HEALTHCARE-ASSOCIATED INFECTIONS IN PAEDIATRIC AND NEONATAL INTENSIVE CARE UNITS: IMPACT OF UNDERLYING RISK FACTORS AND ANTIMICROBIAL RESISTANCE ON 30-DAY CASE-FATALITY

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ABSTRACT

Objectives. Our aims were (i) to describe trends in the epidemiology of Healthcare-associated Infections (HAIs) in paediatric/neonatal ICUs and (ii) to evaluate risk factors and impact of Multidrug-Resistance (MDR) in children admitted to ICUs.

Design. Multicentre, retrospective, cohort study with a nested case-control study conducted between January 2010 and December 2014.

Setting. Three tertiary-care paediatric hospitals in Italy and Brazil with a total of 97 ICU beds.

Patients. Inclusion criteria were (i) admission to ICU during the study period (ii) age at onset <18 years and (iii) microbiologically-confirmed HAI.

Results. 538 HAIs in 454 children were included. 93.3% of patients had comorbidities. Bloodstream infections (BSIs) were the leading pattern (45.4%). The cumulative incidence of HAI was 3.6/100 ICU-admission and the crude 30-day fatality rate was 5.7/1,000-admission. The most frequently isolated pathogens were Enterobacteriaceae, followed by *Pseudomonas aeruginosa* and *Staphylococcus aureus*. 44% of isolates were MDR. Two multivariate logistic regressions were performed. Factors independently associated with an MDR-HAI were Country, previous antibiotics, transplantation, major surgery, and colonisation by an MDR strain. Factors independently associated with 30-day case-fatality were Country, previous transplantation, fungal infection, BSI, LRTI, and infection caused by MDR strains.

Conclusions. Infection control and prevention should be a primary focus to limit the spread of MDR strains and improve the outcome of hospitalised patients. Targeted surveillance programmes collecting neonatal and paediatric HAI/BSI data and outcomes would allow global benchmarking between centres. The next step is to identify simple methods to monitor key HAIs and integrate these into affordable intervention programmes.

INTRODUCTION

Healthcare-associated infections (HAIs) are one of the most frequent adverse event 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 paediatrics 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 showed conflicting results about the impact of different underlying risk factors on clinical outcome of patients with HAI admitted to ICUs. There is no clear independent correlation between antimicrobial resistance (AMR) and patients' mortality.[8-11]

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

MATERIALS AND METHODS

Study design and setting

We conducted a multicentre, retrospective, cohort study with a nested case-control study in one paediatric hospitals in Italy and two in Brazil. These countries were chosen because of the high rates of AMR identified. The Bambino Gesù Children's Hospital (Rome, Italy) is a 607-bed paediatric tertiary-care centre, including one neonatal (NICU), three paediatric (PICU) and one cardiac intensive care unit (CICU) (47 ICU-bed). The Prontobaby Hospital da Criança (Rio de Janeiro, Brazil) is a 135-bed private service including NICU and PICU (45 ICU-bed). The Centro Pediátrico da Lagoa (Rio de Janeiro, Brazil) is a 39-bed private service including an 11-bed PICU.

The study was conducted between the 1st January 2010 and the 31st December 2014. During this period, ongoing prospective surveillance of HAIs was conducted in all the participating ICUs. Patients with a microbiologically-confirmed diagnosis of HAI were retrieved from this data source. Inclusion criteria were (i) admission to ICU during the study period (ii) age at onset <18 years and (iii) 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 CDC HAI case definitions, with only those infections presenting and identified >48 hours after admission to ICU considered as ICU-acquired and included.[12]

The multidrug-resistance (MDR) of the isolates was defined according to *Magiorakos A-P et al*.[13] *Coagulase-negative staphylococci* (CoNS) were considered as MDR if resistant to ≥3 different antibiotics 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.

Microbiological methods

In Italy, isolation and identification of microorganisms were made with accredited routine laboratory methods (Vitek® 128 2, bioMérieux, Durham, NC or Phoenix, BD Diagnostics). The CLSI criteria were used for antibiotic susceptibility testing (AST) from 2010 to 2011 whereas from 2012 the EUCAST breakpoints have been introduced in the Hospital's practice.

