Healthcare-associated Infections in Pediatric Patients in Neurotrauma Intensive Care Unit: A Retrospective Analysis

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Abstract

Background: Healthcare-associated infections (HAIs) can impact the outcome following traumatic brain injury (TBI) in children. We undertook a retrospective observational study to see the incidence, risk factors, and microbiological profile for HAIs in pediatric TBI. We also studied the impact of baseline patient characteristics, HAIs on patient outcome, and antibiotic resistance of different types of bacteria.

Materials and methods: Data on pediatric TBI patients of age up to 12 years were collected via a computerized patient record system (CPRS) from January 2012 to December 2018. Descriptive Chi-square test and Wilcoxon signed rank test were used to characterize baseline parameters. General linear regression models were run to find an unadjusted and adjusted odds ratio (OR).

Results: HAIs were found in 144 (34%) out of 423 patients. The most commonly seen infections were of the respiratory tract in 73 (17.26%) subjects. The most predominant microorganism isolated was *Acinetobacter baumannii* in 188 (41%) samples. *A. baumannii* was sensitive to colistin in 91 (48.4%) patients. Male gender (OR 0.630; *p*-value 0.035), fall from height (OR 0.374; *p*-value 0.008), and higher injury severity scale (ISS) (OR 1.040; *p*-value 0.002) were independent risk factors for development of HAIs. Severe TBI, higher ISS and Marshall grade, and HAIs were significantly associated with poor patient outcome.

Conclusion: Severe TBI poses a significant risk of HAIs. The most common site was the respiratory tract, predominately infected with *A. baumannii*. HAIs in pediatric TBI patients resulted in poor patient outcome.

Keywords: Healthcare-associated infection, Pediatric, Trauma, Traumatic brain injury.

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Highlights

Along with neurological morbidity, pediatric traumatic brain injury poses a significant risk of HAIs. Higher injury severity score, male gender, and fall from height were associated with a significant risk of infections. Respiratory tract infections are the most common in these patients. Severe injuries with HAIs resulted in poor outcome.

Introduction

Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality in children both in the developing and developed world.[1] Along with neurological morbidity, neurotrauma poses a significant risk of infections. Improvement in outcome from TBI can be hampered by the development of healthcare-associated infections (HAIs). The reported incidence rate is as high as 50% and mortality as high as 37%.[2] Among critically ill, pediatric trauma patients are at the highest risk of the development of HAIs.[3] Transient immunosuppression or immunoparalysis associated with neurological insults secondary to cytokine release and brainstem irritation induced activation of the hypothalamus–pituitary–adrenocortical axis contribute to HAIs in TBI.[4] HAIs can also lead to multiple organ dysfunction along with worsening secondary brain injury.[5]

Results of adequate effort to manage such critically ill children can be optimized by knowing epidemiological data and understanding of risk factors for the development of HAIs. We, therefore, undertook a retrospective, observational study to see the HAI on rate in pediatric patients admitted to neurotrauma intensive care units over a period of 7 years.

We analyzed the microbiological samples of all the pediatric TBI patients with suspicion of HAIs submitted for culture and

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antimicrobial susceptibility testing. We also studied risk factors for HAIs and the impact of baseline characteristics, HAI on outcome, and antibiotic resistance in different types of bacteria isolated in these patients.

Materials and Methods

After taking approval from the institutional ethics committee (IEC-887/04.09.2020), we did a retrospective analysis of pediatric

trauma patients admitted at level 1 trauma center. We analyzed microbiological samples of pediatric TBI patients from January 2012 to December 2018, which were submitted to the microbiology laboratory for testing. All the positive culture isolates were identified up to the species level by the Vitek 2 GN card (version 8.1, Inc., Durham, United States of America). Antimicrobial susceptibility testing was performed by Kirby–Bauer disc diffusion method on Mueller Hinton agar and by Vitek 2 system. The results of antibiotic susceptibility were interpreted based on the Clinical and Laboratory Standards Institution guidelines.

