HAI cumulative incidence (HAI episodes/100 ICU admissions), rate of infections (HAI episodes/1,000 ICU-days), and mortality rate at 7 and 30 days after HAI onset (deaths among patients with at least 1 HAI episode/1,000 ICU admissions). For all HAI episodes we collected information about possible risk factors, including demographic, clinical, and microbiologic variables from inpatient clinical and laboratory records. We then compared cases vs controls to evaluate determinants for acquisition of HAI due to MDR compared with non-MDR HAI. Predictors of 30-day HAI case fatality rate were estimated by comparing survivors vs nonsurvivors.

Categorical variables were summarized by absolute frequencies and percentages, and continuous variables by median and interquartile range. To determine statistical differences between groups, the χ^2 test or Fisher exact test was used for categorical variables, whereas the *t* test or Mann-Whitney test was used for continuous variables.

Two multivariate logistic regression models were developed to assess independent predictors of acquisition of MDR-HAI compared with non-MDR-HAI as well as 30-day HAI case fatality rate. Variables for which $P < .20$ in univariate analyses were included in the multivariate models. Final models were computed with a stepwise backward procedure (likelihood ratio test, $P < .05$).

All statistical analyses were performed using Stata, version 13 (StataCorp).

Ethics

The study was approved by the ethical committee of each institution with a waiver of informed consent.

RESULTS

Demographic and Clinical Data

During the study period 14,924 children were admitted to one of the ICUs for a total of 148,243 ICU-days. Overall, 538 HAI episodes in 454 children, fulfilling the inclusion criteria, were identified and included in the analysis.

Characteristics of episodes of HAI are summarized in Table 1. Bloodstream infections (BSIs) were the leading pattern accounting for 244 episodes (45.4%), followed by lower respiratory tract infections (LRTIs) with 149 (27.8%) and urinary tract infections with 85 (15.8%).

The median (interquartile range) age of patients at HAI onset was 7.8 (2.1–26.2) months; 93.3% of HAI cases affected children with comorbidities. The median (interquartile range)

TABLE 1. Characteristics of Episodes of HAI Included in the Study

Variable	Italy	Brazil	Total	*P*
Total no. of episodes	335	203	538	
Gender				.831
M	180 (53.7)	111 (54.7)	291 (54.1)	
F	155 (46.3)	92 (45.3)	247 (45.9)	
Age, median (IQR), months	5.3 (1.8–12.8)	14.9 (4.0–49.7)	7.8 (2.1–26.2)	.001
Age group				.001
0–28 days	51 (15.2)	17 (8.4)	68 (12.6)	
29 days–3 months	74 (22.1)	23 (11.3)	97 (18.0)	
3 months–2 years	151 (45.1)	73 (36.0)	224 (41.6)	
2–5 years	22 (6.6)	39 (19.2)	61 (11.3)	
>5 years	37 (11.0)	51 (25.1)	88 (16.4)	
Underlying disease				.001
No	11 (3.3)	25 (12.3)	36 (6.7)	
Yes	324 (96.7)	178 (87.7)	502 (93.3)	
Admission ward				.001
NICU	84 (25.1)	30 (14.8)	114 (21.2)	
PICU	96 (28.7)	173 (85.2)	269 (50.0)	
CICU	155 (46.3)	0 (0)	155 (28.8)	
LOS in ICU, days				
Overall, median (IQR)	73 (33–135)	55 (26–124)	67 (31–127)	.085
Before HAI, median (IQR)	24 (10–55)	26 (13–67)	24 (11–58)	.186
HAI distribution				.033
Bloodstream infection	159 (47.5)	85 (41.9)	244 (45.4)	
Lower respiratory tract infection[a]	88 (26.3)	61 (30.0)	149 (27.7)	
Urinary tract infection	51 (15.2)	34 (16.7)	85 (15.8)	
Surgical site infection	25 (7.5)	7 (3.4)	32 (5.9)	
Other infections	11 (3.3)	16 (7.9)	27 (5.0)	
Susceptibility of the isolate				.001
MDR	119 (35.5)	122 (60.1)	241 (44.8)	
Non-MDR	216 (64.5)	81 (39.9)	297 (55.2)	
Mortality				
7-day mortality	15 (4.8)	19 (10.7)	34 (6.3)	.014
30-day mortality	25 (7.8)	26 (14.1)	51 (9.5)	.024

NOTE. Data are no. (%) of episodes unless otherwise indicated. CICU, cardiac intensive care unit; HAI, healthcare-associated infection; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MDR, multidrug-resistant; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.

