Clinical Features of Fever Associated With Poor Outcome in Severe Pediatric Traumatic Brain Injury

Pilar Suz, MD, Monica S. Vavilala, MD,*†‡ Michael Souter, MB, ChB,*‡ Saipin Muangman, MD,* and Arthur M. Lam, MD*‡*

Abstract: We describe the incidence and etiology of fever and the relationship between fever characteristics and outcome in children with severe traumatic brain injury (TBI). We conducted a retrospective study of children <14 years and with Glasgow Coma Scale (GCS) score of <9 admitted to a level I pediatric trauma center intensive care unit (PICU) between 1998 and 2003. We examined whether fever characteristics were associated with poor outcome (hospital discharge GCS score <13 and discharge disposition of either death or discharge to a skilled nursing facility). PICU length of stay (LOS) and hospital LOS were also examined. Data are presented as means and medians (SD), and $P < 0.05$ reflects significance. Ninety-three records were reviewed. Patients were 5.7 (SD 4.1) years old, 70% were male, and the average admission GCS score was 5. Mortality rate was 14%. Forty-eight (52%) patients had fever, and 23 (48%) of those patients had infectious fever. Each additional febrile episode was associated with a twofold higher risk of patients having a hospital discharge GCS score of <13 (odds ratio 2.4, 95% confidence interval 1.2–5.0) and having a 0.4-day longer PICU LOS ($P < 0.001$). Patients with infectious fever had a 0.9-day longer PICU LOS ($P < 0.001$). Patients with any fever in the PICU had an increased HLOS (0.9 days; $P < 0.001$). Our data suggest that in severe pediatric TBI, both fever and infection were common, and both were associated with longer LOS. Patients with higher fever burden had poor hospital discharge GCS score.

Key Words: pyrexia, children, temperature, head trauma, fever

(*J Neurosurg Anesthesiol* 2006;18:5–10)

Traumatic brain injury (TBI) is the leading cause of morbidity and mortality in children under 14 years old. Efforts to improve outcome following adult and pediatric TBI commonly focus on preventing secondary injury caused by hypotension, hypocarbia, hypercarbia, and hypoxia. Whereas fever has been described as a risk factor for poor outcome following TBI, the relationship between fever and outcome in pediatric TBI is not well characterized.

The relationship between body temperature and clinical outcome of TBI is complex, but animal and adult data suggest that fever following TBI is associated with poor outcome.[1–4] In patients with TBI, the febrile response is affected by factors besides infections, such as stress response to intra- and extracranial injuries, neurogenic response to trauma, and intensive care unit–ICU related complications such as deep venous thrombosis. The cause–effect relationships between some of these factors and the outcome of TBI can be debated.

There are three studies describing the association between fever and outcome in children with TBI.[2,5,6] In one study of 117 children admitted to the pediatric intensive care unit (PICU) with TBI, Natale and colleagues reported that temperature of >38.5°C within the first day of admission (early hyperthermia) to the PICU occurred in 30% of patients. When classified by TBI severity, early fever was more common in severe (58%) compared with mild and moderate (10%) TBI, but the number of children with severe TBI was small (n = 48). Overall, early hyperthermia was associated with a 13-fold increased PICU length of stay (LOS) and a nearly 10-fold increased risk of Glasgow Coma Scale (GCS) score of <13 at hospital discharge.[2] However, the etiology of fever in children with TBI was not described nor was the impact of fever, occurring beyond the first day after admission, on outcome considered.

To better understand some of these relationships, we undertook a retrospective review of our ICU data. The purpose of the present study was to provide additional information regarding the influence of fever on outcome in children admitted to the PICU with severe TBI. In this study, we describe the incidence and etiology of fever and the relationship between fever characteristics and outcome in children admitted to the PICU with severe TBI.

METHODS

Study Design

A retrospective cohort study of children with severe TBI was performed following approval by the University of Washington's Human Subjects Review Committee.

Subjects and Setting

Children younger than 14 years admitted to Harborview Medical Center (HMC; level I pediatric trauma center) over a 5-year period (1998–2003) with a diagnosis of severe TBI

Received for publication May 25, 2005; revised September 7, 2005; accepted September 26, 2005.

