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High prevalence of hospital-acquired infections caused by gram-negative carbapenem resistant strains in Vietnamese pediatric ICUs

A multi-centre point prevalence survey

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Abstract

There is scarce information regarding hospital-acquired infections (HAIs) among children in resource-constrained settings. This study aims to measure prevalence of HAIs in Vietnamese pediatric hospitals.

Monthly point prevalence surveys (PPSs) in 6 pediatric intensive care units (ICUs) in 3 referral hospitals during 1 year.

A total of 1363 cases (1143 children) were surveyed, 59.9% male, average age 11 months. Admission sources were: other hospital 49.3%, current hospital 36.5%, and community 15.3%. Reasons for admission were: infectious disease (66%), noninfectious (20.8%), and surgery/trauma (11.3%). Intubation rate was 47.8%, central venous catheter 29.4%, peripheral venous catheter 86.2%, urinary catheter 14.6%, and hemodialysis/filtration 1.7%. HAI was diagnosed in 33.1% of the cases: pneumonia (52.2%), septicemia (26.4%), surgical site infection (2%), and necrotizing enterocolitis (2%). Significant risk factors for HAI included age under 7 months, intubation and infection at admission. Microbiological findings were reported in 212 cases (43%) with 276 isolates: 50 *Klebsiella pneumoniae*, 46 *Pseudomonas aeruginosa*, and 39 *Acinetobacter baumannii*, with carbapenem resistance detected in 55%, 71%, and 65%, respectively. *Staphylococcus aureus* was cultured in 18 cases, with 81% methicillin-resistant *Staphylococcus aureus*. Most children (87.6%) received antibiotics, with an average of 1.6 antibiotics per case. Colistin was administered to 96 patients, 93% with HAI and 49% with culture confirmed carbapenem resistance.

The high prevalence of HAI with carbapenem resistant gram-negative strains and common treatment with broad-spectrum antibiotics and colistin suggests that interventions are needed to prevent HAI and to optimize antibiotic use.

Abbreviations: CRF = case record form, ECDC = European Center for Disease Prevention and Control, HAI = hospital-acquired infection, ICU = intensive care unit, LMIC = low and middle income countries, PPS = point prevalence survey.

Keywords: hospital-acquired infections, ICU, pediatric, Vietnam

1. Introduction

Estimates of the burden of hospital-acquired infections (HAI), particularly among children, in low and middle income countries (LMIC) are not well known and most LMIC do not have any published data on HAI prevalence.[1] A recent European multicenter study on HAI in pediatric wards showed an HAI prevalence ranging from 2.5% in general pediatric ward to 23.6% in pediatric intensive care unit (ICU) setting.[2] High rates of HAI have also been reported in Neonatal Intensive Care Units[3] with an HAI prevalence 3 to 20 times higher in resource-limited settings compared to high income settings.[4]

Vietnam is a low middle income country with a rapidly expanding public and private healthcare sector.[5] Gross national income per capita per year is 3620$, total public expenditure on health per capita is around 234$ per year, about 80% of health expenditure is out of pocket payment. In the community, antibiotics are commonly used and mostly obtained through private pharmacies and clinics;[5] this in combination with high

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incidence of infectious diseases makes Vietnam a hotspot for antimicrobial resistance with rates among the highest recorded in Asia.[6] The health care sector is overstrained with a relatively low number of health staff per capita, 7 physicians per 10,000 population, and overcrowding with hospital bed occupancy up to 170%.[5]

Currently, there is no national surveillance system for HAI in Vietnam and there is limited data about HAI in ICUs. The few studies performed on HAI are small and only include a few ICUs. There is 1 published Vietnamese point prevalence survey (PPS) in 36 hospitals that showed high HAI prevalence in ICUs.[7] Additionally, antibiotic resistance is high with up to 70% of Enterobacteriaceae resistant to 3rd-generation cephalosporins and more than 40% of *Acinetobacter* species resistant to carbapenems.[5,7] Increasing prevalence of HAI caused by carbapenem resistant gram-negative bacteria such as Enterobacteriaceae is likely to cause an unprecedented public health crisis in LMIC settings where much of the advances in medical care may be jeopardized.[8]

We performed a 1-year once per month point prevalence study using the European Center for Disease Prevention and Control (ECDC) protocol to estimate HAI on pediatric ICUs. The results can be used to develop contextualized intervention strategies in Vietnam and other countries in the Asian region, where more than 50% of the world population lives.

