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ORIGINAL ARTICLE PEDIATRICS

Risk factors and cost of nosocomial infections in pediatric patients with traumatic brain injury

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ABSTRACT

OBJECTIVE: This study aimed to determine the factors that increase nosocomial infections (NIs) in pediatric patients with traumatic brain injury (TBI) and the effects on both treatment cost and length of hospital stay.

METHODS: We performed a case-control study on patients admitted to the pediatric intensive care unit (PICU) with (n=66) or without (n=120) TBI between 2012 and 2014. The risk factors, length of stay, and costs of NIs were determined.

RESULTS: Data for 186 patients were analyzed. One hundred and twenty patients were controls (54 males vs. 66 females), while 66 were cases (27 males vs. 39 females). Seventeen out of the 186 PICU patients had NIs. About 7.6% of TBI patients had infections whereas 10% of control groups had NIs (p=0.58). The most isolated microbial agent was *Acinetobacter baumannii* (four cases). Thirteen (76.5%) out of the 17 infections were catheter-related bloodstream infections. The mean expenses per PICU patient were $762, with an additional cost of $2081 for patients with nosocomial contamination.

CONCLUSION: The use of catheters was the most critical risk factor for NIs in our study probably underestimated the cost for several reasons. Nevertheless, the findings supported our hypothesis about the additional burden of nosocomial spread on PICU patients. This study's results should help provide evidence on cost-effectiveness or calculate the cost-benefit ratio of reducing NIs in children.

Keywords: Catheter-associated infections; cost; nosocomial infections; pediatric intensive care unit; traumatic brain injury.

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Traumatic brain injury (TBI) may cause several types of head and cerebral injuries (as a result of an external mechanical force), impairments (either permanent or temporary), and cognitive, physical, and psychosocial disorders [1, 2]. TBI is the primary cause of death between 0 and 18 years of age [3].

Nosocomial infections (NIs) appear in patients under medical care due to the hospitalization. The NIs seen in ICUs contain almost 20–25% of total NIs. ICU patients are at high risk 5–10 times more than those in general medical clinics. NI develops in up to 24% of the pediatric ICU patients [4]. Furthermore, NIs are responsible for 30–88% of deaths in these patients [5, 6]. Scientific studies have stated that pediatric intensive care unit (PICU) patients with a TBI are at high risk for the development of NIs [7, 8] and have multiple risk factors, including invasive devices, mechanical ventilation, and immunosuppressive medications due to disruptions in tissue integrity, and impaired host defense mechanisms [9–11]. The most common trauma associated is tracheitis, sepsis, and urinary tract infections [12]. These NIs, especially nosocomial pneumonia, are among the most crucial hospital-associated morbidity, mortality, and elevated costs [13]. Prolonged hospitalization due to the infections increases the cost [14].

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Objectives

This study aimed to determine the factors that increase Nis in pediatric patients with TBI and the effects on treatment cost and hospitalization length.

MATERIALS AND METHODS

Study Design

We performed a case–control study. Our study was conducted in accordance with the Declaration of Helsinki. The Research Ethics Committee approved this study of Marmara University, Faculty of Medicine (Approval date: September 01, 2019; number: 09.2014.124).

Participants

This study was conducted in the PICU of Marmara University Hospital in Istanbul. The study period ran from 2012 to 2014. All patients aged 1 month to 17 years and hospitalized in the PICU for a minimum of 24 h were eligible for inclusion in the study. Patients admitted to the PICU with a TBI were classified as cases (n=66), while those hospitalized in the PICU for other reasons were taken as controls (n=120). Controls were selected randomly from the 1031 patients with diagnoses other than TBI, based on random numbers. All patient files (n=186) were searched for the development of NI from the day of PICU admission. Two patients in each group were excluded due to insufficient or incongruent data (Fig. 1).

Variables

The severity of the patients' condition was estimated using the Pediatric Risk of Mortality III (PRISM) index. On the other hand, the Glasgow Coma Scale (GCS) was used to describe the level of consciousness in patients. Data on demographic features, injury, laboratory results, interventions, and treatments were extracted from the hospital's electronic database system. The following variables were evaluated: Age, gender, length of stay (LOS) in hospital and PICU, mortality, the use of an invasive device, the presence of surgical operation, the type of ventilation (non-invasive or invasive mechanical ventilation), the type of invasive intervention (nasogastric and urinary catheters, central/venous/arterial catheters, hemodialysis, and peritoneal dialysis catheters, gastrostomy and tracheostomy, extra ventricular drainage, ventriculoperitoneal (v-p) shunt, chest tube, the use of total parenteral nutrition), the use of H2 blockers and steroids, the use of antiviral, antifungal and antibiotics, the presence of renal or hepatic dysfunction, the presence of NI, and the microbial agent.