From the *Department of Anesthesiology, University of Washington, Seattle, WA; †Department of Pediatrics, University of Washington, Seattle, WA; and ‡Department of Neurological Surgery, University of Washington, Seattle, WA.

Supported by NIH/NICHD/K23044632 (M.S.V.), Washington State Society of Anesthesiologists (M.S.V., S.M., P.S.), and the Department of Anesthesiology at the University of Washington (M.S.V., M.S., S.M., P.S., A.M.L.).

Reprints: Monica S. Vavilala, Department of Anesthesiology, Harborview Medical Center, Box 359724, 325 Ninth Ave., Seattle, WA 98104 (e-mail: vavilala@u.washington.edu).

were eligible for inclusion in the study. The HMC Trauma Registry was first used to generate a list of patients with severe TBI, defined as Head Abbreviated Injury Score (AIS) ≥3. Subjects were then excluded if PICU admission was GCS score ≥9, if the indwelling endotracheal tube was removed before PICU admission, or if they died in the emergency department.

The following general information was recorded for each patient: demographic data, injury severity score (ISS), PICU admission GCS score, and physiologic markers of secondary insults (hypotension [systolic blood pressure (SBP) <90 mm Hg], hypoxia [P_aO_2 <60 mm Hg], hypercarbia [P_aCO_2 >45 mm Hg], hypocarbia [P_aCO_2 <30 mm Hg], hypothermia [temperature <35°C], intracranial hypertension [intracranial pressure >20 mm Hg], hyperglycemia [glucose >150 mg/dL], and coagulopathy [international normalized ratio >1.5]) from hospital admission through PICU discharge. Admission computed tomography (CT) results were also recorded.

The following fever characteristics were abstracted: history of infection and/or fever prior to hospital admission, exposure to antibiotics preceding and during PICU stay, number of febrile episodes in PICU, days of PICU fever, fever work-up (white blood cell count [WBC], blood, urine, and sputum culture results, and radiographic evaluation), and signs of central storming (hypertension, tachycardia).

Variable Definitions

Medical records were reviewed for each patient to identify fever during PICU stay. Fever was defined as oral, rectal, or tympanic temperature of ≥38.5°C for 2 or more hours. Febrile episodes were defined as fever events (intermittent or continuous) separated by >24 hours of normal body temperature (<38.5°C).

The etiology of each episode of fever, when documented in the medical record, was noted. When an etiologic diagnosis of fever was not described in the medical record, the diagnosis was retrospectively made as infectious or noninfectious using predefined criteria, as follows: Infectious fever episodes were defined by any of the following: isolation of a single organism from culture of the blood, catheterized urine specimen, or sputum, thought by the providers to cause fever; abnormal chest radiograph indicative of infection; response to at least 3 days of antibiotic treatment when given for infection based on clinical suspicion. Patients with at least one episode of infection associated with fever were classified as having infectious fever. Leukocytosis was not used to define infectious fever because even in the presence of fever, it may suggest an inflammatory/stress response rather than infection; similarly, fever in the absence of leukocytosis might also represent infection. The remainder of fever episodes was classed as noninfectious fever. Drug fever, deep vein thrombosis, and unknown etiologies were categorized as noninfectious fever. Because it is not known whether a higher fever burden (more fever episodes) predicts worse outcome than a single episode of fever, we noted the occurrence of fever on an individual patient basis, the number of fever episodes per patient, the maximal temperature experienced, and the percentage of PICU time patients were febrile. We examined the effects of these fever characteristics on outcome.

Outcome

The primary outcome measure was hospital discharge GCS score (hospital discharge GCS score), where poor outcome was defined as hospital discharge GCS score of <13. Secondary outcome measures were: discharge disposition (where poor outcome was defined as discharge to either skilled nursing facility or death), PICU LOS, and hospital LOS (HLOS).

Data Analysis

Data were analyzed with Epi-Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA) and SPSS ver. 12.0 for Windows (SPSS, Chicago, IL). Linear regression was used to analyze continuous outcome variables, and logistic regression was used to analyze dichotomous outcome variables. Demographic features were analyzed as categorical variables. Age was treated as a continuous variable. Laboratory investigations (WBC, culture results, and coagulopathy) were initially examined as continuous variables. None of these reached statistical significance when considered as such and were subsequently treated dichotomously as normal or abnormal results; values outside the hospital reference range were categorized as abnormal.