[a]Including pneumonia.

length of stay in ICU was 67 (31–127) days, whereas the median (interquartile range) time between ICU admission and onset of HAI was 24 (11–58) days.

Overall, 478 (88.8%) of the 538 HAIs were diagnosed in patients with an invasive device in situ. In 443 (82.3%) of the 538 HAIs, the device had been in place for more than 48 hours before the infection. Among 244 BSIs, 195 (79.9%) involved children with a central venous catheter (CVC) in situ when diagnosed (179 [73.4%] of these 244 for >48 hours). Also, 120 (80.5%) of 149 LRTIs were in children mechanically ventilated (100 [67.1%] of these 149 for >48 hours). Among 85 urinary tract infections, 38 were in children who had a urinary catheter (28 [32.9%] of the 85 for >48 hours).

In 318 (59.1%) of 538 episodes, children were already receiving antibiotics when diagnosed with a HAI (141 [44.3%] were on 1 antibiotic, 130 [40.9%] on 2, and 47 [14.8%] on 3).

The cumulative incidence of HAI was 3.6/100 ICU admissions whereas the rate of infections was 3.6/1,000 ICU-days. No significant trends in HAI incidence and rate were identified over the 5-year period. The 7-day mortality rate was 2.3/1,000 admissions and the 30-day mortality rate was 5.7/1,000 admissions. The HAI case fatality rate at 30 days was 18.7% (85/454).

Microbiologic Data

A total of 573 microorganisms were isolated (Table 2). Of these 573 microorganisms, 317 (55%) were Gram-negative bacteria, 184 (32%) were Gram-positive bacteria, and 40 (7%) were fungi. The most frequently isolated pathogens were Enterobacteriaceae (30.9%), followed by *Pseudomonas aeruginosa* (19.2%) and *Staphylococcus aureus* (11.0%). The percentage of

TABLE 2. Distribution and Resistance of Isolates by Type of HAI

	Bloodstream infection			Lower respiratory tract infection[a]			Urinary tract infection			Surgical site infection			Other		
Pathogen	252			164			94			35			27		
Total isolates	n	n MDR	%	n	n MDR	%	n	n MDR	%	n	n MDR	%	n	n MDR	%
Total Gram-positives	110	52	47.3	31	19	61.3	13	3	23.1	16	9	56.3	14	9	64.3
Total Gram-negatives	107	44	41.1	115	52	45.2	66	35	53	16	8	50	12	9	75
Staphylococcus aureus	25	14	56	28	17	60.7	1	0	-	7	3	42.9	2	2	100
CoNS	59	33	55.9	3	2	66.7	0	-	-	7	5	71.4	7	6	85.7
Klebsiella pneumoniae	31	11	35.5	17	8	47.1	17	13	76.5	4	4	100	2	2	100
Escherichia coli	10	3	30	9	3	33.3	18	8	44.4	1	0	-	1	1	100
Pseudomonas aeruginosa	27	13	48.1	57	23	40.4	19	9	47.4	6	3	50	1	0	-
Serratia marcescens	9	1	11.1	3	0	-	4	1	25	0	-	-	1	1	100
Stenotrophomonas maltophilia	4	4	100	14	14	100	1	1	100	0	-	-	0	-	-
Enterobacter spp	16	9	56.3	7	5	71.4	5	3	60	2	1	50	5	4	80
Acinetobacter spp	3	2	66.7	7	3	42.9	1	1	100	1	1	100	1	1	100
Enterococcus spp	25	5	20	0	-	-	14	5	35.7	4	1	25	3	1	33.3
Candida spp	27	0	-	5	0	-	7	0	-	0	-	-	1	0	-
Other Gram-positives	3	0	-	2	0	-	0	-	-	0	-	-	2	0	-
Other Gram-negatives[b]	13	5	38.5	12	6	50	7	2	28.6	3	0	-	1	0	-

NOTE. CoNS, coagulase-negative staphylocci; HAI, healthcare-associated infection; MDR, multidrug-resistant.
[a]Including pneumonia.
[b]There was one missing case.