Highlight key points

- Children with traumatic brain injury may have long hospital stays.
- Nosocomial infections are common in these patients and are responsible for a high rate of morbidity/mortality.
- Identification of risk factors is important for long hospital stays and cost reduction.

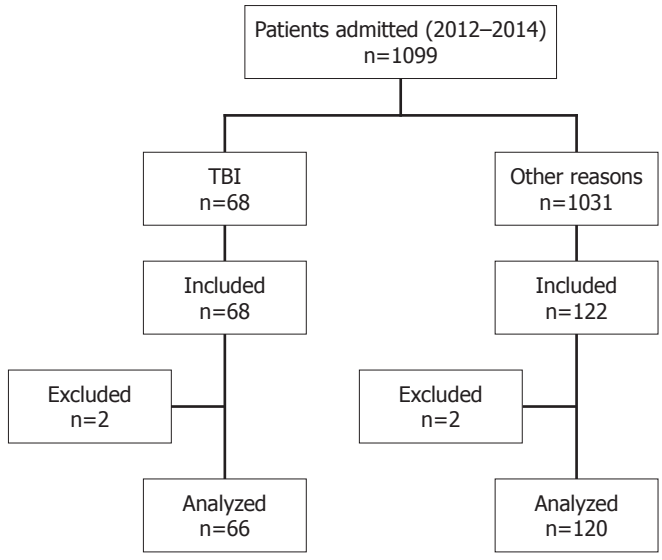

Figure 1. Study flow chart.

The primary outcome variable of the study was the presence of nosocomial spread. Infections were identified from the trauma database and the hospital's infection surveillance systems. All positive microbial cultures (cerebrospinal fluid, peripheral blood, urine, feces, and endotracheal tube samples) were identified during the PICU stay. The definition of NIs is defined 2 days after PICU admission and classified ventilator-associated pneumonia, central line-associated bloodstream infection, and catheter-associated urinary tract infection. There were no clusters or outbreaks of contamination or colonization during the study period.

The information in calculating the cost per patient was derived from the current price list of the Turkish Pharmaceuticals and Medical Devices Agency (https://www.titck.gov.tr/dinamikmodul/100) and the Social Security Department (https://tig.saglik.gov.tr). The total cost for each PICU patient was calculated in US Dollars.

Table 1. Comparison of the baseline features between the study and control groups

	Study groups			
	Control (n=120)	Case (n=66)	χ^2/Z	p
Gender (M) (%)	55	59.1	0.290	0.351
Age (months)	57.17±61.92	73.67±54.86	-2.820	**0.005**
GCS	13.54±3.23	10.73±4.30	-5.759	**<0.001**

GCS: Glasgow coma score.

Sample Size

The sample size calculation was based on the NI variable. To compare a 9% proportion of the expected event with an alternative hypothesis of 15% between two groups, giving an effect size of 0.2 (low) and an alpha error of 5%, a total of 179 patients are required to achieve a power of 80%.

Statistical Methods

Statistical analysis was performed with the Statistical Package for the Social Sciences version 21 (SPSS, IBM, Armonk, NY, USA). The "number (n)," "percentage (%)," "mean," and "standard deviation (SD)" was used for the descriptive statistics of the continuous variables. The Student's t-test or Mann–Whitney U-test compared two independent groups. The Pearson Chi-square or Fisher's exact tests analyzed categorical data. Clinically, significant variables were used to create a logistic regression model to evaluate the factors associated with NI. Since the mean age and GCS differed significantly between the groups, comparisons were made after adjusting for these variables. The results were assessed with a confidence interval of 95%, and the level of significance, p, was set at 0.05.

RESULTS

Data for 186 patients were analyzed. One hundred and twenty patients were controls (54 males vs. 66 females), while 66 were cases (27 males vs. 39 females). There was no statistically significant difference between the patients and controls concerning sex. The mean age was 63.02±59.89 months, and the age range was 1–204 months. There was a statistically significant difference between control and case patients concerning age (Table 1).