Predictors and outcome variables were examined in bivariate analysis using the χ^2 test (with Yates correction) and Kruskal–Wallis, as appropriate. A P value of <0.1 was taken as a criterion for subsequent inclusion into a multivariate logistic regression model. This model also included variables thought to be important clinical contributors to outcome, but for which bivariate analysis did not demonstrate a significant association at the $P < 0.1$ levels.

Variables were then initially discarded from the model on the basis of co-linearity and subsequently in successive iterations of testing, discarding for both a lack of effect on the "goodness of fit" as expressed by the Hosmer and Lemeshow test and accuracy of prediction to yield a final model. Fever characteristics were analyzed separately where possibilities of significant interaction existed to exclude interdependency. These characteristics were then rotated through final models to explore any enhancement of accuracy of prediction as well as goodness of fit. Data are described as means ± SD, unless otherwise specified, and $P < 0.05$ reflected significance.

RESULTS

Subjects

During the study period, 172 patients were identified using the head AIS classification. After excluding patients with PICU admission GCS score of ≥9 or who died before PICU admission, 93 patients met inclusion criteria. All patients were tracheally intubated.

The mean age of the sample was 5.7 ± 4.1 years, and 70% were male. Ninety-one of 93 children had blunt trauma, of which falls (26%) and motor vehicle collisions (26%) were the most common causes (Table 1). PICU admission GCS score was 5 ± 2 (motor GCS 1), and 61% had a PICU

admission GCS score of 3. Seventy (75%) children had leukocytosis (WBC >14,300, HMC reference range) on hospital admission. None of the patients had infection or fever or was treated with antibiotics prior to hospital admission. Overall, 40 patients received blood transfusion at some point during their PICU stay, and there was no difference in transfusion between patients with and without fever. Twenty-eight (30%) patients required surgery. The ISS of the cohort was 16 ± 4, and there was no difference in ISS between patients with and without fever.

TABLE 1. Clinical Characteristics on PICU Admission (n = 93)

Demographics	No. (n)	%
Male gender	65	69.9
Age		
0–4 y	47	50.5
5–9 y	21	22.6
10–14 y	25	26.9
Race		
Caucasian	69	74.2
Black	3	3.2
Asian	1	1.1
Native American	2	2.1
Hispanic	9	9.7
Nonspecified	9	9.7
Blunt trauma	91	97.8
Mechanism of trauma		
Fall	24	25.8
Pedestrian	15	16.1
Motor vehicle crash	24	25.8
Recreational Activities	10	10.8
Other	20	21.5
PICU admission GCS score		
3	57	61.3
4	1	1.1
5	4	4.3
6	6	6.4
7	14	15.1
8	11	11.8
CT findings		
Edema	13	14
Diffuse axonal injury	13	14
Contusion	42	45
Compound skull fracture	12	13
Subdural hemorrhage	31	33
Epidural hemorrhage	11	12
Intraventricular hemorrhage	12	13
Closed fracture	39	42
Subarachnoid hemorrhage	20	21.5
Extracranial injuries	55	59.1
Leukocytosis (WBC >14.3 mm^3)	70	75.2
Secondary insults in emergency department		
Hypoxia (P_aO_2 <60 mm Hg)	5	5.4
Hypotension (SBP <90 mm Hg)	19	20
Hypocarbia (P_aCO_2 <30 mm Hg)	24	26
Hypercarbia (P_aCO_2 >45 mm Hg)	36	39
Intracranial hypertension (>20)	38	41
Hypothermia (temperature <35 °C)	11	12
Hyperglycemia (glucose >150 mg/dL)	66	71
Coagulopathy (INR >1.5)	31	33

SBP = systolic blood pressure; ICP = intracranial pressure; INR = international normalized ratio.

Fever Characteristics

Patients

Forty-eight (52%) of 93 patients had fever during their PICU stay (Table 2). On average, those patients were febrile for 49% ± 26% of their PICU stay. The average maximal temperature of patients with fever was 39.5 °C ± 0.68 °C. Ninety-one of 93 (98%) patients had tympanic temperature measurements, and the mode of measurement was consistent for a given patient.

