

FEVER IN TRAUMA PATIENTS: EVALUATION OF RISK FACTORS, INCLUDING TRAUMATIC BRAIN INJURY

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Background The role of fever in trauma patients remains unclear. Fever occurs as a response to release of cytokines and prostaglandins by white blood cells. Many factors, including trauma, can trigger release of these factors.

Objectives To determine whether (1) fever in the first 48 hours is related to a favorable outcome in trauma patients and (2) fever is more common in patients with head trauma.

Method Retrospective study of trauma patients admitted to the intensive care unit for at least 2 days. Data were analyzed by using multivariate analysis.

Results Of 162 patients studied, 40% had fever during the first 48 hours. Febrile patients had higher mortality rates than did afebrile patients. When adjusted for severity of injuries, fever did not correlate with mortality. Neither the incidence of fever in the first 48 hours after admission to the intensive care unit nor the number of days febrile in the unit differed between patients with and patients without head trauma (traumatic brain injury). About 70% of febrile patients did not have a source found for their fever. Febrile patients without an identified source of infection had lower peak white blood cell counts, lower maximum body temperature, and higher minimum platelet counts than did febrile patients who had an infectious source identified. The most common infection was pneumonia.

Conclusions No relationship was found between the presence of fever during the first 48 hours and mortality. Patients with traumatic brain injury did not have a higher incidence of fever than did patients without traumatic brain injury. About 30% of febrile patients had an identifiable source of infection. Further studies are needed to understand the origin and role of fever in trauma patients. (*American Journal of Critical Care*. 2015; 24:e1-e5)

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This article focuses on fever in trauma patients who are admitted to the intensive care unit (ICU) for at least 2 days. We examine 2 questions: (1) does fever in the first 48 hours portend a favorable outcome and (2) what is the impact of head trauma (traumatic brain injury [TBI]) on fever? The role of fever in trauma patients remains unclear. The following questions remain unanswered: Does fever represent a strong immune response and can it be used to predict a favorable outcome? Does fever have a role in minimizing bacterial invasion? Or does fever, by increasing metabolic rate and cardiac output, predispose patients to an increase in mortality or brain injury?

Several articles have examined the role of fever in ICU patients. Circiumaru et al¹ followed 100 patients admitted to the ICU in a tertiary care, inner city hospital. Fever was present in 70% of patients admitted to the ICU, was apparent early in the ICU course, and correlated with scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II but not with mortality.

Young et al² examined fever in ICU patients with and without infections. Mortality decreased with increased peak temperatures in patients with infections, and mortality increased in patients without infection who had body temperatures greater than 39°C. A second study was conducted in surgical patients with bloodstream infections.³ Fever correlated with survival, but not with white blood cell (WBC) counts or type of

pathogen. These studies suggest a protective effect of fever in patients with infections.

Studies have examined the impact of brain injury on fever and cytokine production in cerebrospinal fluid and blood.^{4,6} Cytokines can be both protective and damaging to the brain depending on the cytokine and the quantity produced. Rincon et al⁷ conducted a retrospective study in patients with acute strokes, intracerebral hemorrhage, or TBI. About

59% of patients with neurological events had fevers develop, compared with 47% in patients without neurological problems ($P=.007$). Fever in these patients with brain injury was associated with increased mortality.

Methods

Trauma patients were identified by using the St Barnabas Hospital registry from 2008 to 2010. St Barnabas Hospital is a level 1 trauma center located in the Bronx, New York. Patients were included if they were age 15 years or older and admitted for at least 2 days to the ICU. Data were collected until discharge or up to 30 days.

Fever was defined as a body temperature of 100.4°F (38.0°C) or greater and was measured orally.⁸ Fever workup was based on clinical assessment⁹ and could include cultures of blood, sputum, urine, wound, or stool and a *Clostridium difficile* toxin assay. At the time of the study, patients with TBI were not undergoing a hypothermia protocol.

Patients were classified as having underlying medical conditions if those conditions predated their trauma admission. Patients were counted as intubated except if they were intubated for a surgical procedure and immediately extubated. Procedures included all surgical procedures except those related to long-term care such as tracheotomy and feeding tubes.

We examined fever at 2 different time points: in the first 48 hours to see if fevers correlated with mortality and during the entire ICU stay to investigate if fever reflected infection and mortality. This study was approved by the hospital's institutional review board.

Statistical Analysis

Groups were compared by using a χ^2 test. Means were compared by using an independent sample t test. Logistic regression was used for multivariate analysis, with 95% confidence intervals and Hosmer-Lemeshow goodness of fit. The threshold for significance is a P value of .05.

