Journal of Clinical Orthopaedics and Trauma 10 (2019) S133–S138

Contents lists available at ScienceDirect

Journal of Clinical Orthopaedics and Trauma

journal homepage: www.elsevier.com/locate/jcot

No increased risk of acute osteomyelitis associated with closed or open long bone shaft fracture

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ARTICLE INFO

Article history:
Received 21 February 2019
Received in revised form
9 April 2019
Accepted 9 April 2019
Available online 12 April 2019

This work was presented at the 38th Annual Surgical Infection Society meeting April 22–25, 2018 at Westlake Village, California.

Keywords:
Osteomyelitis
Trauma
Long bone fracture
Bacteremia

ABSTRACT

Objectives: Osteomyelitis of the long bones can result from hematogenous spread, direct inoculation or from a contiguous focus of infection. The association of osteomyelitis after long bone fractures has widely been believed to be true by practicing surgeons since the 1950s, even though the evidence has been poor. We hypothesized that long bone shaft fracture and major bone surgery are independent risk factors for osteomyelitis in adult trauma patients.

Methods: The National Trauma Data Bank (NTDB) was queried between 2007 and 2015 for patients ≥18 years of age presenting after trauma. Patients with long bone shaft fractures (femur, tibia/fibula, humerus) were identified and rate of acute osteomyelitis was calculated. Univariable logistic regression was performed. A multivariable logistic regression was performed to identify risk factors for development of acute osteomyelitis.

Results: From 5,494,609 patients, 358,406 were identified to have long bone shaft fractures (6.5%) with the majority being tibia/fibula (44.3%). The osteomyelitis rate in long bone shaft fractures was 0.05%. Independent risk factors for osteomyelitis included major humerus surgery and major tibia/fibula surgery. The strongest risk factor was non-*pseudomonas* bacteremia. Long bone shaft fractures were not found to be an independent risk factor for osteomyelitis ($p > 0.05$).

Conclusions: Long bone shaft fractures are not independently associated with increased risk for osteomyelitis. Major extremity surgery on the humerus and tibia/fibula, but not femur, are independent risk factors for osteomyelitis. However, the strongest risk factor is non-*pseudomonas* bacteremia.

1. Introduction

Dating back to Hippocrates, infection after bony fracture is one of the oldest diseases known to man.[1] However, acute osteomyelitis was not described clinically until 1773.[1] In traumatic cases, acute osteomyelitis has been reported to occur most commonly following open long bone fractures with an incidence of 4–63%.[2] Acute osteomyelitis of the long bones can result from hematogenous spread, direct inoculation or from a contiguous focus of infection, with direct inoculation thought to be the primary cause in trauma patients.[3,4]

The rate of open long bone fractures has been reported at 11.5 per 100,000 persons per year, with osteomyelitis complicating up to 30% of cases.[5,6] For this reason, surgical debridement and irrigation should occur as soon as possible. Within six hours of the trauma, the threshold density for open fractures, $\geq 10^5$ organisms per gram of tissue, is reached.[7] However, some studies have suggested that surgical intervention itself may be an independent risk factor for the development of osteomyelitis after open long bone fractures, while others concluded surgical intervention to be protective.[8–10]

Although the relationship between acute osteomyelitis and long bone fracture remains poorly understood, the risk of acute osteomyelitis after long bone fractures has not been studied using a large national trauma database. The purpose of this study was to determine risk factors for development of acute osteomyelitis in adult trauma patients presenting with long bone fracture. We hypothesized that long bone shaft fracture and major bone surgery are risk factors for acute osteomyelitis.

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https://doi.org/10.1016/j.jcot.2019.04.003
0976-5662/

2. Methods

This was a retrospective analysis using the National Trauma Data Bank (NTDB) which consists of a multicenter registry of trauma centers in North America maintained by the American College of Surgeons Committee on Trauma.[11] This study was deemed exempt by the institutional review board of the University of California, Irvine, as the NTDB is a national de-identified database. We queried the NTDB from January 2007 to December 2015 to identify all patients admitted with open or closed long bone (femur, tibia/fibula, humerus) shaft fractures using the International Classification of Diseases (ICD) version-9 diagnosis codes listed in Appendix A. Patients <18 years of age were excluded.

Our primary end-point of interest was the development of acute osteomyelitis during the index hospitalization. To evaluate which patients with long bone shaft fractures are associated with osteomyelitis, we compared patients with femur, humerus and tibia/fibula shaft fractures. In order to identify risk factors for developing osteomyelitis, we additionally compared patients with and without osteomyelitis.

