ORIGINAL ARTICLE

CLINICO-EPIDEMIOLOGIC PROFILE AND OUTCOME OF PEDIATRIC PATIENTS WITH MULTI DRUG RESISTANT GRAM-NEGATIVE HEALTHCARE ASSOCIATED INFECTIONS AT THE PHILIPPINE GENERAL HOSPITAL

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

Introduction: Multi Drug Resistant Organisms (MDRO) are microorganisms that are resistant to one or more classes of antimicrobial agents, and these have become significant pathogens to contend with in the treatment of Healthcare Associated Infections.

Objectives: This study aimed to determine the clinico-epidemiologic profile and outcome of pediatric patients with healthcare-associated multi-drug resistant gram-negative infections, and its antimicrobial susceptibility patterns.

Methodology: This was a retrospective study done on pediatric patients with gram negative healthcare associated MDRO sepsis compared to non-MDRO sepsis admitted at the ICU and pediatric wards of a tertiary government hospital from July 2015 to June 2016. Descriptive statistics was used to summarize the clinical characteristics of patients. Odds ratio and the corresponding 95% confidence interval from binary logistic regression was computed to determine significant predictors for the development of multi drug resistance. Outcome of patients with MDRO gram-negative infection was noted, as well as its antimicrobial susceptibility patterns.

Results: A total of 199 patients developed HAI, and 41% were identified to be gram negative MDR cases. Pediatric patients with healthcare associated infections-due to MDR gram negative organisms had shorter hospital stay and a higher mortality rate of 78% compared to 41% among non MDR patients. The most commonly isolated gram negative organisms were Burkholderia cepacia, 38%; Klebsiella pneumoniae, 31%; and Acinetobacter baumanii, 18%; while the most common MDR gram negative isolates were Klebsiella pneumoniae, 65%; Acinetobacter baumanii, 22%; and Pseudomonas aeruginosa, 7%.

Significant predictors for MDRO were age (0-28 days old), ICU admission, intravascular catheterization and use of total parenteral nutrition.

Conclusion: Profile of pediatric patients with healthcare-associated multi-drug resistant gram-negative infections were neonates admitted in the ICU with a shorter hospital stay and a high mortality rate. The identified risk factors for developing Multi Drug Resistant Gram Negative sepsis were age of 0-28 days, admission to ICU, intravascular catheterization and parenteral nutrition. Patients with gram-negative MDR infections have a high mortality rate and isolates are susceptible mostly to Colistin.

KEYWORDS: *multiple drug resistance, healthcare associated infections, gram negative bacterial infections*

INTRODUCTION

Healthcare-Associated Infections (HAIs) are infections appearing in hospitalized patients not present nor incubating at the time of admission, the onset of which is beyond 48 hours from admission to the hospital, within 3 days of discharge or 30 days after an operation[1]. The rates of multi-drug resistance among pathogens causing healthcare-associated infections are increasing, mainly among gram-negative organisms[2].

Multi Drug Resistant Organisms (MDROs) are microorganisms, predominantly bacteria, that are resistant to one or more classes of antimicrobial agents. Prevalence of MDROs varies temporally, geographically, and by healthcare settings. MDRO infections result in significant morbidity and mortality and have now impacted in the care of infants and children[3]. There is paucity of data addressing treatment options for multi drug resistant Gram-negative (MDRGN) infections in children, so data must be extrapolated from adult literature[1].

The increase in multi-drug resistance in the healthcare setting demonstrates a need for studies on the epidemiology and outcomes of MDRO healthcare-associated infections, thus, this study aimed to determine the clinical and epidemiologic profile of pediatric patients with healthcare-associated gram-negative infections, as well as risk factors for development of infections with MDRO. . Outcome of patients with MDRO gram-negative infections was noted, as well as its antimicrobial susceptibility patterns.

MATERIALS AND METHODS

The study was conducted after approval from the University of the Philippines Manila Research Ethics Board (UPMREB) Panel was obtained.

This is a retrospective study on healthcare associated gram negative MDRO compared to non MDRO cases admitted in the pediatric wards, Pediatric Hematology-Oncology Unit, Pediatric Intensive Care Unit and Neonatal Intensive Care Unit of a tertiary government hospital from July 2015 to June 2016.