Patients were included if they were admitted for at least 2 days to the ICU.

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Results

Demographics and Types of Trauma

For the 162 trauma patients who met the criteria for inclusion in the study, 31% of admissions were due to falls, 16% to motor vehicle accidents, 14% to being hit by a car as a pedestrian, 14% to stab wounds, 12% to assault, and 11% to gunshot wounds. The study group was predominantly male (81%), with a mean (SD) age of 42 (20) years. The mean (SD) for APACHE II score was 13 (8), for score on the Glasgow Coma Scale was 11 (4), and for the Injury Severity Score (ISS) was 17 (6).

Fever During the First 48 Hours

In order to determine if fever in the first 48 hours was a predictor of mortality, we divided all trauma patients into 2 groups: fever or no fever present in the first 48 hours after admission (Table 1).

Patients with fever had significantly lower scores on the Glasgow Coma Scale, higher APACHE II scores, and a higher ISS than did patients without fever. Patients with fever also differed in the number of underlying medical conditions, but no one specific underlying condition (diabetes, dialysis, or alcohol use) was identified as predisposing to fevers. Mortality was greater in febrile than in nonfebrile patients. More febrile patients required intubation and had a surgical procedure (correlated specifically for craniotomy and burr holes). No difference in highest WBC count, highest body temperature, or lowest platelet count was apparent between patients with and without fever.

Table 2 shows the result of the multivariate analysis. Fever correlated with intubation and underlying medical conditions. Fever was not a predictor of mortality.

Source of Fever in the ICU

A total of 82 patients (51%) had fever at some point in their ICU stay. Patients who had a source found for their fever stayed longer in the ICU (mean [SD], 19 [28] days vs 7 [5] days; $P=.02$) and in the hospital (28 [32] days vs 13 [10] days; $P=.01$) than did febrile patients without an infectious source found.

Despite fever workup, no source of infection was found in most patients ($n=57$, 70%). The ability to identify a source of infection did not differ among groups of patients with different risk factors, including TBI, intubation, or undergoing a surgical procedure (Table 3). Patients with an identifiable source for their fever, in contrast to patients where no source was found, had higher maximum body temperature, higher maximum

Table 1
Characteristics of patients with and without fever in the first 48 hours after admission

Characteristic ^a	No fever (n=97)	Fever (n=65)	P
Male sex	74 (76)	57 (88)	.09
Age, mean (SD), y	43 (20)	40 (19)	.34
Age > 60 years	21 (22)	7 (11)	.07
Underlying medical disease	37 (38)	18 (28)	.16
Traumatic brain injury	48 (49)	40 (62)	.13
Penetrating trauma	21 (22)	21 (32)	.23
APACHE II score, mean (SD)	11 (7)	14 (8)	.08
Score on Glasgow Coma Scale, mean (SD)	13 (3)	10 (4)	<.001
Injury Severity Score, mean (SD)	15 (5)	19 (6)	<.001
Intubated	30 (31)	55 (85)	.01
Death	7 (7)	13 (15)	.02
Blood transfusions	9 (9)	9 (14)	.36
Surgical procedures	47 (50)	45 (66)	.04
Open reduction internal fixation	13 (14)	6 (9)	>.99
Craniotomy/burr hole	9 (10)	15 (22)	.02
Exploratory laparotomy	7 (7)	10 (15)	.06
Chest tube	12 (13)	4 (6)	.77
Exploratory laparotomy and chest tube insertion	4 (5)	6 (9)	.16
Other	2 (4)	4 (6)	.18
Days in intensive care unit, mean (SD)	6 (7)	9 (6)	.06
Days in hospital, mean (SD)	13 (22)	15 (11)	.64

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.

^a Values in second and third column are number (percentage) of patients unless otherwise indicated.

Table 2
Multivariate analysis: patients with fever in the first 48 hours of admission and patients with head trauma

Group and variables analyzed	Adjusted odds ratio (95% CI)	P
Patients with fever in the first 48 hours of admission		
Procedures	0.61 (0.17-2.22)	.46
Intubation	0.16 (0.037-0.66)	.01
Underlying medical conditions	0.16 (0.041-0.61)	.007
Injury Severity Score	1.056 (0.94-1.19)	.37
Score on Glasgow Coma Scale	0.82 (0.66-1.020)	.08
APACHE II score	1.039 (0.93-1.16)	.48
Death	5.32 (0.78-36.1)	.09
Patients with head trauma		
APACHE II score	0.97 (0.89-1.06)	.55
Death	0.095 (0.010-0.89)	.04
Injury Severity Score	0.99 (0.90-1.089)	.81
Intubation	0.39 (0.10-1.46)	.16
Procedures	9.083 (2.46-33.58)	.001
Age	0.98 (0.95-1.016)	.29

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.