Seventeen out of the 186 ICU patients had NIs. There was no difference in age and gender in the patient groups with and without infection. The overall mean GCS was 12.5±3.8. Patients with NIs had a higher mean GCS when compared with patients without NIs (14.4±1.9 vs. 12.3±3.9). On the other hand, all 17 patients with NIs had a lower mean PRISM score when compared with patients without NIs (3.4±14.0 vs. 8.9±18.2) (Table 2).

The microorganisms isolated in growth (between 80.000 and 100.000 CFU/mL) were *Acinetobacter baumannii* (four cases), *Klebsiella pneumonia* (three cases), *Candida* spp., *Stenotrophomonas maltophilia* (two cases), coagulase-negative *Staphylococcus* (two cases), *Salmonella* spp., *Giardia intestinalis*, Gram-negative bacilli, and *Enterococcus faecalis*. Antimicrobials (including penicillin, fourth-generation cephalosporins, aminoglycosides, macrolides, glycopeptides, carbapenems, polypeptides, tetracycline, rifampicin, and ciprofloxacin, as well as antifungal and antiviral agents) were administered to patients with NIs as monotherapy or combinations.

About 7.6% of TBI patients had infections whereas 10% of control groups had infections (p=0.58). One of the most probable risk factors was the use of catheters. Thirteen (76.5%) out of the 17 infections were catheter-related bloodstream infections (CRBSI), while the remaining 4 infections (23.5%) were detected in the cerebrospinal fluid, feces, urine, and tracheal aspirate. There was a statistically significant difference between the use of central/venous/arterial/urinary/nasogastric catheters concerning the groups (p<0.001). The mortality rate was 9.1% (n=11) among patients referred to the PICU with other reasons, and 18.1% (n=12) in patients referred with TBI.

The mean LOS in the hospital and PICU was 9.5 and 6.0 days, respectively. The LOS in hospital and PICU for patients with TBI was longer when compared with

Table 2. Comparison of the studied variables regarding the presence and absence of NIs

	Nosocomial infection			
	Present (n=17)	Absent (n=169)	χ^2/Z	p
Gender (M) (%)	64.7	55.6	0.519	0.325
Age (months)	42.29±50.28	65.11±60.51	-1.376	0.169
LOS in the hospital (days)	26.35±23.23	7.82±6.64	-4.200	<**0.001**
LOS in the PICU (days)	20.00±21.36	4.61±4.45	-4.850	<**0.001**
GCS score	14.47±1.94	12.35±3.97	-2.474	**0.013**
PRISM score	3.47±4.00	8.96±18.29	-1.012	0.311
Invasive intervention (%)	5.9	8.9	0.176	1.000
Surgery (%)	17.6	21.9	0.165	1.000
Noninvasive ventilation (%)	5.9	2.4	0.730	0.384
Invasive ventilation (%)	64.7	26	11.091	**0.002**
TPN (%)	11.8	3.6	2.532	0.159
Urinary catheter (%)	64.7	49.7	1.391	0.311
Nasogastric catheter (%)	58.8	40.2	2.191	0.197
Central/venous/arterial line (%)	82.4	30.8	17.953	<**0.001**
Hemodialysis catheter (%)	5.9	0.6	4.065	0.175
Gastrostomy (%)	11.8	0	20.098	**0.008**
V-P shunt (%)	0	1.2	0.203	1.000
EVD (%)	0	0.6	0.101	1.000
Chest tube (%)	0	1.8	0.307	1.000
Mortality (%)	11.8	12.4	0.006	1.000
Renal dysfunction (%)	5.9	1.8	1.238	0.321
Hepatic dysfunction (%)	5.9	8.9	0.176	1.000
Use of steroids (%)	41.2	20.1	3.986	0.063
Use of H_2 blockers (%)	88.2	59.8	5.335	**0.033**
Additional cost of antimicrobials (USD)	2081.54±2334.17	330.00±398.69	-5.123	<**0.001**
The mean cost without antimicrobials (USD)	1162.93±955.39	651.83±687.20	3.044	**0.002**
Total cost of per patients (USD)	2509.30±2468.41	762.68±828.51	-4.069	<0.001

LOS: Length of stay; PICU: Pediatric intensive care unit; GCS: Glasgow coma score; PRISM: Pediatric Risk of Mortality; V-P: Ventriculoperitoneal; EVD: Extra ventricular drainage; TPN: Total parenteral nutrition; HD: Hemodialysis; USD: United State Dollars.

the patients without TBI (11.9 days vs. 8.0 days and 7.7 days vs. 5.0 days, respectively); there were significant differences between the groups concerning the LOS in the hospital or PICU (Table 3). In addition, the LOS in the hospital and PICU for patients with NIs was longer as compared with the patients without NIs (26.3 days vs. 7.8 days and 20.0 days vs. 4.6 days) (p<0.001) (Table 2).