MDR isolates was 44%. On the basis of the susceptibility profile, 79 (45%) of the 175 Enterobacteriaceae were positive for extended-spectrum beta-lactamase. Culture-confirmed carbapenem resistance was reported in 3 (2%) of the 175 Enterobacteriaceae, 46 (42%) of 110 *P. aeruginosa*, and 6 of 10 *Acinetobacter baumannii*. Among Gram-positives, 35 (56%) of 63 *S. aureus* were methicillin-resistant whereas no vancomycin-resistant *Enterococcus* spp. were isolated. Seventy-six coagulase-negative staphylococci were isolated, of which 47 (62%) were classified as MDR. Overall, 40 cultures were positive for *Candida* spp., all of them fully sensitive.

Determinants of HAI Due to MDR and 30-Day Case Fatality Rate

Of a total of 538 episodes, 241 were due to MDR isolates and 297 to non-MDR isolates, with no statistically significant differences in cumulative incidence (1.61 episodes/100 ICU admissions vs 1.99 episodes/100 ICU admissions; $P = .995$). The 30-day case fatality rate was also similar in MDR-HAI episodes compared with non-MDR episodes (19.1% vs 13.1%; $P = .06$).

In the univariate analysis, risk factors significantly associated with HAI caused by MDR isolates compared with non-MDR isolates were country (Brazil), antibiotic use in the month before HAI, minor surgery in the 6 months before HAI, and previous colonization by a MDR strain (Table 3).

In the multivariate analysis, factors independently associated with an MDR-HAI were country (Brazil), antibiotic use in the month before HAI, previous transplantation, major surgery in the 6 months before HAI, and previous colonization by an MDR strain (Table 3).

Risk factors associated with the 30-day case fatality rate are summarized in Table 4. In the univariate analysis, factors significantly associated with the 30-day case fatality rate were country (Brazil), prematurity, type of HAI, and microorganism category. In the multivariate multilevel analysis, factors independently associated with the 30-day case fatality rate were previous transplantation, BSI, LRTI, infection caused by fungi compared with Gram-positive bacteria, and infection caused by an MDR strain. The 2–5 years age group was a protective factor compared with the 0–28 days age group.

DISCUSSION

We reported a 5-year experience of microbiologically confirmed HAIs in 8 ICUs at 3 children's hospitals in Italy and Brazil. Our study involved nearly 15,000 patients admitted in 2010–2014, and data on 538 HAIs were included. This cohort was larger compared with previous studies published in pediatrics. We documented a HAI incidence of 3.6% and an infection rate of 3.6/1,000 ICU-days. Compared with previous reports, our rates were lower than expected, since the incidence of HAIs has been previously reported as between 7% and 12% in pediatric and between 15% and 20% in neonatal ICUs.[4,6,15–18] The great majority of children in our cohort had an underlying disease (93.3%), a proportion quite similar to previous data in pediatric ICUs.[19]

Consistent with previous studies, BSIs represented the leading cause of pediatric HAIs, followed by LRTIs and urinary

TABLE 3. Univariate and Multivariate Regression Analysis of the Impact of Cohort Characteristics on HAIs Caused by MDR Isolates