2. Methods

2.1. Study design and study sites

The prevalence of HAIs, antibiotic use, and antibiotic resistance were assessed using PPS methodology developed by the ECDC.[9] The PPS protocol was contextualized for the local situation, without changing the definitions for HAI.[10,11] The PPS survey was conducted on a single day and repeated once per month from October 2012 to September 2013 at 2 specialized tertiary referral pediatric hospitals serving northern and southern provinces, the National Hospital for Paediatrics in Hanoi and Children Hospital 1 in Ho Chi Minh City and one specialized infectious diseases hospital serving Southern provinces, Hospital of Tropical Disease in Ho Chi Minh City. The hospitals are called Hospital 1, 2, and 3 (H1, H2, and H3) throughout the article due to integrity for the specific hospitals. Ethical approval was obtained from the ethical committee of the National Hospital for Tropical Diseases (code 27/HDDD-NHTD date 06/11/2012), and permission was obtained from the Vietnamese Ministry of Health (code 4921/QD-BYT date 11/12/2012). The need for informed consent for the PPS was waived.

2.2. Data collection

Data on hospital and ICU infrastructure and resources, and patient data were collected using a standardized case record form (CRF; see Supplementary information, http://links.lww.com/MD/B128). A training course on definition of HAI, how to fill in the CRF and entering data into the HELICS-Win database,[9] was provided for participating staff. A study initiation visit was performed in each ICU, which included hands-on training on site. Data were obtained using the CRF once a month from all patients admitted to the ICU before 8 >am on the day of the survey. The data were uploaded monthly to a central database where data were checked for missing or inaccurate data. In case of inconsistencies or inaccuracies, queries were sent to the hospitals. Repeat visits were done by study investigators to assist in reconciliation of data and on-going training.

The following patient data were gathered: age and gender, date of admission to hospital, and date of admission to ICU. Basic clinical information was collected, including primary reason for ICU admission (communicable vs noncommunicable disease), comorbidities, surgical interventions, or invasive procedures. It was also noted whether any family member had actively assisted in patient care during the preceding 24 hours, which is common due to lack of staff and resources in the Vietnamese hospital setting. Antibiotic use was defined as: having received the 1st dose of antibiotics at time of survey, admitted with on-going antibiotic treatment, or antibiotic prophylaxis within the last 24 hours. If the patient had received antimicrobials the type of antibiotic, indication for antibiotic use, route of administration, diagnosis of infection, and reason given in patient notes (if the antibiotic treatment was motivated from clinical or microbiological perspective or not).

HAI was defined using ECDC criteria and is briefly described here at least one of the following criteria: infection beginning ≥48 hours after admission to any hospital, surgical site infection ≤30 days following surgery, patient discharged from acute care hospital ≤48 hours, infection beginning ≤3 days following invasive procedure, or patient on treatment for HAI meeting any of above requirements when treatment was initiated. If a patient had a suffered from HAI the diagnosis and source of infection was documented, along with whether relevant device for administering antibiotics was in situ before onset or not, and origin of infection (current or other hospital). If available, microbiological data including type of culture (blood, sputum, urine, and wound), cultured organism, and antibiotic resistance were collected.