The mean total cost per control patient was $842, while $2509 for the patients with NIs. The only mean cost of having NIs (antibiotics, PICU costs) was $2081, while this was $330 for patients without NIs. As expected, the excess LOS increased the cost of patients with NIs due to antibiotic use and other PICU costs (Table 2).

Logistic regression analysis was used to identify independent risk factors for NIs (Table 4). Patients who had multiple central venous or arterial catheters (p=0.005, 95% CI: 0.000–0.162) and hemodialysis catheters (p=0.009, 95% CI: 0.000–0.207) were more likely to develop bloodstream infections than patients who were not exposed to these factors. The mean scores of LOS in hospital/PICU, GCS, and PRISM points were not associated with the risk factors in our study. This model had a sensitivity of 98.2% and a specificity of 64.7% in predicting NIs.

TABLE 3. Comparison of the outcome variables between the groups

	Study groups			
	Control (n=120)	Case (n=66)	χ^2/Z*	p
LOS in the hospital (days)	8.18±9.56	11.92±12.33	-2.644	**0.008**
LOS in the PICU (days)	5.09±7.93	7.70±10.00	-2.494	**0.013**
Presence of NI (%)	10	7.6	0.165	0.685
PRISM score	5.22±8.63	14.36±26.17	-3.895	<**0.001**
Invasive intervention (%)	8.3	9.1	0.248	0.618
Surgery (%)	25	15.2	6.408	**0.011**
Noninvasive ventilation (%)	4.2	0	3.223	0.073
Invasive ventilation (%)	21.7	43.9	15.739	<**0.001**
TPN (%)	6.7	0	5.735	**0.017**
Urinary catheter (%)	38.3	74.2	28.444	<**0.001**
Nasogastric catheter (%)	28.3	66.7	31.961	<**0.001**
Central/venous/arterial line (%)	25.8	53	21.402	<**0.001**
Hemodialysis catheter (%)	1.7	0	0.793	0.373
Gastrostomy (%)	0.8	1.5	0.645	0.422
V-P shunt (%)	1.7	0	2.381	0.123
EVD (%)	0.8	0	1.594	0.207
Chest tube (%)	0.8	3	1.645	0.200
Mortality (%)	9.2	18.2	6.402	**0.011**
Renal dysfunction (%)	3.3	0	2.404	0.121
Hepatic dysfunction (%)	10	6.1	0.604	0.437
Use of steroids (%)	22.5	21.2	0.147	0.702
Use of H_2 blockers (%)	49.2	86.4	31.681	<**0.001**
Additional cost of antimicrobials (USD)	392.07±866.31	668.30±1028.12	-3.148	**0.002**
Mean cost without antimicrobials (USD)	672.08±717.85	746.66±748.51	-1.874	0.061
Total cost per patient (USD)	842.16±1087.10	1068.08±1342.38	-1.758	0.079

LOS: Length of stay; PICU: Pediatric intensive care unit; GCS: Glasgow coma score; PRISM: Pediatric risk of mortality; V-P: Ventriculoperitoneal; EVD: Extraventricular drainage; TPN: Total parenteral nutrition; HD: Hemodialysis; USD: United State Dollars; *: Calculations were done after adjusting by age and GCS.

DISCUSSION

NIs are common complications of more extended hospitalizations that result in severe mortality, morbidity, and excessive cost [15]. Bloodstream infections caused by catheters or related invasive interventions are common sources of NIs in patients admitted to PICUs [16]. In this study, there was no significant association between TBI and NIs in PICU patients. According to the multiple regression analysis, the presence of catheters (central/venous/arterial) increased the risk of CRBSI in both the cases and the control patients.