Clinical characteristics and admission variables were collected via the computerized patient record system (CPRS) database. CPRS (version 1.0.26.76), supported by Edgeware Technologies India PVT limited, was used. Data of all the trauma patients were entered and updated in this system by all the concerned clinical and technical staff. We used predecided proforma to retrieve the data of patients who met inclusion and exclusion criteria. All the data were entered into an excel worksheet for final analysis.

Patients up to 12 years of age, of either gender, with TBI admitted to neurotrauma intensive care unit were included. Children who were brought dead or had signs of infection at the time of admission or up to 48 hours after admission were excluded from the study. Patients with a length of hospital stay less than 48 hours were excluded. We retrieved data of culture and sensitivity results along with details of corresponding samples. Data of 423 patients were included for analysis after screening for inclusion and exclusion criteria. Data collected included patient demographics (age, gender), admission Glasgow coma score (GCS), mechanism of injury, computed tomography (CT) findings at admission, Marshall grading, injury severity score, details of invasive devices, microbiological infections, antimicrobial sensitivity, the outcome in terms of length of hospital stay, GCS at discharge, and mortality.

Patients were classified into two groups: group A (with HAIs) and group B (without HAIs). For descriptive purposes, microorganisms were divided into Gram-negative bacilli (GNB), Gram-positive cocci (GPC), and fungi. For all analysis purposes, patients were further subclassified into age-groups 0–2 years, 2–4 years, and 4–12 years. TBI was divided into mild, moderate, and severe head injuries based on admission GCS (13–15 mild, 9–12 moderate, and 3–8 severe). The injury type was described as either polytrauma or isolated TBI. Mechanism of injury was categorized into fall from a height, road traffic accident (RTA), penetrating injuries, and others (suffocation, drowning, and poisoning). Marshall grading was done based on findings of admission CT scan.[6] The injury severity scale (ISS) calculation was based on the highest abbreviated injury scale (AIS) code of the three most injured body regions.[7] All the different types of samples like respiratory samples [broncho-alveolar lavage (BAL), tracheal aspirate, endotracheal tubes], blood, urine, cerebrospinal fluid (CSF), bone/tissue, and invasive devices were analyzed. Invasive devices included intracranial pressure (ICP) monitoring catheters, external ventricular drains (EVD), and intercostal drains (ICD). The outcome was calculated based on the length of hospital stay and neurological status at discharge. Latter was classified into mild, moderate, and severe categories based on GCS at discharge along with class 4 given to dead patients. Duration of hospital stay was calculated in days.

Statistical Methods

Descriptive statistical methods were used to analyze intragroup characteristics. Intergroup baseline characteristics were compared using Chi-square tests for categorical variables and Wilcoxon signed rank test for continuous nonparametric variables. Incidence of all infections and antibiotic sensitivity were calculated using descriptive analysis cross-tab model. The unadjusted and adjusted odds ratios (OR) of risk factors for different HAIs and mortality were derived using univariate and multiple logistic regression analyses, respectively. Models were run first without adjustment for confounding variables to find potential risk factors. The final multiple regression model was run based on the level of significance (p-value<0.05) seen in the unadjusted logistic regression model to find confounder adjusted risk factors for infections and mortality. The impact of infections and binary baseline characteristics on the outcome (hospital stay and discharge status) was analyzed using the Mann–Whitney U test. Spearman's rho and Pearson's correlation coefficient were derived to find out the relation between categorical and continuous baseline characteristics of patient outcome, respectively. Chi-square tests were run to find the association between mortality and all categorical variables. Statistical analysis was performed using the SPSS for Windows 25 (SPSS, Chicago, Illinois, United States). A p-value of less than 0.05 was considered statistically significant.