2.3. Data analysis

Statistical analysis included descriptive statistic analysis for the calculation of percentage, frequency, mean and median values, and 95% confidence interval (95%CI). Risk factors for HAI were analyzed with univariate analysis using Chi-square, odds ratio (OR), and 95%CI; and all variables significant in the univariate analysis at a P-value <0.10 were included in a multivariate regression analysis using binary logistic regression. The analysis was based on cases (not unique patients). The IBM SPSS Statistics software (version 22 IBM, CA) was used for data analysis. P-value <0.05 was considered significant, using 2-sided for general variables as sex and age, and 1-sided for variables considered risk factors for HAI as invasive procedures.

3. Results

In total 1363 pediatric cases were included in the PPS representing 1143 unique patients. The mean was 1.19 surveys per patient, 118 patients (10.3%) were included in more than 1 survey, 82 patients in 2 surveys, and 36 in 3 or more surveys. The majority of surveyed cases, 1010/1363 (74.1%), were collected at H1 of which 409 (40.5%) were from neonatal ICU, 329 (32.6%) from medical ICU, and 272 (26.9%) from the surgical ICU. The other 2 hospitals included cases from medical pediatric ICUs. H2 had 191 cases (14%) and H3 had 162 cases (11.9%).

Boys were overrepresented: 812/1363 (59.6%). The mean age was 11 months with a median of 3 months. The most common reason for admission was an infectious disease (n=900; 66%), followed by noncommunicable disease (n=283; 20.7%), emergency surgery (n=96; 7%), elective surgery (n=58;

Table 1

Prevalence of HAI in the different hospitals and wards.

	Hospital	H1			Total H1	H2	H3		Total
	Ward	NICU	MICU	SICU		PICU	AICU	PICU	
HAI	No	258	227	190	675	95	17	121	908
	Unknown	1	0	0	1	0	0	0	1
	Yes	150	102	82	334	96	3	21	454
Total		409	329	272	1010	191	20	142	1363
% HAI		36.7%	31.0%	30.1%	33.1%	50.3%	15.0%	14.8%	33.3%

AICU = acute ICU, H = hospital, HAI = hospital-acquired infection, ICU = intensive care unit, MICU = medical ICU, NICU = neonatal ICU, PICU = pediatric ICU, SICU = surgical ICU.

4.3%), and trauma (n = 5; <1%). The intubation rate was 659 (44.6%).

An HAI was diagnosed in 454/1363 child surveys (33.3%). The prevalence of HAI varied between the hospitals and wards from 14.8% to 50% (Table 1). At H1 the HAI prevalence varied between wards from 30.1% in the surgical ICU to 36.7% in the neonatal ICU. Of the 454 child surveys that fulfilled the criteria for HAI, 45 (9.9%) were noted to have 2 HAIs and 6 children (1.3%) had 3 HAIs.

Significant risk factors ($P < 0.05$) for HAI (Table 2) in univariate (Chi-square) and multivariate analysis (binary logistic regression) were: age 6 months and under (OR 2.06; 95%CI 1.59–2.65); source of the patient was the same hospital as the surveyed ICU, hence not referred from another hospital (OR 1.46, 95%CI 1.16–1.84); that the reason for hospital admission was infectious disease (OR 1.60, 95%CI 1.25–2.06); any comorbidity (OR 2.5, 95%CI 1.35–4.64); and intubation (OR 1.99, 95%CI 1.59–2.51). Family involvement in patient care was

Table 2

Risk factors for HAI, uni- and multivariate analysis.