Multidrug-resistant gram negative and non-multidrug-resistant gram negative infections with isolates which grew on culture of blood obtained via aseptic technique 48 hours after admission, or within 3 days after discharge, or within 30 days post-surgery were identified. Risk factors such as presence of intravascular catheter, initiation of targeted antimicrobial therapy, surgery, and the presence of clinical manifestations of infection, i.e. at least one clinical finding of temperature >38^{o}C or <36^{o}C, chills, hypotension for age, tachycardia or bradycardia for age were noted.

Reports of gram-negative blood isolates in pediatric patients were obtained from the central laboratory. Cases of healthcare associated bacteremia were selected among these gram-negative blood isolates, and correlated with the clinical course of the patient.

These cases of gram-negative blood isolates which were correlated with clinical data were double checked with the Nosocomial Infection Report Form of the Section of Infectious and Tropical Diseases in Pediatrics. The investigator subsequently retrieved the medical charts of these patients with healthcare associated gram-negative bacteremia.

The following information were obtained from the Nosocomial Infection Report Form (NIR): age, gender, location, type of healthcare-associated infection and the blood isolate and its antimicrobial susceptibility. Patient risk factors noted were presence or absence of malnutrition, malignancy/blood dyscrasia, steroid intake, catheterization, prematurity, central line, parenteral nutrition, nasogastric tube, surgery, mechanical ventilation, and antibiotic use for more than two weeks.

All data were entered into a case report form containing pertinent demographic data from the NIR form as well as identified risk factors.

MDROs cases were determined from the antibiotic susceptibility pattern of the blood isolates.

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and Inter-Quartile Range for ordinal variables, and mean and Standard Deviation for interval/ratio variables. Mann-Whitney U and Fisher's Exact/Chi-square test was used to determine the difference of mean, median and frequencies between groups, respectively. Odds ratio and the corresponding 95% confidence interval from binary logistic regression was computed to determine significant predictors for the development of multi drug resistance. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 12.0 was used for data analysis.

RESULTS

A total of 199 patients were identified to be HAI sepsis cases, and 41% were identified to be MDR cases (Table 1). Profile of MDR and non-MDR patients were compared and the variables noted to significantly differ for the two groups were age (p=0.000), distribution in the pediatric age group (p=0.000), weight (p=0.000), height (p=0.000), area of admission (p=0.000), underlying conditions and comorbidities, and duration of nosocomial infection (p=0.001) as seen in table 1.

A look into the clinical outcomes of patients showed that there were significant differences in the duration of hospital stay between MDR and Non-MDR patients (p=0.012) and in mortality rates (p=0.000) as seen in Table 2.

The most commonly isolated microorganisms in HAIs were Burkholderia cepacia (38%) Klebsiella pneumoniae (31%), and Acinetobacter baumanii (18%).

The top MDROs isolated among patients with HAIs were K. pneumoniae (65%), A. baumanii (22%), and P. aeruginosa (7%) as seen in Table 4.

The top non-MDR Gram negative organisms isolated among patients were B. cepacia (64%), A. baumanii (14%), and K. pneumoniae (7%) as seen in Table 5.

We analyzed select patient characteristics to determine whether these were associated with the development of MDR. Significant factors identified were admission to the ICU (p=0.006) and intravascular catheterization (p=0.040).

For the final model for predicting multidrug resistance (Table 6), significant factors were age of 0-28 days old (p=0.042), admission to ICU (p=0.002), intravascular catheterization (p=0.009) and use of PPN/TTN (p=0.044). This model however accounted for only 22.42% of the variability of developing into an MDR among patients (p-value = 0.000; R^2= 22.42%).

DISCUSSION

Infections with Multi-Drug Resistant Organisms have become a significant global health problem. Our study conducted in a national university hospital showed that we have not been spared from this occurrence.

One-hundred ninety-nine patients with Gram Negative Bacteremia were included in the study, and 41% of these were MDRO. Among these patients with MDRGNB, 80% were neonates, while in those with non-MDRGNB, 40% were neonates. A review by Zaidi et al. showed that hospital-born babies in developing countries are at increased risk of neonatal infections because of poor intrapartum and postnatal infection-control practices. Reported rates of neonatal infections were 3–20 times higher than those reported for hospital-born babies in industrialized countries.[4]

Majority of cases of MDRGNB were admitted at the ICUs (83%), compared to non-MDRGNB which were at the regular wards (59%). The type and level of care also influence the prevalence of MDRO

infections. Admission to ICUs, especially those in tertiary care facilities, may contribute to a higher prevalence of MDROs than those admitted in non-ICU settings[5].