Table 3
Univariate and multivariate analysis of febrile patients with and without an identifiable source of infection

Variable	Source of fever ^a		
	Not found	Found	P
Univariate analysis			
Age, mean (SD), y	40 (18)	46 (20)	.11
Traumatic brain injury (n=57)	40 (70)	17 (30)	.56
Underlying medical conditions (n=33)	21 (64)	12 (36)	.30
Score on Glasgow Coma Scale, mean (SD)	11 (4)	10 (4)	.40
APACHE II score, mean (SD)	13 (7)	14 (8)	.95
Injury Severity Score, mean (SD)	18 (6)	18 (5)	.85
Intubation (n=67)	41 (61)	26 (39)	.06
Procedures (n=71)	47 (66)	24 (34)	.92
Blood transfusions (n=17)	11 (65)	6 (35)	.28
Death (n=18)	12 (67)	6 (33)	.89
Highest white blood cell count, mean (SD)	16 (6)	22 (11)	.006
Lowest platelet count, mean (SD)	147 (74)	117 (62)	.04
Highest body temperature, mean (SD)	102 (1)	103 (2)	.01
Multivariate analysis			
	Adjusted odds ratio (95% CI)		
Highest white blood cell count	1.078 (1.015-1.14)		.01
Highest body temperature	1.19 (0.85-1.67)		.30
Lowest platelet count	1.00 (0.99-1.00)		.34

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.
^a Values are number (percentage) of patients with that variable unless otherwise indicated in first column.

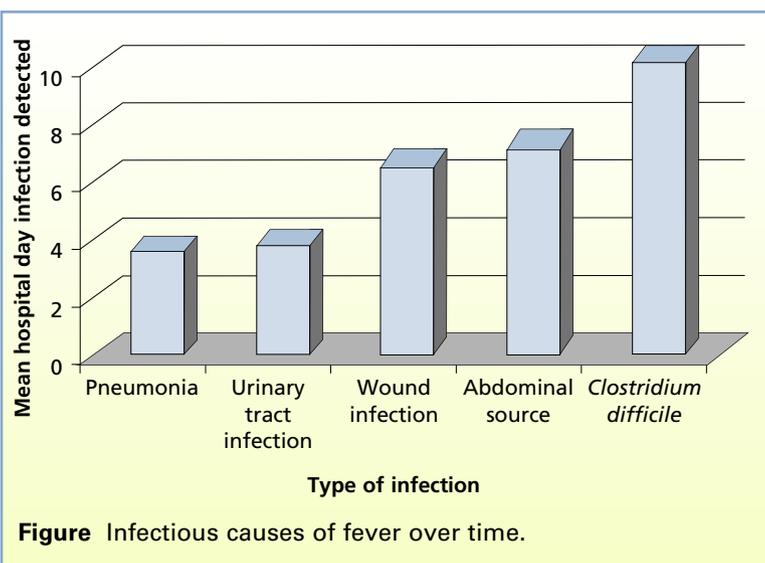


Figure Infectious causes of fever over time.

WBC count, and lower platelet counts. Table 3 shows the multivariate analysis where peak WBC count remained significantly higher in febrile patients with an identifiable source for their infection.

The most common infectious source was pneumonia (34%), followed by urinary tract infection (20%), wound infections (14%), abdominal source (14%), and *C difficile* (12%). Two patients had a deep vein thrombosis. The timing for an infection developing is illustrated in the Figure. Three-quarters of patients with pneumonia were intubated.

The yield of blood cultures was low. Of 341 sets sent, 11 (3%) showed growth of microorganisms. Four grew gram-negative organisms, 6 grew coagulase-negative *Staphylococcus*, and 1 grew an anaerobe.

Impact of TBI on Mortality

Patients with TBI compared with no TBI were older (mean [SD], 45 [21] years vs 38 [18] years; $P=.02$), had higher APACHE II scores (15 [7] vs 11 [8]; $P=.03$), and a higher ISS (18 [6] vs 15 [5]; $P=.005$). They were more likely to be intubated ($P=.005$), have a surgical procedure ($P<.001$), and die ($P<.001$). Age, blood transfusions, underlying medical disease, highest body temperature, highest WBC count, and lowest platelet count did not correlate with TBI. In a multivariate analysis, TBI correlated with mortality and undergoing a surgical procedure (Table 2).