In Brazil, isolation of microbiological species was done by semi-quantitative process (Auto-Scan 4-SIEMENS). AST were done by disk-diffusion according to CLSI recommendations until 2013 and to EUCAST from 2014.

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

Data source and statistical analysis

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

Categorical variables were summarized by absolute frequencies and percentages, and continuous variables by median and interquartile range (IQR).

To determine statistical differences between groups, the Chi square test or Fischer's exact test were used for categorical variables, while the t-test or Mann-Whitney test were used for continuous variables.

Two multivariate logistic regression models were developed to assess independent predictors of: 1) acquisition of MDR-HAI compared to non-MDR-HAI, and 2) 30-day HAI case-fatality rate. Variables for which the p-value was <0.20 in univariate analyses were included in the multivariate models. Final models were computed with a stepwise backward procedure (likelihood ratio test $p<0.05$).

All statistical analyses were performed using STATA, Statistical Software: Release 13. College Station, Tx: StataCorp 2013.

Ethics

The study was approved by the Ethical Committee of all institutions 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 summarised 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 (UTIs) with 85 episodes (15.8%).

The median age of patients at HAI onset was 7.8 months (IQR 2.1-26.2 months). 93.3% of HAI cases affected children with comorbidities. The median length of stay (LOS) in ICU was 67 days (IQR 31-127 days) whereas the median time between ICU admission and onset of HAI was 24 days (IQR 11-58 days).

Overall, 478 out of the 538 HAIs (88.8%) were diagnosed in patients with an invasive device in situ. In 443 of them (82.3%), the device had been in place for more than 48 hours before the infection. Among BSIs, 195/244 (79.9%) interested children with a Central Venous Catheter (CVC) in situ when diagnosed (179 (73.4%) of them for >48 hours). 120 out of 149 (80.5%) LRTIs were in children mechanically-ventilated (100 (67.1%) of them for >48 hours). Among UTIs, 38/85 were in children who had a Urinary Catheter (28 (32.9%) of them for >48 hours).

In 318 out of 538 episodes (59.1%), children were already on antibiotics when diagnosed with a HAI (141 (44.3%) were receiving monotherapy, 130 (40.9%) were on two, and 47 (14.8%) on three antibiotics).

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

Microbiological data

A total of 573 microorganisms were isolated (Table 2). Among them, 317/573 were Gram-negative bacteria (55%), 184/573 were Gram-positive bacteria (32%), and 40/573 were Fungi (7%). The most frequently isolated pathogens were Enterobacteriaceae (30.9%), followed by *Pseudomonas aeruginosa* (19.2%) and *Staphylococcus aureus* (11.0%). The percentage of MDR isolates was 44%. Based on the susceptibility profile, 79/175 (45%) of the Enterobacteriaceae were ESBL-positive. Culture-confirmed carbapenem resistance was reported in 3/175 (2%) of the Enterobacteriaceae (CRE), 46/110 (42%) of *P. aeruginosa* and 6/10 of *Acinetobacter baumannii*. Among Gram-positives, 35/63 (56%) of *S. aureus* were methicillin-resistant (MRSA) whereas no vancomycin-resistant *Enterococcus spp* (VRE) was isolated. 76 *Coagulase-negative Staphylococci* (CoNS) were isolated, 47 of which were classified as MDR (62%). 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

Out 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* 1.99/100; p=0.995). 30-day case-fatality rate was also similar in MDR-HAI episodes compared to non-MDR episodes (19.1% *vs* 13.1%; p=0.06).

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

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

DISCUSSION

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

Consistent with previous studies, BSIs represented the leading cause of paediatric HAIs, followed by LRTIs and UTIs.[6, 16-18, 20] These findings underline how children differ from adults in HAI

distribution, emphasising 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 ICU the majority of HAIs is due to Gram-negative bacteria, with Enterobacteriaceae counting for 25-30% of all isolates.[4]