Majority of patients with MDRGNB are neonates, thus prematurity, use of gastric tubes, Hypoxemic Ischemic Encephalopathy (HIE), Hyaline Membrane Disease (HMD), Necrotizing Enterocolitis (NEC), and other Gastrointestinal (GI) abnormalities were seen more in MDRGNB patients. These findings were found to be statistically significant.

The top 4 Gram Negative Isolates were B. cepacia, K. pneumoniae, A. baumanii and P. aeruginosa. The susceptibility pattern of these isolates to various antibiotics were determined. B. cepacia was susceptible to Ceftazidime and Cotrimoxazole. K. pneumoniae was susceptible to Colistin. A. baumanii was susceptible to Colistin and Ciprofloxacin. P. aeruginosa was susceptible to Colistin. These susceptibility patterns reflect the presence of MDR K. pneumoniae, A. baumanii, and P. aeruginosa since the organisms showed resistance to one or more drugs in three or more classes of antimicrobial agents for which they are known to be susceptible (such as carbapenems, fluoroquinolones, and third generation cephalosporins).

Isolates known to have MDR resistance in Southeast Asia in the study of Zaidi, AK et al, were, Klebsiella, E. coli, and S. aureus.[4]

Outcomes of pediatric patients with healthcare associated gram-negative infections showed that patients with MDRGNB have shorter hospital stay due to high mortality rates of 78% compared to 41% among patients with non-MDRGNB. Previous studies on MDRO showed increased length of stay, increased cost, and high mortality rate with associated outbreaks[5].

We identified possible risk factors for developing MDRO among patients with Healthcare-associated GNB. Neonates, admission to intensive care units, intravascular catheterization, and use of parenteral nutrition were found to be significant risk factors.

Pediatric patients in the ICU are particularly susceptible to nosocomial infections due to use of invasive devices and multiple procedures. Although any serious infection will warrant admission to the ICU, infection may also be a complication after ICU admission. Multiple studies documented the increase in the incidence of nosocomial infections due to antibiotic-resistant organisms, particularly in Pediatric Intensive Care Units .[6]

A research done in Greece in 2014, reported risk factors for MDR K. pneumoniae in a NICU as follows: neonates who received parenteral nutrition, delivery by Cesarean Section, low gestational age, and low birth weight. Transmission of MDROs in high risk units can occur at the time of delivery, or by person-to-person transfer through the hands of the nursing staff, contaminated equipment, food, or the environment.[7]

On the contrary, another study done by Tsai et al in Taiwan on risk factors and outcomes for MDRGNB in the NICU revealed that extremely low birthweight, prematurity and underlying chronic conditions are not associated with MDRGNB.[8]

A study done in the Philippines by Litzow et al, revealed that prematurity and low birthweight infants requiring mechanical ventilation were significant risk factors for invasive MDRGNB in the NICU. [9]

Preventing the occurrence of healthcare-associated infections depends on appropriate clinical practices that should be incorporated in routine patient care. These include optimal management of vascular and urinary catheters, prevention of lower respiratory tract infections in intubated patients, accurate diagnosis of infectious conditions, and judicious antimicrobial selection and utilization.[5] If these processes are consistently observed it can have a significant impact on HAIs and on MDRGB infections as well.