One study detected a similar result about the independent risk factors of NIs and reported that the use of multiple central venous and arterial catheters increased the risk of catheter-borne bloodstream infections 6-fold. Another related study also reported that numerous central catheters increased the risk of CRBSI almost 10 fold [17]. The same study also stated that the use of TPN was another risk factor for CRBSI. However, TPN was not a risk factor in our research. On the other hand, most related studies declared that NIs were associated with a statistically significant increased mortality rate [18, 19]. Although there was no apparent influence of NIs on mortality in our study, they were associated with a longer LOS in the hospital and PICU.

In the present study surprisingly, the logistic regression model revealed a significantly lower incidence of

Table 4. Risk factors for nosocomial infections in PICU patients

Risk factors	Beta	Wald	p	95% CI for Exp (B)	
				Lower	Upper
GCS	1.469	2.020	0.155	-0.573	32.922
PRISM	0.040	0.392	0.531	0.918	1.181
LOS in hospital	0.123	3.592	0.058	0.996	1.284
LOS in PICU	0.128	1.671	0.196	0.936	1.379
Renal dysfunction (present/absent)	-0.225	0.013	0.910	0.016	38.706
Hepatic dysfunction (present/absent)	-3.951	3.998	**0.046**	0.000	0.925
Invasive intervention (present/absent)	3.553	1.194	0.275	0.060	20473.561
Surgery (present/absent)	2.564	2.895	0.089	0.678	249.011
Noninvasive ventilation (present/absent)	-1.330	0.071	0.790	0.000	4641.017
Invasive ventilation (present/absent)	2.306	1.958	0.162	0.397	253.562
TPN (present/absent)	0.359	0.039	0.844	0.040	51.326
Catheter (present/absent)	-6.177	7.718	**0.005**	0.000	0.162
HD catheter (present/absent)	-6.221	6.890	**0.009**	0.000	0.207
Urinary catheter (present/absent)	1.812	1.965	0.161	0.486	77.050
Nasogastric catheter (present/absent)	0.455	0.100	0.752	0.093	26.563
Use of steroids (present/absent)	-0.617	0.294	0.291	0.058	5.007

CI: Confidence interval; LOS: Length of stay; PICU: Pediatric intensive care unit; GCS: Glasgow coma score; PRISM: Pediatric risk of mortality; TPN: Total parenteral nutrition; HD: Hemodialysis; USD: United State Dollars.

NIs in patients with hepatic dysfunction (OR 3.9). We attribute this finding to the special attention given to these patients concerning their care. These patients received medications, including antibiotics, in especially adjusted doses, and medications metabolized by the liver were avoided. Furthermore, in our study, only one patient with NI had hepatic dysfunction. Thus, this interpretation requires caution from the sample size perspective. This apparent discrepancy needs to be studied in future investigations.

The mean duration of stay in the hospital and PICU for the cases in our study was 3.9 and 2.0 days longer than that of the controls (8.0 and 5.0 days, respectively). These data confirmed the excess LOS in hospitals and ICUs, ranging from 3.1 to 23 days [20–22]. There were statistically significant differences between both case/control groups and patients with/without NIs regarding LOS in hospital and PICU in our study. The literature shows that if a patient has a NI in the ICU, the length of hospitalization will be longer [23]. Besides, an increased mortality rate (up to 35%) was detected depending on the excessive LOS in hospitals and ICUs [24, 25].

As expected, the excess LOS by NIs leads to an increase in hospital costs and frequency of antibiotic use. In developing countries, the expenditure on antibiotics constitutes a large part of the cost [26]. We detected that only antimicrobial use and related expenses were $474 (mean per patient) for traumatic PICU patients without NIs, while this amount was $3030 (mean per patient) for traumatic PICU patients with NIs. On the other hand, the mean total cost per control patient was $842, while it was $2509 for the patients with NIs. Some similar national studies support our findings. The additional cost for ICU patients was reported as ranging between $1500 and $5800 [27–30]. However, this range expands considerably ($2500–40000) in international studies, leading to a 2–47% of additional cost in ICUs per patient [31–33].

Limitations

Our work has some limitations. First, it is conducted retrospectively in a single center. A larger data set may allow more accurate sampling and detailed results. Second, we calculated costs using the price chart issued by the Turkish Ministry of Health, which uses a diagnosis-related grouping. Hence, some expense items such as anesthesia fees during surgery,

hospital/PICU standard expenses, and workforce expenses were not calculated. At that point, an itemized price list, including all interventions, could be obtained from the Hospital Billing Unit to get more accurate cost data.