Secondary outcomes included total hospital length of stay (LOS), intensive care unit (ICU) LOS, ventilator days, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), myocardial infarction (MI), pulmonary embolism (PE), pneumonia, unplanned intubation, unplanned ICU admission, pseudomonas and non/pseudomonas bacteremia, blood transfusion requirement and mortality. We also identified patients that underwent major bone surgery. For the purposes of this study, major bone surgery was defined as any surgery involving application of external fixation device, reconstructive operation, internal fixation without reduction, closed reduction with and without internal fixation, open reduction with and without internal fixation, debridement and unspecified bone surgery. The relationship between acute osteomyelitis and baseline patient demographics, comorbidities, injury profile, interventions and hospital outcomes were analyzed.

Patient demographic information including age, gender and pre-hospital comorbidities including diabetes, end stage renal disease (ESRD), steroid use, smoking and peripheral arterial disease (PAD) were collected. The injury profile included the injury severity score (ISS), abbreviated injury scale (AIS) for body region, blunt mechanism of injury, hypotension on arrival (systolic blood pressure $\leq$ 90 mmHg) and presence of positive blood alcohol concentration (BAC) or illegal drug screen on admission. Associated injuries were identified by the appropriate ICD-9 diagnosis codes and included spine injury, traumatic brain injury (TBI) and extremity fracture. All variables were coded as present or absent.

Descriptive statistics were performed for all variables. A Student's *t*-test was used to compare continuous variables and chi-square was used to compare categorical variables for bivariate analysis. Categorical data were reported as percentages, and continuous data were reported as medians with interquartile range or means with standard deviation.

The magnitude of the association between predictor variables and acute osteomyelitis was first measured using a univariable logistic regression model. We included previously reported risk factors for osteomyelitis into a univariable linear regression model.[12–17] Covariates with statistical significance ($p \leq 0.20$) were included in a hierarchical multivariable logistic regression model and the adjusted risk for acute osteomyelitis was reported with an odds ratio (OR) and 95% confidence intervals (CI). The reference group used in our analysis comparing long bone shaft fractures included all adult patients with documented long bone shaft fractures. The reference group used in our analysis to determine risk for acute osteomyelitis included all adult patients in the dataset. All p-values were two-sided, with a statistical significance level of <0.05. All missing data points were not imputed but treated as missing data. All analyses were performed with IBM SPSS Statistics for Windows (Version 24, IBM Corp., Armonk, NY).

3. Results

3.1. Demographics of patients with long bone shaft fractures and primary outcome

From 5,494,609 adult trauma admissions between 2007 and 2015, 358,406 patients were identified to have long bone shaft fractures (6.5%), with the largest percentage being tibia/fibula (44.3%). The majority of long bone shaft fractures were closed (femur, 82.2%; tibia/fibula 69.4%; humerus, 82.3%, $p < 0.001$). Compared to all patients with long bone shaft fractures, those with femur shaft fractures were younger (mean age, 44.6 vs. 45.3, $p < 0.001$) with a higher median ISS (10.0 vs. 9.5, $p < 0.001$) and higher rate of TBI (20.5% vs. 19.0%, $p < 0.001$). Patients with tibia/fibula shaft fractures were younger (mean age, 43.7 vs. 45.3, $p < 0.001$) with a lower median ISS (9.0 vs. 9.5, $p < 0.001$) while those with humerus shaft fractures were older (mean age, 49.2 vs. 45.3, $p < 0.001$) with a lower median ISS (9.0 vs. 9.5, $p < 0.001$) and higher rate of TBI (24.8% vs. 19.0%, $p < 0.001$) (Table 1). Compared to patients with closed long bone shaft fractures, those with open fractures were younger (mean age, 39.0 vs. 47.1, $p < 0.001$), more likely to be male (76.5% vs. 59.7%) and less likely to have a blunt mechanism of injury (77.7% vs. 98.8%) (Table 2). The overall rate of acute osteomyelitis was 0.05%. Compared to all patients with long bone shaft fractures, those with femur (0.01% vs. 0.05%, $p < 0.05$) and humerus (0.03% vs. 0.05%, $p < 0.001$) shaft fractures had a lower rate of acute osteomyelitis while those with tibia/fibula shaft fractures had a higher rate of acute osteomyelitis (0.1% vs. 0.05%, $p < 0.001$) (Table 3). ISS and age were missing in 4.8% and 6.7% of patients; these patients were excluded from regression analysis.