Twenty-three (48%) of 48 patients had infectious fever while in the PICU (Table 3). Eighteen of 23 patients had pneumonia, 8 of 23 had urinary tract infections (UTIs), 5 of 23 had wound infection, and 3 of 23 had other types of infection. Six patients had more than one infectious source. In patients with noninfectious fever (25/48), the cause was either undetermined in 96% or drug mediated (4%). There was no difference in time to onset of febrile episodes (1.7 ± 1.1 versus 1.5 ± 0.7 days; $P = 0.35$) or maximal temperature (39.6 °C ± 0.68 °C versus 39.3 °C ± 0.64 °C; $P = 0.08$) between patients with infectious versus noninfectious fever, respectively.

Febrile Episodes

Overall, patients had their first febrile episode between the first and second PICU days (1.6 days; range 1–6 days); of these patients, 56% (27/48) had their first febrile episode during the first day. There was a median of one episode of fever (range 1–6) experienced by each patient during his or her PICU stay (Fig. 1), and the average duration of each febrile episode lasted 1.3 ± 1.6 days. Of the total 79 febrile episodes experienced by 48 patients, 42 episodes were associated with infection. There was no significant difference in the duration of febrile episodes based on infection ($P = 0.57$).

Outcomes

Overall outcomes for this cohort (Table 4) were as follows: mean hospital discharge GCS score 12 ± 4, PICU LOS 6.8 ± 8.0 days (median 4 days, range 1–38 days), HLOS 12.3 ± 14.2 days (median 7 days, range 1–71 days), and poor disposition 22%. Thirteen patients (14%) died while in the PICU. Patients with infectious fever had longer PICU LOS (14.7 ± 11.0 days) compared with patients with noninfectious fever (5.4 ± 5.8 days; $P < 0.001$). HLOS for patients with

TABLE 2. Fever Characteristics

Febrile patients (n [%])	48/93 (52)
No. of febrile episodes per patient	2 ± 1 (1–6 episodes)
Duration of each episode (d)	1.3 ± 1.6
% PICU time with fever per patient	49 ± 26
Maximal temperature (°C)	39.5 ± 0.68
Onset of fever (d)	1.6 ± 0.9
Patients with infectious fever (n [%])	24/48 (50)

TABLE 3. Outcome Characteristics in Patients With and Without Infectious Fever

	Fever (n = 48)	Infectious Fever (23/48)	Noninfectious Fever (25/48)	*P*
Hosp. D/C GCS <13 (n [%])	13 (27.1)	8/23 (34.8)	5/25(20)	0.41
Hosp. D/C GCS (mean ± SD)	11.5 ± 4.1	11 ± 4	12 ± 4	0.23
HLOS (days;mean ± SD)	15.1 ± 14.6	23.7 ± 16.7	12.3 ± 16	0.02
PICU LOS (days;mean ± SD)	10.1 ± 9.9	14.7 ± 11	5.4 ± 5.8	<0.001
Poor disposition (n [%])	9/48 (18.8)	5/23 (21.7)	4/25 (16)	0.89
Mortality (n [%])	5/48 (10.4)	2/23 (8.7)	3/25 (12.0)	0.92

D/C, discharge.

infectious fever was also longer (23.7 ± 16.7 days) than for patients with noninfectious fever (12.3 ± 16.0 days; $P = 0.02$; see Table 3).

The previously described variables were analyzed for significant univariate effect on poor outcomes. After retaining the variables that predicted poor outcome ($P < 0.1$) in the final multivariate model, a number of fever characteristics were related to poor outcome (Tables 5–7). Each additional febrile episode increased the risk of patients having a hospital discharge GCS <13 by 2.4 fold (adjusted odds ratio = 2.4, 95% confidence interval 1.2–5.0]) and longer PICU LOS by 0.4 days ($P < 0.001$). Patients with infectious fever had longer PICU LOS by 0.9 days ($P < 0.001$), and patients with noninfectious or infectious fever in the PICU had a 0.9-day longer HLOS ($P < 0.001$). Fever was not associated with poor disposition as it was defined for this cohort of patients. Noninfectious fever did not predict poor discharge GCS or poor disposition.