RESULTS

Microbiological samples for 423 pediatric TBI patients were analyzed. Demographic data and baseline characteristics of patients are described in Table 1. A total of 232 (54.8%) children had severe TBI. The majority of the patients, 395 (93.4%), had isolated TBI. The most common mechanism of injury was fall from height in 274 (64.8%) patients. The baseline variables were comparable across the groups except for gender, mechanism of injury, and ISS. Group A patients had significantly higher ISS value (p-value 0.003) as shown in Table 1.

A total of 2,781 samples of 423 patients were received for culture, out of which 454 (16.3%) samples turned positive in 144 (34%) patients. Maximum infections were found in respiratory samples, 73 (17.3%) patients followed by blood in 45 (10.6%). Next in sequence were wound 39 (9.2%), CSF 21 (4.9%), urine 18 (4.3%), bone/tissue 12 (2.8%), and invasive device 4 (0.9%) (Table 2). GNB grown in cultures of 351 (12.6%) isolates while GPC in 103 (3.2%) (Supplementary Table 1).

Acinetobacter baumannii was the most commonly isolated [188 (41%)] microorganisms in blood, respiratory tract, 92 (60%); CSF, 45 (52%); and invasive device, 5 (31%). *Staphylococcus aureus* was the most common microorganism isolated in wound 39 (45.4%) and bone/tissues 3 (75%). *Escherichia coli* grew commonly in urine 9 (30%) (Supplementary Table 2).

GNB and GPC bacteria were classified separately as per their sensitivity to antibiotics. *A. baumannii* was found to be sensitive to colistin in 91 (48.4%) cases followed by tigecycline in 65 (34.5%) and netilmicin in 26 (13.83%). It was resistant to all remaining antibiotics. *S. aureus* was sensitive to linezolid in 74 (91.4%), teicoplanin in 73 (90.1%), and vancomycin in 73 (90.1%). Colistin in 30 (78.9%), tigecycline in 24 (63.2%), amikacin in 22 (57.9%), and meropenem in 19 (50%) were found effective against *E. coli* (Supplementary Tables 3 and 4).

Potential and independent risk factors for HAIs were derived using univariate and multiple logistic regression analysis, respectively. Sample-wise specific risk factors for different HAIs were also listed (Table 3). Male gender, fall from height, and higher ISS were found as potential as well as independent risk factors for HAIs (OR 0.630; p-value 0.035,OR 0.374; p-value 0.008, and OR 1.040;

Table 1: Demographic profile and baseline characteristics of patients

| Variable | Intragroup (N = 423) | Intergroup | | p value |
		Group A (N = 144)	Group B (N = 279)	
Age (mean, SD)	5.44 (3.41)	5.63 (3.31)	5.33 (3.46)	0.269
Age distribution (n, %)				
0–2 years	106 (25.1)	34 (23.6)	72 (25.8)	0.307
2–4 years	97 (22.9)	28 (19.4)	69 (24.7)	
4–12 years	220 (52.0)	82 (56.9)	138 (49.5)	
Sex (M:F)	279:144	85:59	194:85	0.031
Admission GCS (median, IQR)	7 (3–15)	7 (3–15)	8 (3–15)	0.181
Admission status (n, %)				
Mild (GCS 13–15)	123 (29.1)	40 (27.8)	83 (29.7)	0.532
Moderate (GCS 9–12)	68 (16.1)	20 (13.9)	48 (17.2)	
Severe (GCS 3–8)	232 (54.8)	84 (58.3)	148 (53.0)	
Type of injury (n, %)				
Polytrauma	28 (6.6)	12 (8.3)	16 (5.7)	0.308
Isolated TBI	395 (93.4)	132 (91.7)	263 (94.3)	
Mechanism of injury (n, %)				
Fall from height	274 (64.8)	80 (55.6)	194 (69.5)	0.032
Road traffic accident	104 (24.6)	44 (30.6)	60 (21.5)	
Penetrating injury	9 (2.1)	3 (2.1)	6 (2.2)	
Others	36 (8.5)	17 (11.8)	19 (6.8)	
Marshall grade (n, %)				
Grade 1	78 (11.3)	17 (11.8)	31 (11.1)	
Grade 2	270 (63.8)	85 (59.0)	185 (66.3)	0.565
Grade 3	22 (5.2)	11 (7.6)	11 (3.9)	
Grade 4	15 (3.5)	5 (3.5)	10 (3.60)	
Grade 5	65 (15.4)	25 (17.4)	40 (14.3)	
Grade 6	3 (0.7)	2 (0.7)	1 (0.7)	
Injury severity scale (mean, SD)	11 (8.29)	12.70 (8.20)	10.13 (8.16)	0.003
Invasive devices (ICP sensor, EVD, ICD) (n, %)	90 (21.3)	36 (25.0)	54 (19.4)	0.179