Variable	MDR (n = 241)	Non-MDR (n = 297)	*P*	Crude OR	(95% CI)	*P*	Adj OR	(95% CI)	*P*
Country			.001						
Italy	119 (35.5)	216 (64.5)		1 [Ref]			1 [Ref]		
Brazil	122 (60.1)	81 (39.9)		2.73	(1.91–3.92)	.001	3.11	(1.86–5.20)	<.001
Age group			.070				N.I.		
0–28 days	25 (36.8)	43 (63.2)		1 [Ref]					
29 days–3 months	40 (41.2)	57 (58.8)		1.21	(0.64–2.28)	.563			
3 months–2 years	95 (42.4)	129 (57.6)		1.27	(0.72–2.22)	.408			
2–5 years	35 (57.4)	26 (42.6)		2.32	(1.14–4.70)	.020			
>5 years	46 (52.3)	42 (47.7)		1.88	(0.99–3.59)	.055			
Male gender	136 (46.7)	155 (53.3)	.326	1.19	(0.84–1.67)	.326			
Underlying conditions			.319						
No	19 (52.8)	17 (47.2)		1 [Ref]					
Yes	222 (44.2)	280 (55.8)		0.71	(0.36–1.40)	.321			
Risk category			.212						
Surgery	72 (38.3)	116 (61.7)		1 [Ref]			1 [Ref]		
Immunodeficiency	6 (40.0)	9 (60.0)		1.07	(0.37–3.14)	.896	1.51	(0.46–4.96)	.500
Transplantation	8 (66.7)	4 (33.3)		3.22	(0.94–11.09)	.063	4.17	(1.12–15.61)	.034
Cancer	10 (62.5)	6 (37.5)		2.69	(0.94–7.70)	.066	1.17	(0.37–3.66)	.790
Renal failure	5 (45.5)	6 (54.6)		1.34	(0.40–4.56)	.637	0.89	(0.22–3.63)	.874
Prematurity	17 (44.7)	21 (55.3)		1.30	(0.65–2.63)	.459	2.25	(0.96–5.31)	.063
Other	102 (46.4)	118 (53.6)		1.39	(0.94–2.07)	.101	1.41	(0.82–2.43)	.211
AB use in the month before HAI			.001						
No	20 (27.8)	52 (72.2)		1 [Ref]			1 [Ref]		
Yes	217 (48.2)	233 (51.8)		2.42	(1.40–4.19)	.002	2.10	(1.14–3.88)	.017
Type of AB									
Penicillin/ampicillin	7 (36.8)	12 (63.2)	.442	1.52	(0.52–4.40)	.443			
Combination of penicillin, incl. beta-lactamase inhibitor	15 (41.7)	21 (58.3)	.146	1.86	(0.80–4.30)	.148	N.I.		
Cephalosporin 2nd	23 (32.9)	47 (67.1)	.510	1.30	(0.63–2.67)	.474			
Cephalosporin 3rd	21 (53.9)	18 (46.2)	.007	3.03	(1.34–6.84)	.008	1.85	(0.90–3.81)	.093
Carbapenem not combined with enzyme	48 (57.1)	36 (42.9)	.001	3.47	(1.77–6.79)	.001	1.60	(0.93–2.66)	.093
Combination of sulfonamized/trimethoprim	2 (40.0)	3 (60.0)	.620	1.73	(0.27–11.15)	.563			
Macrolide	7 (58.3)	5 (41.7)	.048	3.64	(1.03–12.81)	.044	N.I.		
Aminoglycoside	15 (44.1)	19 (55.9)	.095	2.05	(0.88–4.81)	.098	N.I.		
Quinolone	24 (50.0)	24 (50.0)	.023	2.60	(1.21–5.59)	.014	N.I.		
Glycopeptide	32 (48.5)	34 (51.5)	.012	2.45	(1.21–4.96)	.013	N.I.		
Surgery in the previous 6 months			.063						
No	91 (43.5)	118 (56.5)		1 [Ref]			1 [Ref]		
Minor	40 (58.0)	29 (42.0)		1.80	(1.04–3.13)	.036	1.81	(0.98–3.33)	.058
Major	110 (42.5)	149 (57.5)		0.97	(0.68–1.39)	.851	1.99	(1.10–3.58)	.022
Invasive devices			.833						
No	18 (43.9)	23 (56.1)		1 [Ref]					
Yes	218 (45.6)	260 (54.4)		1.01	(0.54–1.91)	.963			
Previous colonization by MDR			.001						
No	139 (38.7)	220 (61.3)		1 [Ref]			1 [Ref]		
Yes	87 (63.0)	51 (37.0)		2.70	(1.80–4.05)	.001	1.72	(1.08–2.76)	.023

NOTE. Data are no. (%) of isolates in that column unless otherwise indicated. AB, antibiotic; HAI, healthcare-associated infection; MDR, multidrug-resistant; N.I., not included in the final model; OR, odds ratio.