DISCUSSION

In the present study, we examined the incidence and etiology of fever in the PICU and the relationship between fever characteristics and outcome in children admitted to the PICU with severe TBI. The main findings of this study are that in children with severe TBI, (a) fever was common, occurred early, and lasted for a significant portion of PICU stay; (b) infection (pneumonia or UTI) was common in febrile patients; and (c) the number of febrile episodes per patient predicted prolonged PICU LOS and poor hospital discharge GCS. Any fever predicted longer HLOS, and infectious fever predicted prolonged PICU LOS.

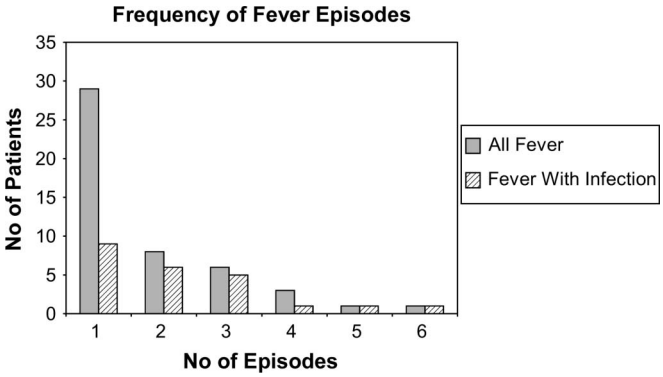

FIGURE 1. Frequency of fever episodes. The median number of febrile episodes experienced by each patient was 1 (range 1–6).

The present data in severe pediatric TBI show that not only are children with fever febrile for nearly half of their PICU stay despite treatment with commonly used antipyretics but that a greater fever burden predicts poor hospital discharge GCS. This is similar to adult TBI, where the incidence of fever at some point during hospitalization may exceed 65%[7–11] and confirms Natale's findings relating early fever and poor discharge GCS. At present, it is unclear which fever characteristics (ie, number of episodes versus duration of fever versus height of fever) exert the most influence on outcome. Whereas previous studies have examined the relationship between fever and outcome, they have not compared the influence of different fever characteristics such as number of fever episodes. The number of episodes may be deleterious as it may represent a high fever burden. Therefore, it is possible that one episode of fever minimally impacts outcome, whereas a greater number of episodes is particularly problematic.

Whereas fever may be a normal and coordinated response to tissue injury, including the release of pro-inflammatory cytokines,[12] it has been correlated with injury severity, longer ICU stay, and poor outcome.[2,13–16] In one study of 846 patients (3 months to 87 years of age), Jiang et al reported worse 1-year neurologic outcome in patients with fever (>39°C) occurring within 3 days of injury compared with patients without fever.[12] Although we cannot definitively say whether fever is a marker or cause of poor outcome or an inflammatory/thermoregulatory response to TBI, our data provide new information suggesting that some fever characteristics adversely impact hospital discharge GCS or disposition in severe pediatric TBI.

In contrast to studies of adult TBI, fever characteristics of children in the PICU with severe TBI are not well described. Whereas Natale and colleagues reported nearly a sixfold higher incidence of early hyperthermia in severe compared with mild TBI, the small number of children with severe TBI precluded an analysis of more detailed fever characteristics in these patients.[2] Because fever beyond the first day after severe TBI may be due to infection and/or may worsen outcome at a time when the brain is still susceptible to secondary brain insults, we expanded Natale's definition of fever to span the entire PICU LOS. Using this definition, we report a high incidence of fever and infectious fever in children with severe TBI. Whereas it may not be surprising that pneumonia and UTI account for the majority of infections in critically ill

TABLE 4. Outcome Characteristics in Patients With and Without Fever

	All (n = 93)	Fever (48/93)	No fever (45/93)	*P*
PICU D/C GCS <13 (n [%])	55 (59)	35 (64)	20 (36)	0.005
PICU D/C GCS (mean ± SD)	10 ± 5	9.7 ± 3.8	11.2 ± 4.2	0.02
Hospital D/C GCS <13 (n [%])	30 (32)	19 (40)	11 (24)	0.12
Hospital D/C GCS (mean ± SD)	12 ± 4	12 ± 4	12 ± 5	0.13
HLOS (d; mean ± SD)	12.3 ± 14.2	15.1 ± 14.6	5.6 ± 4.6	<0.0001
PICU LOS (d; mean ± SD)	6.8 ± 8	10.1 ± 9.9	3.4 ± 2.8	<0.0001
Poor disposition (n [%])	20 (22)	11/48 (23)	9/45 (20)	0.80
Mortality (n [%])	13 (14)	5/48 (10)	8/45 (18)	0.37