Risk factors		Cases N (%)	Cases with HAI N (%)	*P*-value Chi-square	Odds ratio 95% CI	Binary logistic regression
Gender	Male	817 (59.9)	278 (34.0)	0.43	1.11	NA
	Female	575 (42.2)	173 (30.1)		0.88–1.40	
	Missing	3				
Age group	<=6 months	906 (66.5)	348 (38.4)	<0.000**	2.06	0.000**
	>6 months	456 (33.5)	106 (23.2)		1.59–2.65	
	Missing	1				
Comorbidity	Yes	43 (3.2)	23 (53.5)	0.004**	2.5	0.017*
	No	1295 (95.0)	420 (32.4)		1.35–4.64	
	Missing	26	11 (42.3)			
Intubation	Yes	652 (47.8)	269 (41.3)	<0.000**	1.99	0.000**
	No	710 (52.1)	185 (26.1)		1.59–2.51	
	Missing	1				
Central catheter	Yes	401 (29.4)	140 (34.9)	0.22	1.11	NA
	No	961 (70.5)	314 (32.7)		0.87–1.42	
	Missing	1	0			
Urinary catheter	Yes	199 (14.6)	56 (28.1)	0.054	0.75	NA
	No	1163 (85.3)	398 (34.2)		0.54–1.05	
	Missing	1	0			
Hemodialysis	Yes	23 (1.7)	8 (34.8)	0.52	1.07	NA
	No	1339 (98.2)	446 (34.1)		0.45–2.54	
	Missing	1	0			
Peripheral catheter	Yes	1175 (86.2)	401 (34.1)	0.070	1.31	NA
	No	186 (13.6)	53 (28.5)		0.93–1.84	
	Missing	2	0			
Family involved in patient care	Yes	61 (4.5)	10 (16.4)	<0.009*	0.38	0.037*
	No	1300 (95.4)	444 (34.1)		0.19–0.75	
	Missing	2				
Source of patients	Current hospital	492 (36.1)	190 (38.6)	<0.004**	1.46	0.010*
	Community, Other hospital	852 (62.5)	256 (30.0)		1.16–1.84	
	Missing	19	8			
Reason for admission	Infectious disease	900 (66.0)	330 (36.6)	< 0.001**	1.60	0.000**
	Noninfection	442 (32.4)	116 (26.2)		1.25–2.06	
	Missing	21	8			
Surgery since admission	Yes	262 (19.2)	89 (34)	0.54	1.03	NA
	No	1098 (80.6)	365 (33.2)		0.92–1.11	
	Missing	3				

CI = confidence interval, HAI = hospital-acquired infection, NA = not available.
*,** separates the explanation of abbreviations.

Table 3

HAI case definitions, microorganisms, and resistance.

Micro-organism	Diagnosis n (number)										Resistance n (%)	
	PNEU	SEP	SSI	NEC	CPI	STI	UTI	OTH	TOT	RD	Ceph R	Carba R
Klebsiella pneumoniae/sp	34	14	0	0	1	0	0	1	50	42	38 (90%)	23 (55%)
Pseudomonas aeruginosa	38	5	2	0	0	0	0	1	46	36	NA	24 (71%)
Acinetobacter baumannii/sp	34	4	0	0	0	0	0	0	38	36	NA	24 (67%)
Candida sp	1	24	0	0	1	0	1	1	28	NA	NA	NA
Staphylococcus aureus	12	5	2	0	0	1	0	0	20	15	MRSA 13 (87%)	
Escherichia coli	11	2	0	0	0	1	1	0	15	12	12 (100%)	5 (42%)
Staphylococcus sp	3	5	2	0	0	0	0	0	12	12	9 (75%)	1 (8%)
Enterobacter sp	7	4	0	0	0	0	0	0	11	11	8 (73%)	6 (55%)
Serratia sp	2	7	0	0	0	0	0	0	9	6	5 (83%)	0
Burkholderia cepacia	1	6	0	0	0	0	0	0	7	7	5 (71%)	3 (43%)
Stenotrophomonas maltophilia	5	1	0	0	1	0	0	0	7	7	1 (11%)	0
Providencia sp	5	0	0	0	0	0	0	0	5	5	4 (80%)	0
Enterococcus faecium	1	2	0	0	0	0	0	0	3	3	1 (33%)	1 (33%)
Proteus mirabilis sp	2	1	0	0	0	0	0	0	3	3	3 (100%)	2 (67%)
Achromobacter sp	2	0	0	0	0	0	0	0	2	2		
Citrobacter sp	0	0	2	0	0	0	0	0	2	2	0	0
Haemophilus influenzae	1	0	0	0	1	0	0	0	2	3		
Helicobacter pylori	2	0	0	0	0	0	0	0	2	2	2 (100%)	0
Shigella sp	1	0	1	0	0	0	0	0	2	2	2 (100%)	1 (50%)
Enterobacteriaceae not specified	1	0	0	0	0	0	0	0	1	1	1(100%)	1 (100%)
Fungi other	1	0	0	0	0	0	0	0	1	1		
No growth	126	41	0	9	2	0	0	0	178			
Total	296	120	9	9	6	2	2	3	454	249	91 (35%)	92 (40%)