TABLE 4. Univariate and Multivariate Regression Analysis of the Impact of Cohort Characteristics on Mortality

Variable	Survived (n = 453)	Non-survived (n = 85)	*P*	Crude OR	(95% CI)	*P*	Adj OR	(95% CI)	*P*
Country			.002						
Italy	295 (88.1)	40 (11.9)		1 [Ref]			1 [Ref]		
Brazil	158 (77.8)	45 (22.2)		2.10	(1.32–3.35)	.002	3.58	(1.96–6.52)	<.001
Age group			.187						
0–28 days	51 (75.0)	17 (25.0)		1 [Ref]			1 [Ref]		
29 days–3 months	81 (83.5)	16 (16.5)		0.59	(0.28–1.28)	.181	0.59	(0.25–1.38)	.226
3 months–2 years	195 (87.0)	29 (13.0)		0.45	(0.23–0.87)	.019	0.52	(0.23–1.17)	.112
2–5 years	53 (86.9)	8 (13.1)		0.45	(0.18–1.14)	.093	0.32	(0.11–0.95)	.039
>5 years	73 (83.0)	15 (17.0)		0.62	(0.28–1.35)	.225	0.51	(0.19–1.37)	.181
Male gender	245 (84.2)	46 (15.8)	.995	1.00	(0.63–1.59)	.995			
Underlying conditions			.635						
No	32 (88.9)	4 (11.1)		1 [Ref]					
Yes	421 (83.9)	81 (16.1)		1.54	(0.53–4.47)	.428			
Risk category			.120						
Surgery	161 (85.6)	27 (14.4)		1 [Ref]			1 [Ref]		
Immunodeficiency	11 (73.3)	4 (26.7)		2.17	(0.64–7.31)	.212	2.00	(0.52–7.77)	.315
Transplantation	8 (66.7)	4 (33.3)		2.99	(0.84–10.59)	.091	5.98	(1.38–25.94)	.017
Cancer	13 (81.3)	3 (18.8)		1.38	(0.37–5.15)	.635	0.96	(0.21–4.33)	.958
Renal failure	10 (90.9)	1 (9.1)		0.60	(0.07–4.85)	.629	0.38	(0.04–3.51)	.395
Prematurity	27 (71.0)	11 (29.0)		2.43	(1.07–5.47)	.032	1.70	(0.67–4.28)	.262
Other	188 (85.5)	32 (14.5)		1.01	(0.58–1.77)	.958	0.85	(0.44–1.63)	.616
Previous colonization by MDR			.401						
No	305 (85.0)	54 (15.0)		1 [Ref]					
Yes	113 (81.9)	25 (18.1)		1.25	(0.74–2.10)	.402			
LOS in ICU before HAI, median (IQR), days	24.0 (11–59)	24.0 (13–51)	.912	1.00	(0.99–1.00)	.867			
Type of HAI			0.001						
Urinary tract infection	79 (92.9)	6 (7.1)		1 [Ref]			1 [Ref]		
Bloodstream infection	193 (79.1)	51 (20.9)		3.48	(1.43–8.43)	.006	4.01	(1.50–10.61)	.005
Lower respiratory tract infection[a]	123 (82.6)	26 (17.4)		2.78	(1.10–7.07)	.031	2.93	(1.08–8.00)	.036
Surgical site infection	32 (100.0)	0 (0)		1.00	-	-	1.00	-	-
Other infections	25 (92.6)	2 (7.4)		1.05	(0.20–5.55)	.951	0.88	(0.15–5.00)	.881
Organisms			.031						
Gram-positive	161 (87.5)	23 (12.5)		1 [Ref]			1 [Ref]		
Gram-negative	266 (83.9)	51 (16.1)		1.34	(0.79–2.28)	.276	1.51	(0.83–2.75)	.182
Fungi	26 (70.3)	11 (29.7)		2.96	(1.29–6.79)	.010	4.93	(1.88–12.90)	.001
Susceptibility			.060						
Non-MDR	258 (86.9)	39 (13.1)		1 [Ref]			1 [Ref]		
MDR	195 (80.9)	46 (19.1)		1.56	(0.98–2.49)	.061	1.85	(1.06–3.22)	.030

NOTE. Data are no. (%) unless otherwise indicated. HAI, healthcare-associated infection; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MDR, multidrug-resistant; OR, odds ratio.