D/C, discharge.

children,[17] the high incidence of early infection in these patients questions the often-held assumption that most of the TBI-related fever in severe pediatric TBI is central in origin. Although infectious fever predicted longer HLOS, it did not predict poor hospital discharge GCS score, because either a) infection was recognized and treated appropriately, (b) our definition of infection included treatment with antibiotics and may have overestimated the number of infection cases, or (c) fever adversely impacts hosp discharge GCS more than infection. Finally, although we cannot comment on the differential effect of infection versus fever on our primary and secondary outcomes, our data suggests that infection should be suspected early in the presence of fever. Fever, even if within the first day, should also trigger a workup for infection. We speculate that aspiration at the scene may be responsible for many of the early pneumonias in the present study.

In this study, mortality as an outcome was not predicted by the presence or absence of fever or its etiology. More patients in the nonfever group died in our series, which may be due to early deaths in patients with severe TBI. Because most of the deaths (69%) occurred within the first day, these patients did not have enough time to develop in-hospital fever. Given that the total number of patients who died was low (n = 13/93 or 14%), it is also possible that statistical significance for the association between fever, etiology, and mortality was not reached to detect this infrequent outcome.

The present retrospective study has some limitations. To determine the effect of fever on outcome, such a study could not be done prospectively as it would be ethically undesirable to let the temperature rise in the setting of neurotrauma. We used hospital discharge GCS, PICU LOS, HLOS, and discharge disposition to describe outcome, as we did not have 3- and 6-month Glasgow Outcome Scores. The lack of association between fever and disposition is important to note and may be related to the difficulty in using disposition as an outcome measure, given the numerous variables involved in disposition decision making and/or the broad range of conditions that may be triaged to similar facilities. Early mortality influenced PICU LOS and HLOS results because the majority (69%) of the 13 deaths occurred before onset of the first febrile episode (1.7 days). Some assumptions regarding the etiology of fever were made. First, we used temperature >38.5°C to define fever to confirm Natale's findings and cannot comment on the effect of increasing temperature on outcome. Second, although most patients (98%) had tympanic measurements of temperature, all did not. We therefore had to assume that the routes of measurement were equivalent. However, because the same route of measurements was made for a given patient, this may not be problematic. Third, we cannot comment about the optimal strategy to prevent or treat fever in children with severe TBI. Finally, we included treatment with antibiotics based on clinical suspicion as probable infectious etiology because early antibiotic therapy precludes obtaining objective microbiological confirmation of infection. This may overestimate infectious fever, but to do otherwise requires a protocol for fever investigation that was not in place at the time of clinical data collection.

Our findings suggest that children with severe TBI who survive beyond PICU admission have a high incidence of fever and infection. In this study, fever characteristics predicted poor hospital discharge GCS, prolonged PICU LOS, and longer HLOS. Given the high incidence of infection in febrile children with severe pediatric TBI, a study to evaluate whether aggressive and systematic measures to identify and treat

TABLE 5. Fever and Hospital Discharge GCS Score of <13

Variable	AOR (95% CI)
No. of febrile episodes per patient	2.4 (1.2–5.0)
Age (y)	0.8 (0.7–1.0)
Coagulopathy	8.8 (2.2–36.0)
CT edema	11.7 (1.2–107.8)

Logistic regression analysis with forward entry. Nagelkere $R^2 = 0.648$; Hosemer and Lemeshow goodness of fit = 0.980; prediction accuracy = 84.9%.

AOR, adjusted odds ratio; CI, confidence interval.

TABLE 6. Fever and PICU LOS

Variable	Days	*P*
No. of febrile episodes per patient	0.4	0.00
Patients with infectious fever	0.9	0.00
PICU hypercarbia	0.3	0.00
Surgery	0.4	0.00
CT intraventricular hemorrhage	0.7	0.05
CT cerebral contusion	0.4	0.00
Closed skull fracture	0.3	0.13

Linear regression model using a log transform of PICU LOS. $R^2 = 0.669$.