Conclusion

In light of the findings, parallel with the current literature, we detected that NIs had an essential effect on the LOS in hospitals and PICU, as well as on additional and total costs of both controls and cases. In our study, it can be concluded that hospital infections are less common in patients followed up with TBI compared to the control group, due to the need for a shorter duration of invasive ventilation, TPN, and interventions such as invasive catheterizations. However, TBI did not have any significant extra effect on the presence of NIs. On the other hand, the NIs caused a substantial burden to both PICU patients and the health-care system regarding the treatment and hospitalization costs. In our study, the cost was probably underestimated for several reasons. Nevertheless, the findings supported our hypothesis about the additional burden of NIs on PICU patients. The results of this study should help provide evidence on cost-effectiveness or calculate the cost-benefit ratio of reducing nosocomial bloodstream infections in children.

Ethics Committee Approval: The Marmara University Clinical Research Ethics Committee granted approval for this study (date: 01.09.2019, number: 09.2014.124).

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Authorship Contributions: Concept – FIG, MNO; Design – FIG, MNO; Supervision – FIG; Fundings – FIG; Materials – FIG; Data collection and/or processing – FIG; Analysis and/or interpretation – FIG, MNO; Literature review – FIG; Writing – FIG; Critical review – FIG, MNO.

REFERENCES

1. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–91. [CrossRef]
2. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. NeuroRehabilitation 2007;22:341–53. [CrossRef]
3. Türkiye İstatistik Kurumu. İstatistiklerle Çocuk, 2017. Available at: https://data.tuik.gov.tr/Bulten/Index?p=Statistics-on-Child-2017-27596. Accessed Oct 13, 2023. Turkish Statistics Institute [Child statistics]. https://www.tuseb.gov.tr/enstitu/tacese/yuklemeler/istatistik/istatistiklerle_cocuk_2017_tablolar.xls 2018.
4. Gurskis V, Asembergiene J, Kefalas R, Miciuleviciene J, Pavilonis A, Valinteliene R, et al. Reduction of nosocomial infections and mortality attributable to nosocomial infections in pediatric intensive care units in Lithuania. Medicine (Kaunas) 2009;45:203–13. [CrossRef]
5. Aydogdu S, Karamese M, Altoparlak U. Evaluation of the activities of antimicrobial agents on multi-drug resistant gram-positive bacteria isolated from intensive care units. SOJ Microbiol Infect Dis 2014;2:1–5.
6. Calik Z, Karamese M, Acar O. Prevalence and antimicrobial-resistance of staphylococcus aureus isolated from blood culture in university hospital, Turkey. Glob J Infect Dis Clin Res 2015;1:10–3.
7. Pittet D, Davis C, Li N, Wenzel R. Identifying the hospitalized patient at risk for nosocomial bloodstream infection: a population-based study. Proc Assoc Am Physicians 1997;109:58–67.
8. Singh-Naz N, Sprague BM, Patel KM, Pollack MM. Risk assessment and standardized nosocomial infection rate in critically ill children. Crit Care Med 2000;28:2069–75. [CrossRef]
9. Alharfi IM, Charyk Stewart T, Al Helali I, Daoud H, Fraser DD. Infection rates, fevers, and associated factors in pediatric severe traumatic brain injury. J Neurotrauma 2014;31:452–8. [CrossRef]
10. Glance LG, Stone PW, Mukamel DB, Dick AW. Increases in mortality, length of stay, and cost associated with hospital-acquired infections in trauma patients. Arch Surg 2011;146:794–801. [CrossRef]
11. Peterson K, Carson S, Carney N. Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis. J Neurotrauma 2008;25:62–71. [CrossRef]
12. Stein F, Trevino R. Nosocomial infections in the pediatric intensive care unit. Pediatr Clin North Am 1994;41:1245–57. [CrossRef]
13. Tejada Artigas A, Bello Dronda S, Chacon Valles E, Munoz Marco J, Villuendas Uson MC, Figueras P, et al. Risk factors for nosocomial pneumonia in critically ill trauma patients. Crit Care Med 2001;29:304–9. [CrossRef]
14. Faul M, Rutland-Brown MM, Frankel W, Sullivant EE, Sattin RW. Using a cost-benefit analysis to estimate outcomes of a clinical treatment guideline: testing the brain trauma foundation guidelines for the treatment of severe traumatic brain injury. J Trauma 2007;63:1271–8.
15. Girou E, Stephan F, Novara A, Safar M, Fagon JY. Risk factors and outcome of nosocomial infections: results of a matched case-control study of ICU patients. Am J Respir Crit Care Med 1998;157:1151–8.
16. Slonim AD, Kurtines HC, Sprague BM, Singh N. The costs associated with nosocomial bloodstream infections in the pediatric intensive care unit. Pediatr Crit Care Med 2001;2:170–4. [CrossRef]
17. Almuneef MA, Memish ZA, Balkhy HH, Hijazi O, Cunningham G, Francis C. Rate, risk factors and outcomes of catheter-related bloodstream infection in a paediatric intensive care unit in Saudi Arabia. J Hosp Infect 2006;62:207–13. [CrossRef]
18. Juan-Torres A, Harbarth S. Prevention of primary bacteraemia. Int J Antimicrob Agents 2007;30:80–7. [CrossRef]
19. Niven DJ, Fick GH, Kirkpatrick AW, Grant V, Laupland KB. Cost and outcomes of nosocomial bloodstream infections complicating major traumatic injury. J Hosp Infect 2010;76:296–9. [CrossRef]
20. Asembergiene J, Gurskis V, Kefalas R, Valinteliene R. Nosocomial infections in the pediatric intensive care units in Lithuania. Medicine (Kaunas) 2009;45:29–36. [CrossRef]
21. Piednoir E, Bessaci K, Bureau-Chalot F, Sabouraud P, Brodard V, Andreoletti L, et al. Economic impact of healthcare-associated rotavirus infection in a paediatric hospital. J Hosp Infect 2003;55:190–5.
22. Ringenbergs ML, Davidson GP, Spence J, Morris S. Prospective study of nosocomial rotavirus infection in a paediatric hospital. Aust Paediatr J 1989;25:156–60. [CrossRef]