In order to isolate the effect of TBI, patients with TBI were further divided into 2 groups as follows: those with TBI alone and those with TBI plus injuries at other sites. The groups were similar except that more patients in the group with additional injuries had higher ISS, higher APACHE II scores, and had undergone surgery. The multivariate analysis revealed no significant differences between these 2 groups. The mortality in the group with TBI alone was 17%, compared with 30% mortality in the group with TBI plus other injuries ($P=.18$).

Impact of TBI on Fever

Fever in the first 48 hours did not differ between patients with or without TBI or between patients with TBI alone or TBI plus other injuries: 41% in TBI only, 53% in TBI plus other injuries, 27% in patients without TBI ($P=.35$). The number of days febrile did not differ between patients with or without TBI.

The source of fever was identified in 30% of febrile patients with TBI and in 35% of febrile patients without TBI ($P=.67$). The most common source of fever was pneumonia. This occurred in 12% of febrile patients with TBI and 11% of febrile patients without TBI. The highest fever, the greatest WBC count, and the lowest platelet count did not differ between patients with and without TBI.

Discussion

Fever in the first 48 hours after trauma was not a predictor of dying or of not dying. Fever was seen more often in patients who were intubated, even after the data were adjusted for severity of injury. These results suggest that the "stress" of trauma as manifested by fever did not protect the patient from death. One limitation is that the stress response can manifest in ways other than fevers. Further studies

are needed to examine the roles of specific cytokine production after trauma and the roles that cytokines play in fever and survival.

The next question focused on the effect of TBI on fever and mortality. The patients with TBI were similar to the patients without TBI as far as developing fevers in the first 48 hours and the number of days febrile in the ICU. However, fever in TBI patients was not a predictor of mortality as Rincon et al⁷ had reported. Rincon et al, however, included patients with strokes and intracerebral hemorrhage in addition to TBI. They reported that fever on admission to the ICU was common and was independently associated with in-hospital mortality.

Our results highlight the difficulty in finding a source of fever in trauma patients admitted to the ICU. Other parameters of infection such as maximum WBC count, highest body temperature, and lowest platelet counts were seen more often in febrile patients with a source of infection than in febrile patients without a source found. Very few patients had a bacteremia, but we did not control for patients who clinically appeared to have sepsis. This finding suggests that infections are not the main reason for fever in these trauma patients. Other possible causes of fever such as the severity of injuries or undergoing surgery were not significant factors on multivariate analysis.

Limitations of this study include the retrospective nature of the study, the number of patients recruited, the lack of measurement of cytokines, and the inability to compare febrile and afebrile patients with infections (as there were too few infected patients). Many questions remain about the etiology of fever and its benefits in trauma patients.

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FINANCIAL DISCLOSURES

None reported.

eLetters

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REFERENCES

1. Circiumaru B, Baldock G, Cohen J. A prospective study of fever in the intensive care unit. *Intensive Care Med.* 1999; 25:668-673.
2. Young PJ, Saxena M, Beasley R, et al. Early peak temperature and mortality in critically ill patients with and without infection. *Intensive Care Med.* 2012;38:437-444.
3. Swenson BR, Hedrick TL, Popovsky K, et al. Is fever protective in surgical patients with bloodstream infection? *J Am Coll Surg.* 2007;204(5):815-821.
4. Helmy A, De Simoni MG, Guilfoyle MR, et al. Cytokines and innate inflammation in the pathogenesis of human traumatic brain injury. *Prog Neurol.* 2011;95(3):352-372.
5. LaPar DJ, Rosenberger LH, Walters DM, et al. Severe traumatic head injury affects systemic cytokine expression. *J Am Coll Surg.* 2012;214(4):478-486.
6. Bohman LE, Levine JM. Fever and therapeutic normothermia in severe brain injury: an update. *Curr Opin Crit Care.* 2014(2):182-188.
7. Rincon F, Patel U, Schorr C, et al. Brain injury as a risk factor for fever upon admission to the intensive care unit and association with in-hospital case fatality: a matched cohort study [published online October 16, 2013]. *J Intensive Care Med.* doi:10.1177/0885066613508266.
8. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/ Society of Critical Care Medicine. *Chest.* 1992;101(6):1644-1655.
9. O'Grady NP, Barie PS, Bartlett JG, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Crit Care Med.* 2008;42(6):1330-1349.

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