Ceph R = cephalosporin resistant, CPI = CVC/PVC related infection, CR = carbapaenem resistant, HAI = hospital-acquired infection, MRSA = methicillin-resistant *Staphylococcus aureus*, NA = not available, OTH = other, PNEU = pneuminia, RD = resistance data, SEP = sepsis, SSI = surgical site infection, STI = soft tissue infection, TOT = total, UTI = urinary tract infection.

significantly related to a decreased risk for HAI (OR 0.38; 95%CI 0.19–0.75).

HAI diagnosis and culture results can be seen in Table 3. Pneumonia was the most common HAI with 296 cases (65.2%) diagnosed. Blood stream infection was the 2nd most common cause of HAI with 96 cases (21.1%), with 46 (9.1%) in neonates (Table 3). Among cases with reported HAI 269/454 (59.2%) where intubated, whereas among the cases without HAI 346/909 (38.1%) were intubated ($P < 0.001$). Among the 296 cases diagnosed with hospital-acquired pneumonia (HAP) 208 were intubated (70.1%).

Out of the 454 cases with HAI, 212 (46.9%) had positive culture results with 276 isolates (1.3 isolates per survey). Most common isolated species were: *Klebsiella pneumoniae*, *Pseudomonas* spp, *Acinetobacter* spp, and *Staphylococcus aure*us (Tables 3 and 4). Resistance patterns were known in 171 instances. Culture confirmed carbapenem resistant (CarbR) strains were reported in 87 cases with carbapenem resistance detected in 55% (23/42) of *K pneumoniae* isolates, 69% (25/36) *P aeruginosa*, and in 67% (24/36) of *A baumannii* isolates.

K pneumoniae was the most common pathogen isolated from patients with HAI, 58 strains out of 276 cultures with defined pathogen (21%). Of these 42 were from patients diagnosed with pneumonia (72%), 50 had resistance data and out of those 23 were carbapenem resistant (46%). In the neonatal ICU 30% of the isolated strains were *K pneumoniae* and of these, where resistance data were available, 82% were carbapenem resistant.

Of all 95 Enterobacteriaceae organisms (including *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp, *Proteus* spp, *Citrobacter* spp, *Serratia* spp, and *Morganella* spp) 88% showed resistance to 3rd-generation cephalosporins, 40% showed resistance to both cephalosporins and carbapenems. Resistance to 3rd-generation cephalosporins was found in 56% of the *K pneumoniae* isolates and 46% were resistant to both cephalosporins and carbapenems. Among *Pseudomonas* isolates 56% were carbapenem resistant and *A baumannii* isolates 64%.

Of gram-positive bacteria *S aureus* was the most common with 18 isolates, methicillin-resistant *Staphylococcus aureus* (MRSA) accounting for 81% (13 out of 16, 2 isolates were lacking resistance data).

Table 4

The most common HAI isolates and resistance per hospital including neonatal unit (neo).