23. Elward AM, Hollenbeak CS, Warren DK, Fraser VJ. Attributable cost of nosocomial primary bloodstream infection in pediatric intensive care unit patients. Pediatrics 2005;115 868–72. [CrossRef]
24. Plowman R, Graves N, Griffin MA, Roberts JA, Swan AV, Cookson B, et al. The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialties of a district general hospital in England and the national burden imposed. J Hosp Infect 2001;47:198–209. [CrossRef]
25. Rosenthal VD, Guzman S, Migone O, Crnich CJ. The attributable cost, length of hospital stay, and mortality of central line-associated bloodstream infection in intensive care departments in Argentina: a prospective, matched analysis. Am J Infect Control 2003;31:475–80. [CrossRef]
26. Arslan A, Birgili B, Akinci AT, Simsek O, Kilincer C. Infection in patients with isolated head injury: risk factors and the impact on treatment cost. [Article in Turkish]. Ulus Travma Acil Cerrahi Derg 2012;18:501–6. [CrossRef]
27. Aygencel G, Turkoglu M. Characteristics, outcomes and costs of prolonged stay ICU patients. Turk J Med Surg Intensive Care 2012;3:53–8.
28. Esatoglu AE, Agirbas I, Onder OR, Celik Y. Additional cost of hospital-acquired infection to the patient: a case study in Turkey. Health Serv Manage Res 2006;19:137–43. [CrossRef]
29. Kara I, Yildirim F, Basak DY, Kucuk H, Turkoglu M, Aygencel G, et al. Comparison of patient costs in internal medicine and anaesthesiology intensive care units in a tertiary university hospital. Turk J Anaesthesiol Reanim 2015;43:142–8. [CrossRef]
30. Yalcin AN, Hayran M, Unal S. Economic analysis of nosocomial infections in a Turkish university hospital. J Chemother 1997;9:411–4.
31. Chen YY, Wang FD, Liu CY, Chou P. Incidence rate and variable cost of nosocomial infections in different types of intensive care units. Infect Control Hosp Epidemiol 2009;30:39–46. [CrossRef]
32. Higuera F, Rangel-Frausto MS, Rosenthal VD, Soto JM, Castanon J, Franco G, et al. Attributable cost and length of stay for patients with central venous catheter-associated bloodstream infection in Mexico City intensive care units: a prospective, matched analysis. Infect Control Hosp Epidemiol 2007;28:31–5. [CrossRef]
33. Laupland KB, Gregson DB, Flemons WW, Hawkins D, Ross T, Church DL. Burden of community-onset bloodstream infection: a population-based assessment. Epidemiol Infect 2007;135:1037–42.