GCS, Glasgow Coma Scale; ICP, intracranial pressure; EVD, external ventricular drain; ICD, intercostal drain

Table 2: Incidence of infections in studied patient population

	Number of patients	Percentage
Any healthcare-associated infection	144	34.04
Blood infections	45	10.64
Wound infections	39	9.22
Respiratory infections	73	17.26
CSF infections	21	4.96
Urine infections	18	4.26
Invasive device infections	12	2.84
Bone/tissue infections	4	0.95

CSF, cerebrospinal fluid

p-value 0.002, respectively) Severe TBI (OR 0.371; p-value 0.018) and higher ISS (OR 1.061; p-value <0.001) turned as independent predictors for respiratory tract infection while male gender was found as risk factor (OR 0.216; p-value 0.004) for urinary tract infections. Confounder adjusted risk factors for CSF infection were higher ISS (OR 0.937; p-value 0.019). Severe TBI (OR 2.416; p-value 0.022) and fall from height (OR 0.248; p-value 0.003) came out as independent risk factors for wound infections while lower age-group (0–2 years) was a risk factor for device-related infections (OR 9.140; p-value 0.004).

The outcome was analyzed in terms of length of hospital stay 12 (2–1,289) days, discharge GCS 13 (3–15), and mortality in 29 (6.9%)

patients (Table 4). Severe TBI and higher ISS (p-value <0.001 for both) significantly prolonged hospital stay, while the same factors along with advanced Marshall grade were found as significant predictors for poor GCS at discharge (p-value <0.001 for all) and mortality (p-value 0.020, <0.001 and <0.001, respectively).

HAIs were found to prolong the hospital stay (p-value <0.001) and predict poor GCS at discharge (p-value 0.003) (Table 5). Among HAIs, blood infections (p-value 0.021), respiratory infections (p-value <0.001), urinary infections (p-value 0.001), and device-related infections (p-value 0.032) were found to significantly increase the duration of hospital stay. Poor discharge GCS was associated with respiratory infections (p-value <0.001) and device-related infections (p-value 0.001). CSF infections (p-value 0.013) were found to be significantly associated with patient mortality (Supplementary Table 5).

DISCUSSION

Along with other ailments, neurotrauma is a constant threat to the health of children both in the developed and developing world. HAIs in pediatric TBI patients pose a special challenge while managing pediatric TBI patients. Such infections can have a significant impact on the length of hospital stay, patient outcome, and healthcare costs.[8] Infection rate, microorganisms type, and antimicrobial susceptibility pattern may vary across the globe. Keeping these facts in mind, we planned this retrospective study

Table 3: Risk factors for HAIs overall and specific for different infection sites