	Strains	*Klebsiella* spp		*Pseudemonas* spp		*Acinetobacter* spp		*S Aeurus*		Other	
Hospital	N	N (%)	CR (%)	N (%)	CR N (%)	N (%)	CR N (%)	N (%)	MRSA (%)	N	%
H1*	126	23[a] (18%)	14 (70%)	31[b] (25%)	15 (71%)	20[c] (16%)	10 (55%)	13[d] (10%)	9 (82%)	39	31%
H1 Neo	53	16[e] (30%)	9 (82%)	4 (8%)	3 (75%)	0	0	4 (8%)	4 (100%)	29	55%
H2	49	9 (18%)	0	6 (12%)	2 (40%)	12 (24%)	9 (75%)	0	0	20	41%
H3	34	2 (6%)	0	5 (15%)	5 (100%)	6 (18%)	5 (83%)	0	0	21	62%
Total	262	50 (19%)	23 (55%)	46 (18%)	25 (69%)	38 (15%)	24 (67%)	18 (7%)	13 (81%)	109	42%

CR = carbapenem resistant, HAI = hospital-acquired infection, ICU = intensive care unit, MRSA = methicillin-resistant *Staphylococcus aureus*.

* Excluding neonatal ICU. Number of specimen lacking resistance data: [a]3, [b]10, [c]2, [d]2, [e]5 (resistance rates based on samples with resistance data).

Table 5

Specific antibiotics used for treatment. Antibiotics were given to 1194 children with an average of 1,6 antibiotics per child. Of all antibiotics used, 43% were administered to treat HAI.

Antibiotic	No HAI	HAI	TOT	% For HAI
Meropenem	139	156	295	53%
Cefoperazone	240	45	285	16%
Imipenem and enzyme inhibitor	93	86	180*	48%
Metronidazole	116	52	168	31%
Vancomycin	84	77	161	48%
Ceftriaxone	98	11	109	10%
Colistin	7	89	96	93%
Levofloxacin	42	52	94	55%
Ceftazidime	38	22	60	37%
Tobramycin	37	23	60	38%
Ciprofloxacin	15	37	52	71%
Piperacillin and enzyme inhibitor	21	24	45	53%
Cefotaxime	38	3	41	7%
Amikacin	24	9	33	27%
Pefloxacin	3	29	32	91%
Fluconazole	7	22	29	76%
Amphotericin B	1	24	26*	92%
Cefepime	11	13	24	54%
Fosfomycin	4	16	20	80%
Azithromycin	10	2	12	17%
Gentamicin	8	4	12	33%
Fosfomycin	4	6	10	60%
Ampicillin and enzyme inhibitor	4	4	8	50%
Cefuroxime	6	1	7	14%
Sulfamethoxazole and trimethoprim	1	6	7	86%
Clindamycin	1	3	4	75%
Sulbactam	3	1	4	25%
Ampicillin	3	0	3	0%
Moxifloxacin	2	1	3	33%
Norfloxacin	3	0	3	0%
Oxacillin	2	1	3	33%
Other	16	8	24	33%
Total	1081	827	1910	43%

HAI = hospital-acquired infection, No HAI = antibiotics used for treatment of other diagnosis then HAI, TOT = total.
* 1 Unknown.

Antibiotics were given to 1194 children (87.6%), 1 antibiotic was given to 354 (29.6%) children, 2 antibiotics to 522 (43.7%), 3 antibiotics to 137 (11.5%), and 4 antibiotics to 8 patients (0.6%). In total 1910 courses of antibiotics were given, with an average of 1.6 antibiotics per child. Of all antibiotics used, 43% were administered to treat HAI (Table 5).

Colistin was given to 96 children in 2 hospitals (H1 and H3) of these 48 (49%) had reported carbapenem resistant strains. Of the 87 children with carbapenem resistant isolates 43 (49%) were treated with colistin. The most common antibiotics administered in combination with colistin were: carbapenems (n = 36), fluoroquinolones (n = 20), piperacillin-tazobactam (n = 9), vancomycin (n = 7), and other (n = 12). In H2 where no colistin was used in children, there were 13 reported carbapenem resistant strains (18% of isolated strains) and the most common treatment for these cases was perfloxacine, either as monotherapy or as part of a combination therapy.