TABLE 7. Fever and HLOS

Variable	Days	*P*
Patients with any fever in PICU	0.9	0.00
Emergency dept. leukocytosis	0.02	0.50
Leukocytosis on PICU day 5	1.5	0.00
Emergency dept. hyperglycemia	0.6	0.01
Surgery	0.44	0.01
CT intraventricular hemorrhage	0.99	0.00
CT cerebral contusion	0.43	0.02
CT diffuse axonal injury	−0.516	0.05

Linear regression analysis with Log transform of HLOS. $R^2 = 0.487$.

infection in febrile children with severe TBI improve outcome may be warranted.

REFERENCES

1. Dietrich WD, Alonso O, Halley M, et al. Delayed post-traumatic brain fever worsens outcome after fluid percussion brain injury: a light and electron microscopic study in rats. *Neurosurgery.* 1996;38:533–541.
2. Natale JE, Joseph JG, Helfaer MA, et al. Early hyperthermia after traumatic brain injury in children: risk factors, influence on length of stay, and effect on short-term neurologic status. *Crit Care Med*. 2000;28:2608–2615.
3. Dietrich WD, Busto R, Valdes I, et al. Effects of normothermic versus mild febrile forebrain ischemia in rats. *Stroke*. 1990;21:1318–1325.
4. Kinoshita K, Chatzipanteli K, Alonso OF, et al. The effect of brain temperature on hemoglobin extravasation after traumatic brain injury. *J Neurosurg*. 2002;97:945–953.
5. Heindl UT, Laub MC. Outcome of persistent vegetative state following hypoxic or traumatic brain injury in children and adolescents. *Neuropediatrics*. 1996;27:94–100.
6. Jiang JY, Gao GY, Li WP, et al. Early indicators of prognosis in 846 cases of severe traumatic brain injury. *J Neurotrauma*. 2002;19:869–874.
7. Stocchetti N, Rossi S, Zanier ER, et al. Fever in head-injured patients admitted to intensive care. *Intensive Care Med*. 2002;28:1555–1562.
8. Albrecht RF, Wass C, Lanier WL. Occurrence of potentially detrimental temperature alterations in hospitalized patients at risk for brain injury. *Mayo Clin Proc*. 1998;73:629–635.
9. Rossi S, Roncati-Zanier E, Mauri I, et al. Brain temperature, body core temperature, and intracranial pressure in acute cerebral damage. *J Neurol Neurosurg Psychiatry.* 2001;71:448–454.
10. Geffroy A, Bronchard R, Merckx P, et al. Severe traumatic head injury in adults: which patients are at risk of early fever? *Intensive Care Med*. 2004; 30:785–790.
11. Childers MK, Rupright J, Smith DW. Post-traumatic fever in acute brain injury rehabilitation. *Brain Inj*. 1994;8:335–343.
12. McKeating EG, Andrews PJ, Sighorini DF, et al. Transcranial cytokine gradients in patients requiring intensive care after acute brain injury. *Br J Anaesth*. 1997;78:520–523.
13. Chatzipanteli K, Alonso OF, Kraydieh S, et al. Importance of posttraumatic hypothermia and fever on the inflammatory response after fluid percussion brain injury: biochemical and immunocytochemical studies. *J Cereb Blood Flow Metab.* 2000;20:531–542.
14. Bayir H. Kochanek PM, Clark RSB. Traumatic brain injury in infants and children: Mechanisms of secondary damage and treatment in the intensive care unit. *Crit Care Clin*. 2003;19:529–549.
15. Hayes RL, Jenkins LW, Lyeth BG. Neurotransmitter-mediated mechanisms of traumatic brain injury: acetylcholine and excitatory aminoacids. *J Neurotrauma*. 1992;9:S173–S187.
16. Jones PA, Andrews PJ, Easton VJ, et al. Traumatic brain injury in childhood: intensive care time series data and outcome. *Br J Neurosurg*. 2003;17:29–39.
17. Sarginson RE, Taylor N, Reilly N, et al. Infection in prolonged pediatric critical illness: A prospective four-year study based on knowledge of the carrier state. *Crit Care Med*. 2004;32:839–847.