Variable	Odds of infection		Adjusted odds of infection	
	OR	p value	OR (lower CI, upper CI)	p value
Age distribution				
0–2 years	0.795	0.359		
2–4 years	0.683	0.148		
Male sex	0.631	0.031	0.630 (0.410, 0.967)	0.035
Admission GCS				
Mild	0.849	0.488		
Moderate	0.734	0.302		
Polytrauma	1.494	0.311		
Mechanism of injury				
Fall from height	0.461	0.031	0.374 (0.171, 0.774)	0.008
Road traffic accident	0.820	0.609		
Penetrating injury	0.559	0.457		
Marshal Grading	1.077	0.359		
Injury severity scale	1.037	0.003	1.040 (1.015, 1.066)	0.002
Any invasive device	0.720	0.180		
Blood	No significant risk factor found			
Respiratory tract				
Male sex	0.603	0.054	0.640 (0.375, 1.094)	0.103
Severe head injury	0.229	<0.001	0.371 (0.163, 0.844)	0.018
Injury severity scale	1.075	<0.001	1.061 (1.028, 1.095)	<0.001
Urine				
Male sex	0.242	0.005	0.216 (0.076, 0.612)	0.004
CSF				
Injury severity scale	1.056	0.019	0.937 (0.888, 989)	0.019
Wound				
Severe head injury	3.392	0.001	2.416 (1.134, 5.151)	0.022
Fall from height	0.183	<0.001	0.248 (0.100, 0.616)	0.003
Road traffic accident	0.246	0.006	0.436 (0.150, 1.266)	0.127
Any invasive device	5.500	0.021	4.005 (9.12, 17.589)	0.066
Device				
0–2 years age group	5.905	0.010	9.140 (2.043, 40.898)	0.004
Bone/tissue	No significant risk factor found			

GCS, Glasgow Coma Scale

Table 4: Impact of baseline characteristics on outcome

Variable	Prolonged hospital stay		Poor discharge status (GCS)		Mortality	
	Mean rank	p value	Mean rank	p value	Chi-square value	p value
Type of Injury		0.347		0.008	2.207	
Polytrauma	191.00		159.13		(n = 0)	0.137
Isolated TBI	213.49		215.75		(n = 29)	
	r value	p value	r value	p value	Chi-square value	p value
Admission GCS	0.306	<0.001	0.449	<0.001	7.802	0.020
Mechanism of injury	0.036	0.459	0.049	0.319	3.707	0.295
Marshall grading	0.089	0.068	0.180	<0.001	24.773	<0.001
Injury severity scale	0.191	<0.001	0.701	<0.001	85.10	<0.001

GCS, Glasgow Coma Scale; TBI, traumatic brain injury

to see HAIs profile and associated risk factors to address challenges during care and prognostication of pediatric TBI patients.

We found a 34% incidence of HAIs in pediatric TBI patients admitted to neurotrauma intensive care units. Data from West report a 13.3–50% incidence of HAIs in pediatric polytrauma patients.[2,9] A study by Osborn and colleagues reports a 2% incidence of sepsis among 30,303 trauma patients across all age-groups.[10] Sbrinick et al. reported a 13% incidence of infection in pediatric polytrauma with TBI.[9] However, we found higher incidence HAIs in predominately TBI patients. The incidence of infection is more in trauma care units as compared to other critically ill patients. We witnessed a high incidence of respiratory tract infections (17%), which is higher as

Table 5: Comparison of effect of HAIs on outcome in both the groups

Infection sites	Prolonged hospital stay			Poor discharge status			Mortality	
	Group A (mean rank)	Group B (mean rank)	p value	Group A (mean rank)	Group B (mean rank)	p value	Chi-square value	p value
Any infection	248.50	193.16	<0.001	234.40	200.44	0.003	0.746	0.388
Blood	251.72	207.27	0.021	231.08	209.73	0.216	0.326	0.568
Respiratory	261.16	201.75	<0.001	263.35	201.29	<0.001	1.032	0.310
Urine	304.64	207.88	0.001	244.44	210.56	0.199	0.050	0.823
CSF	239.55	210.56	0.289	254.02	209.80	0.071	9.946	0.002
Wound	229.44	210.23	0.350	196.35	213.59	0.349	4.894	0.027
Device	286.50	209.32	0.032	295.25	209.57	0.001	1.872	0.172
Bone/tissue	180.63	212.30	0.606	190.00	212.21	0.701	2.082	0.149