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

In the multivariate analysis, previous colonisation by an MDR pathogen was independently associated with an MDR-HAI. Children have been proved to show particularly high colonisation rates, representing a reservoir from which bacteria can spread.[25] However, the actual mechanisms leading from colonisation to infection are still debated and little 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, 30-day fatality rate for children with HAIs was 5.7/1,000-admission. This proportion was comparable to previous reports in paediatric ICUs,[4] but lower compared to 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, as 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 ICU are a highly heterogeneous population, characterised 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 multicentre study was conducted in two Countries; differences in population demographic, organization of care, and laboratory technics 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 proved to be effective measures to reduce the rate of central line-associated BSIs (CLABSIs) in paediatric intensive care.[30] Facility data submission mandates at national and international level

demonstrated to improve CLABSI prevention and reduce CLABSI rates in hospitalised children.[31] Targeted surveillance programmes collecting neonatal and paediatric HAI/BSI data and clinical outcomes may be useful to allow global benchmarking between centres. However, the data collected for this study are just too labour intensive for routine use, especially in the low-middle income countries setting. Web-based Point Prevalence Surveys (PPSs) seem to be an effective tool to allow simple-to-collect data to be used to set benchmark and monitor interventions. The Global Antimicrobial Resistance, Prescribing, and Efficacy among Neonates and Children (GARPEC) Project,[32] the repeated PPSs of HAIs and antimicrobial use in European hospitals conducted by the ECDC,[33] or the International Nosocomial Infection Control Consortium (INICC)[34] represent good examples of international initiatives aiming at reducing HAIs burden and their attributable mortality. The next step is to identify simple methods to monitor key HAIs and integrate these into affordable intervention programmes.

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Table 1: Characteristics of episodes of HAI included in the study

Variable	Italy (%)	Brazil (%)	Total (%)	*p*
Total number of episodes	335	203	538	
Gender				0.831
M	180(53.7)	111(54.7)	291(54.1)	
F	155(46.3)	92(45.3)	247(45.9)	
Median age in months (range IQR)	5.3(1.8-12.8)	14.9(4.0-49.7)	7.8(2.1-26.2)	0.001
Age group				0.001
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				0.001
No	11(3.3)	25(12.3)	36(6.7)	
Yes	324(96.7)	178(87.7)	502(93.3)	
Admission ward				0.001
NICU[a]	84(25.1)	30(14.8)	114(21.2)	
PICU[b]	96(28.7)	173(85.2)	269(50.0)	
CICU[c]	155(46.3)	0(-)	155(28.8)	
Median length of stay (LOS) in ICU				
ICU-days (IQR)	73(33-135)	55(26-124)	67(31-127)	0.085
LOS pre-HAI[d] (IQR)	24(10-55)	26(13-67)	24(11-58)	0.186

HAI distribution				0.033
Bloodstream infection	159(47.6)	85(41.9)	244(45.4)	
Lower respiratory tract infection[e]	88(26.4)	61(30.1)	149(27.8)	
Urinary tract infection	51(15.3)	34(16.8)	85(15.8)	
Surgical site infection	25(7.5)	7(3.5)	32(6.0)	
Other infections	11(3.3)	16(7.9)	27(5.0)	
Susceptibility of the isolate				0.001
MDR[f]	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(7.0)	0.014
30-day mortality	25(7.8)	26(14.1)	51(10.1)	0.024

[a]NICU: Neonatal intensive Care Unit; [b]PICU: Paediatric Intensive Care Unit; [c]CICU: Cardiac Intensive Care Unit; [d]HAI: Healthcare-associated Infections; [e]Including Pneumonia; [f]MDR: Multidrug-Resistant

1 **Table 2: Distribution and resistance of isolates by type of Healthcare-associated Infection**

Pathogen	Bloodstream infection			Lower Respiratory Tract Infection[a]			Urinary Tract Infection			Surgical Site Infection			Other		
Total isolates	**252**			**164**			**94**			**35**			**27**		
	n	**n MDR[b]**	**%**	**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[c]	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	45.1	17	13	46.5	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[d]	13	5	38.5	12	6	50	7	2	28.6	3	0	-	1	0	-

[a]Including Pneumonia; [b]MDR: Multidrug-Resistant; [c]CoNS: Coagulase-negative staphylococci; [d]1 missing case

Table 3: Univariate and multivariate regression analysis of the impact of cohort characteristics on Healthcare-associated Infections caused by Multidrug-Resistant isolates