[a]Including pneumonia.

tract infections.[6,16–18,20] These findings underline how children differ from adults in HAI distribution, emphasizing the need to target interventions focused on BSI prevention in neonates and children.[9]

Of the isolated pathogens, 55% were Gram-negatives, 32% were Gram-positives, and 7% were fungi. This distribution is consistent with previous studies, conducted both in adults and children, showing that in ICUs most HAIs are due to Gram-negative bacteria, with Enterobacteriaceae counting for 25%–30% of all isolates.[4]

In our cohort, nearly half of the organisms grown were classified as MDR. Among Enterobacteriaceae, 45% of the isolates were positive for extended-spectrum beta-lactamase. This proportion was high compared with previous reports in hospitalized children.[21,22] However, this could have been overrepresented since our definition was based only on susceptibility profile. Culture-confirmed carbapenem resistance was reported in only 2% of Enterobacteriaceae in our cohort. Infections due to carbapenem-resistant Enterobacteriaceae in adult populations have been associated with mortality rates as high as 40%.[23] Carbapenem-resistant Enterobacteriaceae infections are still relatively uncommon in children, with prevalence being reported less than 1% and mortality rate lower compared with adults.[24]

In the multivariate analysis, previous colonization by an MDR pathogen was independently associated with an MDR-HAI. Children have been proven to show particularly high colonization rates, representing a reservoir from which bacteria can spread.[25] However, the actual mechanisms leading from colonization to infection are still debated and few surveillance data have been published so far on resistant bacteria causing invasive disease in children.

One of our aims was to evaluate the impact of different patient-level risk factors on ICU mortality. In our cohort, the 30-day case fatality rate for children with HAIs was 5.7/1,000 admissions. This proportion was comparable with previous reports in pediatric ICUs[4] but lower compared with adults.[26] In the multivariate analysis, factors independently associated with 30-day HAI case fatality were BSI, LRTI, and infection caused by an MDR strain. Many studies have so far failed to demonstrate a clear relationship between antimicrobial resistance and mortality.[8,10,11,27] A possible explanation is that the currently used definitions for MDR bacteria may not be directly applicable in clinical care, because they do not take into account infection type, age, or risk adjustment.[13]

The other factor independently associated with mortality was type of infection. In our cohort, children with BSI and LRTI had a respective risk of death 4.0 and 2.9 times higher than children with other HAIs. This finding is consistent with previous studies.[4,6,16]

This study has some limitations. Children admitted to an ICU are a highly heterogeneous population, characterized by different medical/surgical underlying diseases. This very variable case-mix could have influenced the analysis and misrepresented the impact of different risk factors on the outcomes. We assessed risk factors with a retrospective nested case-control study design; the independent role of determinants of HAI due to MDR and of case fatality were assessed by logistic regression analysis. Other approaches, including multistate regression analysis, could be adopted to investigate multiple events associated with HAI, such as excess length of hospital stay and mortality.[28] Our multicenter study was conducted in 2 countries; differences in population demographic characteristics, organization of care, and laboratory techniques for confirming HAIs and diagnosing MDR may have influenced our results. Further studies should be conducted in multiple countries to better address geographical variability. To this regard, multilevel regression analysis could be a useful tool to simultaneously investigate how population-level and individual-level factors contribute to disease outcomes.[29]

Education of healthcare personnel about intravascular catheter use and procedures in ICUs have proven to be effective measures to reduce the rate of central line–associated BSIs in pediatric intensive care.[30] Facility data submission mandates at national and international levels have been demonstrated to improve the prevention of central line–associated BSIs and reduce the rates of central line–associated BSIs in hospitalized children.[31] Targeted surveillance programs collecting neonatal and pediatric HAI/BSI data and clinical outcomes may be useful to allow global benchmarking between centers. However, the data collected for this study are just too labor intensive for routine use, especially in the setting of low- or middle-income countries. Web-based point prevalence surveys seem to be an effective tool to allow simple-to-collect data to be used to set benchmarks and monitor interventions. The Global Antimicrobial Resistance, Prescribing, and Efficacy among Neonates and Children Project,[32] the repeated point prevalence surveys of HAIs and antimicrobial use in European hospitals conducted by the European Centre for Disease Prevention and Control,[33] and the International Nosocomial Infection Control Consortium[34] represent good examples of international initiatives aiming at reducing the burden of HAIs and their attributable mortality. The next step is to identify simple methods to monitor key HAIs and integrate these into affordable intervention programs.

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