Table 1. Demographic and clinical profile of pediatric patients with healthcare-associated Gram-negative infections, Philippine General Hospital (n=199)

	MDR GNB (n=81)	Non MDR GNB (n=118)	P- value
	Frequency (%); Mean ± SD; Median (Range)		
Age (Months)	0 (0 to 216)	2 (0 to 216)	0.000‡
Age Group			0.000§
0-28 days	65 (80.25)	47 (39.83)	
29 days to 3 months	13 (16.05)	16 (13.56)	
4 months to <2 years	2 (2.47)	17 (14.41)	
2 to 5 years	0	11 (9.32)	
> 5 years	1 (1.23)	27 (22.88)	
Sex			0.641
Male	48 (59.26)	66 (55.93)	
Female	33 (40.74)	52 (44.07)	
Weight (kg)	2 (0.65 to 25)	3.85 (0.70 to 67)	0.000‡
Height (cm)	42 (23 to 144)	57.5 (28 to 176)	0.000‡
Admission Ward			0.000§
Ward 9 or 11	14 (17.28)	70 (59.32)	
PICU/NICU	67 (82.72)	43 (36.44)	
Hema onco ward	0 (0)	5 (4.24)	
Underlying conditions*			
With Malnutrition	6 (7.41)	26 (22.03)	0.006
With Catheterization	37 (45.68)	31 (26.27)	0.005
With PPN/TTN	38 (46.91)	22 (18.64)	0.000
With Malignancy/blood dyscracia	0 (0)	16 (13.56)	0.001
With Prematurity	46 (56.79)	31 (26.27)	0.000
With Mechanical ventilation	71 (87.65)	76 (64.41)	0.000
With Steroid intake	0 (0)	3 (2.54)	0.272§
Central line	8 (9.88)	9 (7.63)	0.577
On antibiotics > 2 weeks	24 (29.63)	31 (26.27)	0.603
With NGT	81 (100)	92 (77.97)	0.000
With Surgery	18 (22.22)	24 (20.34)	0.749
Comorbities*			
Pneumonia	9 (11.11)	32 (27.12)	0.006
Congenital Heart Disease	14 (17.28)	20 (16.95)	0.951
Malignancy	2 (2.47)	19 (16.10)	0.002
Hyaline Membrane Disease	22 (27.16)	13 (11.02)	0.003
GI abnormalities	2 (2.47)	13 (11.02)	0.025
Necrotizing Enterocolitis	20 (24.69)	9 (7.63)	0.001

	MDR GNB (n=81)	Non MDR GNB (n=118)	P- value
	Frequency (%); Mean ± SD; Median (Range)		
CNSI	2 (2.47)	9 (7.63)	0.205§
Down Syndrome	4 (4.94)	8 (6.78)	0.515§
Intracranial Bleed	1 (1.23)	1 (0.85)	1.000§
Chiari II malformation	3 (3.70)	2 (1.69)	0.399§
Bronchopulmonary Dysplasia	3 (3.70)	4 (3.39)	1.000§
ARDS	0	3 (2.54)	0.272§
Persistent Pulmonary Hypertension	7 (8.64)	4 (3.39)	0.126
Pneumothorax	4 (4.94)	2 (1.69)	0.227§
Rheumatic Heart Disease	0	1 (0.85)	1.000§
Tuberculosis	0	3 (2.54)	0.272§
Gastroschisis	8 (9.88)	3 (2.54)	0.053§
Gut Obstruction	2 (2.47)	5 (4.24)	0.703§
Omphalocoele	1 (1.23)	2 (1.69)	1.000§
Peripheral Nervous system abnormalities	0	3 (2.54)	0.272§
Cerebral Palsy	0	2 (1.69)	0.515§
Genetic Abnormalities	1 (1.23)	1 (0.85)	0.765§
Kidney Diseases	2 (2.47)	3 (2.54)	1.000§
Malnutrition	2 (2.47)	3 (2.54)	1.000§
Intestinal Parasitism	0	3 (2.54)	0.002§
Caustic Ingestion	0	2 (1.69)	0.272§
Hypoxic Ischemic Encephalopathy	10 (12.35)	4 (3.39)	0.015
Multiple Congenital Anomalies	3 (3.70)	3 (2.54)	0.689
Infective Endocarditis	0	1 (0.85)	1.000§
Septic Shock	0	4 (3.39)	0.147§
Endocrine Abnormalities	0	1 (0.85)	1.000§
Dextroscoliosis	0	1 (0.85)	1.000§
Status Epilepticus	0	1 (0.85)	1.000§
Acute Gastroenteritis	0	1 (0.85)	1.000§
Transient tachypnea of the newborn	7 (8.64)	0	1.000§
Duration of nosocomial infection (days)	9 (1 to 23)	14 (1 to 15)	0.001‡
Previous nosocomial infection	38 (46.91)	45 (38.14)	0.217