Variable	MDR[a] (n=241)	non-MDR (n=297)	*p*	Crude OR	(95%CI)	*p*	Adj OR	(95%CI)	*p*
Country (%)			0.001						
Italy	119(35.5)	216(64.5)		1			1		
Brazil	122(60.1)	81(39.9)		2.73	(1.91-3.92)	0.001	3.11	(1.86-5.20)	<0.001
Age group (%)			0.070				N.I.[b]		
0-28 days	25(36.8)	43(63.2)		1					
29 days-3 months	40(41.2)	57(58.8)		1.21	(0.64-2.28)	0.563			
3 months-2 years	95(42.4)	129(57.6)		1.27	(0.72-2.22)	0.408			
2-5 years	35(57.4)	26(42.6)		2.32	(1.14-4.70)	0.020			
>5 years	46(52.3)	42(47.7)		1.88	(0.99-3.59)	0.055			
Male gender (%)	136(46.7)	155(53.3)	0.326	1.19	(0.84-1.67)	0.326			
Underlying conditions (%)			0.319						
No	19(52.8)	17(47.2)		1					
Yes	222(44.2)	280(55.8)		0.71	(0.36-1.40)	0.321			
Risk category (%)			0.212						
Surgery	72(38.3)	116(61.7)		1			1		
Immunodeficiency	6(40.0)	9(60.0)		1.07	(0.37-3.14)	0.896	1.51	(0.46-4.96)	0.500
Transplantation	8(66.7)	4(33.3)		3.22	(0.94-11.09)	0.063	4.17	(1.12-15.61)	0.034
Cancer	10(62.5)	6(37.5)		2.69	(0.94-7.70)	0.066	1.17	(0.37-3.66)	0.790
Renal failure	5(45.5)	6(54.6)		1.34	(0.40-4.56)	0.637	0.89	(0.22-3.63)	0.874
Prematurity	17(44.7)	21(55.3)		1.30	(0.65-2.63)	0.459	2.25	(0.96-5.31)	0.063
Other	102(46.4)	118(53.6)		1.39	(0.94-2.07)	0.101	1.41	(0.82-2.43)	0.211
AB use in the month before HAI[c] (%)			0.001						

No	20(27.8)	52(72.2)		1			1		
Yes	217(48.2)	233(51.8)		2.42	(1.40-4.19)	0.002	2.10	(1.14-3.88)	0.017
Type of AB (%)									
Penicillin/Ampicillin	7(36.8)	12(63.2)	0.442	1.52	(0.52-4.40)	0.443			
Combination of penicillin, incl. beta-lactamase inhibitor	15(41.7)	21(58.3)	0.146	1.86	(0.80-4.30)	0.148	N.I.		
Cephalosporin 2nd	23(32.9)	47(67.1)	0.510	1.30	(0.63-2.67)	0.474			
Cephalosporin 3rd	21(53.9)	18(46.2)	0.007	3.03	(1.34-6.84)	0.008	1.85	(0.90-3.81)	0.093
Carbapenem not combined with enzyme	48(57.1)	36(42.9)	0.001	3.47	(1.77-6.79)	0.001	1.60	(0.93-2.66)	0.093
Combination of sulfonamised/trimethoprim	2(40.0)	3(60.0)	0.620	1.73	(0.27-11.15)	0.563			
Macrolide	7(58.3)	5(41.7)	0.048	3.64	(1.03-12.81)	0.044	N.I.		
Aminoglycoside	15(44.1)	19(55.9)	0.095	2.05	(0.88-4.81)	0.098	N.I.		
Quinolone	24(50.0)	24(50.0)	0.023	2.60	(1.21-5.59)	0.014	N.I.		
Glycopeptide	32(48.5)	34(51.5)	0.012	2.45	(1.21-4.96)	0.013	N.I.		
Surgery in the previous 6 months (%)			0.063						
No	91(43.5)	118(56.5)		1			1		
Minor	40(58.0)	29(42.0)		1.80	(1.04-3.13)	0.036	1.81	(0.98-3.33)	0.058
Major	110(42.5)	149(57.5)		0.97	(0.68-1.39)	0.851	1.99	(1.10-3.58)	0.022
Invasive devices (%)			0.833						
No	18(43.9)	23(56.1)		1					
Yes	218(45.6)	260(54.4)		1.01	(0.54-1.91)	0.963			
Previous colonisation by MDR (%)			0.001						
No	139(38.7)	220(61.3)		1			1		