GCS, Glasgow Coma Scale

compared to data reported from Western countries.[11] The incidence of bloodstream infections varies across different pediatric intensive care units around the globe. Incidence of bloodstream infection was reported up to 30% in the pediatric intensive care unit in north India earlier; however, an incidence as low as 0.06% has been reported in critically ill pediatric patients without trauma.[12,13] Our data suggest around 11% incidence of bloodstream infections in pediatric TBI patients. Urinary tract and invasive device-related infections were less as compared to available data from Western countries.[14,15]

A. baumannii was the most common (41%) overall isolate in our study. *Klebsiella pneumoniae* (24%) and *S. aureus* (18%) were isolated earlier as the most common microorganisms in blood in other pediatric intensive care units from developing countries;[12] however, we found *A. baumannii* (21%) and *K. pneumoniae* (19%) to be more prevalent in pediatric TBI patients. *S. aureus* in our study were reported in only 6% of blood infections. *A. baumannii* was also the most common colonizer in the respiratory tract, CSF, and invasive device, which was in contrast to that reported from Western countries where *S. aureus* is the most common pathogen.[14–16]

A. baumannii was also found to be multidrug resistant in more than half of the patient population. It was found susceptible to colistin in 48.4% and tigecycline in 34.5% of patients. So, the largest portion of difficult-to-treat microbiota is shared by *A. baumannii* in our setup. Up to 77% susceptibility of *A. baumannii* was reported in a study in Kenya.[17] Carbapenem resistance has been reported in 4.25–16% of *K. pneumoniae* to carbapenem in recent years.[18] Our findings also suggest an alarming 40–50% carbapenem resistance for *K. pneumoniae*. The sensitivity pattern of *S. aureus* was derived as linezolid (91%), teicoplanin (90%), and vancomycin (90%), similar to that described in Western countries as linezolid (97%), teicoplanin (97%), and vancomycin (95%).[19]

In our study, male gender, fall from height, and higher ISS at admission were derived as independent risk factors for HAIs. The predictive ability of ISS for HAIs was supported by findings of Sribnick et al.[9] Severe TBI and higher ISS are defined as risk factors for respiratory tract infections.[11] Male gender was found to be a risk factor for urinary tract infections in our study contrary to the findings described earlier.[20] Few studies also reported a significantly higher incidence of urinary tract infections in uncircumcised male children (20.1%) than in circumcised ones (2.4%). However, retrospectively we could not look into that aspect. Higher ISS was found as an independent predictive factor for CSF infection in pediatric TBI patients.[14] Younger age-group (0–2 years) was found

more vulnerable for invasive device-related infection, probably owing to immunosuppression after TBI.[4]

In our study, severe TBI, higher ISS and Marshall grade were significantly associated with poor outcomes as reported in the literature.[21,22] Also, the HAIs were found to be associated with an increased hospital stay, poor discharge GCS, and increased mortality. HAIs result in increased intensive care unit and hospital stay and more discharge to the rehabilitation center.[9,14]

Our study represents HAIs and their impact on the outcome in pediatric TBI patients, which is not widely reported. Though, our study is a single-center retrospective study that can be considered as limitations of this analysis; however, this could be mitigated to some extent due to large sample (>400) and long duration data (7 years) of one of the largest level 1 trauma care hospital in the country.

Conclusion

Pediatric TBI patients are prone to develop HAIs. Multidrug-resistant *A. baumannii* was the most common microorganism isolated in nosocomial pediatric TBI patients in our study. Male gender, severe TBI, and higher ISS were the main risk factors identified for HAIs. Severe TBI, HAIs, higher ISS, and Marshall grade were found to be significantly associated with poor outcome in the present study.[23]

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