Statistical Tests Used: Chi Square test; ‡ - Mann-Whitney U test; § - Fisher's Exact test
*Note: * - Multiple Response Variable*

Table 2. Clinical outcomes of the pediatric patients with healthcare-associated Gram-negative infections, Philippine General Hospital (n=199) suggested

	MDR GNB (n=81)	Non MDR GNB (n=118)	P-value
	Frequency (%); Mean ± SD; Median (Range)		
Number of Hospital Stay (days)	25 (3 to 180)	32 (3 to 289)	0.012‡
Days from admission and symptoms (days)	9 (3 to 146)	10 (3 to 279)	0.993‡
Mortality	63 (77.78)	48 (40.68)	0.000

Statistical Tests Used: Chi Square test; ‡ - Mann-Whitney U test; § - Fisher's Exact test

Table 3. Microorganisms isolated from pediatric patients with healthcare-associated Gram-negative infections, Philippine General Hospital (n=199)

	Frequency (%)
B. cepacia	76 (38.19)
K. pneumoniae	61 (30.65)
A. baumanii	35 (17.59)
P. aeruginosa	6 (3.03)
A. iwoffi	5 (2.51)
E. coli	4 (2.01)
Achromobacter sp.	3 (1.51)
S. marcescens	2 (1.01)
E. cloaceae	2 (1.01)
E. aerogenes	1 (0.50)
B. mallei	1 (0.50)
B. gladioli	1 (0.50)
S. paucimonilis	1 (0.50)
A. faecalis	1 (0.50)

Table 4. Multi-Drug Resistant Organisms isolated from pediatric patients with healthcare-associated bacteremia, Philippine General Hospital (n=81)

	Frequency (%)
K. pneumoniae	53 (65.43)
A. baumanii	18 (22.22)
P. aeruginosa	6 (7.4)
A. iwoffi	2 (2.47)
Achromobacter sp.	2 (2.47)

Table 5. Microorganisms isolated from the pediatric patients with healthcare-associated non-MDR Gram-negative infections, Philippine General Hospital (n=118)

	Frequency (%)
B. cepacia	76 (64.4)
A. baumanii	17 (14.4)
K. pneumoniae	8 (6.78)
E. coli	4 (3.39)
A. iwoffi	3 (2.54)
S. marcescens	2 (1.69)
E. cloaceae	2 (1.69)
Achromobacter sp.	1 (0.85)
E. aerogenes	1 (0.85)
B. mallei	1 (0.85)
B. gladioli	1 (0.85)
S. paucimonilis	1 (0.85)
A. faecalis	1 (0.85)

Table 6. Final Model for predicting multi-drug resistance

	Odds Ratio	CI 95%	P-value
Age 0-28 days 29 days and above	2.4538 (reference)	1.0315 to 5.8374	0.042 -
Admission Ward PICU/NICU Wards (Ward 9-11/ Hema ward)	4.1535 (reference)	1.7099 to 10.0888	0.002 -
With Catheterization	2.5582	1.2621 to 5.1852	0.009
With PPN/TTN	2.1029	1.0205 to 4.3334	0.044

P-value = 0.000 ; R^2= 22.42%

CONCLUSION

This study showed that healthcare associated Multi Drug Resistant Gram-Negative infections usually occur in neonates admitted in the ICU, who had a short hospital stay and a higher mortality rate. The most common healthcare-associated MDR gram negative isolates were K. pneumoniae, A. baumanii and P. aeruginosa. The identified risk factors for Multi Drug Resistant Gram-Negative infections were age of 0-28 days, admission in the ICU, intravascular catheterization and use of parenteral nutrition.

Options for treating patients with Healthcare Associated MDRGNB are extremely limited. In this study, MDRGNB isolates were mostly susceptible to Colistin.

RECOMMENDATIONS

A prospective study using a risk assessment tool for predicting MDRO infection can be done based on the results of this study. Diagnostic tools such as molecular based biologic tests can also be done on isolates. There is a need to look into treatment options for MDROs among pediatric patients. Other aspects in the control of MDRGNB infections such as observance of standard and contact precautions, surveillance systems, judicious use of antimicrobials, and education should also be emphasized.

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