Yes	87(63.0)	51(37.0)	2.70	(1.80-4.05)	0.001	1.72	(1.08-2.76)	0.023

1 [a]MDR: Multidrug-Resistant; [b]Not included in the final model; [c]HAI: Healthcare-associated

2 Infection

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 (%)			0.002						
Italy	295(88.1)	40(11.9)		1			1		
Brazil	158(77.8)	45(22.2)		2.10	(1.32-3.35)	0.002	3.58	(1.96-6.52)	<0.001
Age group (%)			0.187						
0-28 days	51(75.0)	17(25.0)		1			1		
29 days-3 months	81(83.5)	16(16.5)		0.59	(0.28-1.28)	0.181	0.59	(0.25-1.38)	0.226
3 months-2 years	195(87.0)	29(13.0)		0.45	(0.23-0.87)	0.019	0.52	(0.23-1.17)	0.112
2-5 years	53(86.9)	8(13.1)		0.45	(0.18-1.14)	0.093	0.32	(0.11-0.95)	0.039
>5 years	73(83.0)	15(17.1)		0.62	(0.28-1.35)	0.225	0.51	(0.19-1.37)	0.181
Male gender (%)	245(84.2)	46(15.8)	0.995	1.00	(0.63-1.59)	0.995			
Underlying conditions (%)			0.635						
No	32(88.9)	4(11.1)		1					
Yes	421(83.9)	81(16.1)		1.54	(0.53-4.47)	0.428			
Risk category (%)			0.120						
Surgery	161(85.6)	27(14.4)		1			1		
Immunodeficiency	11(73.3)	4(26.7)		2.17	(0.64-7.31)	0.212	2.00	(0.52-7.77)	0.315
Transplantation	8(66.7)	4(33.3)		2.99	(0.84-10.59)	0.091	5.98	(1.38-25.94)	0.017
Cancer	13(81.3)	3(18.8)		1.38	(0.37-5.15)	0.635	0.96	(0.21-4.33)	0.958
Renal failure	10(90.9)	1(9.1)		0.60	(0.07-4.85)	0.629	0.38	(0.04-3.51)	0.395
Prematurity	27(71.0)	11(29.0)		2.43	(1.07-5.47)	0.032	1.70	(0.67-4.28)	0.262
Other	188(85.5)	32(14.6)		1.01	(0.58-1.77)	0.958	0.85	(0.44-1.63)	0.616

Previous colonisation by MDR[a] (%)			0.401						
No	305(85.0)	54(15.0)		1					
Yes	113(81.9)	25(18.1)		1.25	(0.74-2.10)	0.402			
Median ICU-stay pre-HAI[b] (IQR)	24.0 (11-59)	24.0 (13-51)	0.912	1.00	(0.99-1.00)	0.867			
Type of HAI			0.001						
Urinary tract infection	79(92.9)	6(7.1)		1			1		
Bloodstream infection	193(79.1)	51(20.9)		3.48	(1.43-8.43)	0.006	4.01	(1.50-10.61)	0.005
Lower respiratory tract infection[c]	123(82.6)	26(17.5)		2.78	(1.10-7.07)	0.031	2.93	(1.08-8.00)	0.036
Surgical site infection	32(100.0)	0(-)		1.00	-	-	1.00	-	-
Other infections	25(92.6)	2(7.4)		1.05	(0.20-5.55)	0.951	0.88	(0.15-5.00)	0.881
Organisms			0.031						
Gram-positive	161(87.5)	23(12.5)		1			1		
Gram-negative	266(83.9)	51(16.1)		1.34	(0.79-2.28)	0.276	1.51	(0.83-2.75)	0.182
Fungi	26(70.3)	11(29.7)		2.96	(1.29-6.79)	0.010	4.93	(1.88-12.90)	0.001
Susceptibility			0.060						
non-MDR	258(86.9)	39(13.1)		1			1		
MDR	195(80.9)	46(19.1)		1.56	(0.98-2.49)	0.061	1.85	(1.06-3.22)	0.030

1 [a]MDR: Multidrug-Resistant; [b]HAI: Healthcare-associated Infection; [c]Including Pneumonia