4. Discussion

This study showed that one third of the surveyed children fulfilled the criteria for HAI, with a high variation between types of ICUs. The most common causes of HAI were hospital-acquired pneumonia and septicemia including neonatal sepsis. About half of the HAI cases were culture verified, commonly with gram-negative bacteria resistant to cephalosporins and carbapenems. MRSA was also commonly reported.

Comparing to the levels of HAI found in previous point prevalence studies, as 9.4% in Iran[12] and between 21% and 28% in European ICUs,[9,13] the mean HAI prevalence of 31% across these 3 Vietnamese pediatric ICUs is comparably high. The prevalence of patients with HAI ranged widely between the ICUs: from 14.8% to 50.3%. The wide range in HAI prevalence between ICUs may be explained by differences in patient population, severity of disease, proportion of referred patients previously treated in other hospitals, intubation rates, and infection control measures.

The significant risk factors for HAI in uni- and multivariate analysis were age <6 months, source of patients current hospital (referral between departments), infection as reason for admission, and any comorbidity. The only invasive procedure showing a significant relation to increased risk for HAI was mechanical ventilation (intubation). A recent report from the International Nosocomial Infection Control Consortium (INICC) 2007 to 2012[2] from 503 ICUs shows that ventilator-associated pneumonia is 15 times more common and catheter-associated urinary tract infection 4 times more common in LMICs than in HICs. This may be explained by inadequate resources or training in infection control in LMIC. According to a study of the efficacy of nosocomial infection control (SENIC), up to a 3rd of HAI may be preventable by appropriate infection control measures.[14]

This study shows an alarming rate of carbapenem resistance among gram-negative bacteria. Of all Enterobacteriaceae the vast majority was resistant to 3rd-generation cephalosporins and 40% were also carbapenem resistant. Carbapenem resistant gram-negative bacteria are an urgent threat requiring immediate action, since BSI in children caused by carbapenem resistant Enterobacteriaceae has a high fatality rate.[15] Compared to other studies, these are very high levels of resistance.[16,17] As multidrug resistant (MDR) gram-negative pathogens are associated with a 3- to 4-fold increase in infection-related mortality,[18] these high resistance rates are alarming. There might be some bias as mainly severe patients not responding to treatment may have been cultured.

In the COMPACT II study surveying resistance over several Asia-Pacific countries, the highest incidence of ESBL-producers came from Vietnam, with 81% incidence among isolates from ICU patients.[6] A lower incidence of 44% was found in non-ICU patients, but our survey was carried out solely in ICU setting, hence in an environment with the higher overall level of resistance.

Due to high ESBL rates, carbapenems are often used empirically, leading to further increased carbapenem resistance rates in ICUs, likely through selection of resistant bacteria. Other studies have also shown high levels of nosocomial infections with carbapenem resistant *A baumannii* in Vietnam.[18,11] As mentioned previously, rates of carbapenem resistant *A baumannii* in our survey ranged up to 65% but were based only on few isolates.

K pneumoniae was the most common pathogen isolated from patients with HAI with 46% carbapenem resistance, in the neonatal ICU 82% were carbapenem resistant. *K pneumonia* has previously been reported as an infectious cause in Vietnamese neonatal ICUs[19] as well as strains with carbapenem resistance;[20] however, no prevalence has previously been reported. The high rates of carbapenem resistant *K pneumoniae* in H1 is

suggestive of a clonal outbreak which is corroborated by genotyping results showing most isolates harbored *K pneumoniae* carbapenemase 2 (unpublished data, on-going work). There are no previous reports of *K pneumoniae* carbapenemase 2 in Vietnam, however from neighboring China.[21] New Delhi metallo-beta-lactamase 1 (NDM-1) has previously been reported in Vietnamese patients and in the environment.[20,22]

There was a big variation in what antimicrobials or combinations of antimicrobials that were used to treat HAI caused by carbapenem resistant Enterobacteriaceae. Colistin was used in 49% of the cases with culture confirmed carbapenem resistant strains – either as monotherapy or in combination. Carbapenem was used alone or in combination in half of the cases. In the cases with diagnosed carbapenem resistant Enterobacteriaceae, the variety of treatments given in the survey highlights a very important point; despite being a dominating etiology of HAI, there are no clear treatment guidelines available in Vietnam to treat carbapenem resistant Enterobacteriaceae. A meta-analysis based on 20 studies concluded that for critically ill patients with severe infections due to carbapenemase-producing Enterobacteriaceae combination antibiotic treatment may offer a comparative advantage over monotherapy with regard to the mortality.[23] It is concerning that colistin was used in half of patients without culture confirmed carbapenem resistance. However, in case of poor response to given treatment, there may be good reasons to suspect that the etiology is carbapenem resistant strains. Increased use of colistin will induce selective pressure for colistin-resistance isolates to emerge, which has been documented in Asia.[24]

This study highlights the importance of functioning infection control including hand hygiene, antibiotic stewardship, and good laboratory capability.[25] Change in antibiotic policy, for example, substitution of piperacillin/tazobactam for extended-spectrum cephalosporins in community acquired infections, has shown to be successful in decreasing the prevalence of ESBL producing *K pneumoniae* and *E coli*,[26] and could be considered as treatment option. Evidence-based actions to improve antibiotic use and prevent further selection of carbapenem and colistin resistance are urgently needed. The effect of the actions should be continuously monitored, and standard treatment guidelines should regularly be updated at national, regional, and local levels.[27]

4.1. Limitations of the study

This is a PPS presenting cross-sectional study data. In order to assess treatment outcome in relation to resistance a longitudinal design would be required. Comparing neonatal wards with general pediatric wards may not be entirely appropriate as there is a variation between age groups and type of HAI – for example BSI or surgical site infection may be more likely in neonates whereas UTI may be more common in children over 5 years age, as shown in this study *K pneumoniae* infections were more common in neonates, also shown in earlier studies.[28] Patients were entered at 0 months of age regardless if they were pre- or full-term, and considering that the included Neonatal Intensive Care Units is a large tertiary referral center, the patients were mostly preterm. Perinatal risk factors such mode of delivery, gestational age, birth weight, asphyxia, respiratory distress syndrome, or congenital malformations were not obtained but have a relevance for susceptibility to HAI. There may be an overrepresentation of severe cases, as increased length of stay means increased chance of being in a survey. There are also difficulties interpreting the microbiology given that much was from cultured of nonsterile sites (e.g., tracheal aspirate) and may represent colonization. Antibiotic sensitivity data were not available for all cultures which might induce a bias. There is also a difficulty on assessing "appropriateness of therapy" when no longitudinal data are collected.

In order to design appropriate interventions, there is a need to assess the pediatric HAI and antibiotic resistance situation[28] using longitudinal study designs and assessing the burden of resistance including additional morbidity, treatment time, and costs as well as comparing patients with carbapenem resistance and those with susceptible strains. Also there is a need to assess the most effective treatment for carbapenem resistant infections in children and neonates including PK/PD studies as dosing in children is often based on limited data and may lead to underdosing with risk of increasing resistance, or overdosing with risk for adverse drug reactions.[29] Interventions to decrease the incidence of HAI is urgent and should however not be delayed but implemented continuously.[24,25]

5. Conclusion

This PPS in 3 pediatric ICUs found a high prevalence of HAI. The microbiological results showed that most of the positive cultures where gram-negative bacteria with high levels of carbapenem-resistance in *K pneumoniae* isolates. There was common use of broad spectrum antibiotics as cephalosporins and carbapenems, and the last resort antibiotic colistin was one of the most frequently used. The high levels of resistance and common use of broad-spectrum antibiotics suggest that interventions are needed to prevent HAI and to rationalize antibiotic use.

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