3.2. Demographics of patients with acute osteomyelitis

Compared to those without acute osteomyelitis, trauma patients with acute osteomyelitis were younger (mean age, 47.8 vs. 49.6, $p < 0.001$), less likely to be involved in a blunt mechanism (79.6% vs. 95.4%, $p < 0.001$) and had a higher median ISS (10.0 vs. 8.0, $p < 0.001$). Patients with acute osteomyelitis had a higher rate of associated spine injury (28.7% vs. 16.4%, $p < 0.001$) and isolated lower extremity fracture (38.2% vs. 19.8%, $p < 0.001$), but less TBI (22.4% vs. 30.7%, $p < 0.001$) and isolated upper extremity fracture (11.0% vs. 14.5%, $p < 0.05$) (Table 4).

3.3. Univariable analysis for risk of acute osteomyelitis

On univariable analysis for risk of osteomyelitis in adult trauma patients, the strongest risk factors, in order, were *non-pseudomonas* bacteremia (OR 41.85, 95% CI 28.49–61.48, $p < 0.001$), PAD (OR 11.14, 95% CI 7.59–16.35, $p < 0.001$) and open tibia/fibula shaft fracture (OR 9.30, 95% CI 7.26–11.92, $p < 0.001$). *Pseudomonas* bacteremia and long-term steroid use were not associated with an increased risk for acute osteomyelitis ($p > 0.05$) (Table 5).

3.4. Multivariable analysis for risk of acute osteomyelitis

After adjusting for covariates in a multivariable logistic regression analysis, *non-pseudomonas* bacteremia continued to be the strongest independent risk factor for osteomyelitis (OR 9.30, 95% CI 3.74–23.10, $p < 0.001$) followed by tibia/fibula major surgery (OR 5.31, 95% CI 3.81–7.41, $p < 0.001$), blood transfusion (OR 3.74, 95% CI 2.74–5.10, $p < 0.001$) and humerus major surgery (OR 2.74, 95% CI

Table 1
Patient characteristics of all adult trauma patients with long bone shaft fractures.

Characteristic	Long bone shaft fracture	Femur		Tibia/fibula		Humerus	
	(n = 358406)	(n = 146685)	p-value	(n = 158749)	p-value	(n = 69856)	p-value
Age, year, mean (SD)	45.3 (18)	44.6 (22)	<0.001	43.7 (27)	<0.001	49.2 (21)	<0.001
Sex, male, n (%)	226305 (63.1)	92313 (63.2)	<0.05	107996 (68.3)	<0.001	37588 (54.0)	<0.001
Blunt mechanism, n (%)	328507 (91.7)	134550 (93.7)	<0.001	147105 (95.7)	<0.001	63127 (92.6)	<0.001
ISS, median (IQR)	9.5 (6)	10.0 (10)	<0.001	9.0 (9)	<0.001	9.0 (9)	<0.001
Shaft fracture, n (%)							
Open	82791 (23.1)	26109 (17.8)	<0.001	48577 (30.6)	<0.001	12364 (17.7)	<0.001
Closed	287083 (80.1)	120629 (82.2)	<0.001	110175 (69.4)	<0.001	57473 (82.3)	<0.001
Injuries, n (%)							
Traumatic brain injury	68233 (19.0)	30140 (20.5)	<0.001	27218 (17.1)	<0.001	17309 (24.8)	<0.001
Spine	56561 (15.8)	24653 (16.8)	<0.001	23339 (14.7)	<0.001	14300 (20.5)	<0.001
Upper extremity fracture	121430 (33.9)	34162 (23.3)	<0.001	28322 (17.8)	<0.001	69856 (100)	–
Lower extremity fracture	304977 (85.1)	146685 (100)	–	158749 (100)	–	16427 (23.5)	<0.001
AIS (severe)[a], n (%)							
Head	23058 (6.4)	10394 (7.1)	<0.001	8876 (5.6)	<0.001	6300 (9.0)	<0.001
Spine	1586 (0.4)	670 (0.5)	<0.001	596 (0.4)	<0.001	462 (0.7)	<0.001
Thorax	16537 (4.6)	7798 (5.3)	<0.001	5890 (3.7)	<0.001	4861 (7.0)	<0.001
Abdomen	7365 (2.1)	3973 (2.7)	<0.001	2336 (1.5)	<0.001	2094 (3.0)	<0.001

SD = standard deviation, IQR = interquartile range, AIS = abbreviated injury scale.
[a] = severe (grade>3).

Table 2
Patient characteristics of all adult trauma patients with open and closed long bone fractures.

Characteristic	Closed	Open	p-value
	(n = 279375)	(n = 79031)	
Age, years, mean (SD)	47.1 (20.6)	39.0 (16.7)	<0.001
Sex, male, n (%)	166065 (59.7)	60240 (76.5)	<0.001
Blunt mechanism, n (%)	268618 (98.8)	59889 (77.7)	<0.001
Injuries, n (%)			
Traumatic brain injury	52942 (19.0)	15291 (19.3)	<0.05
Spine	43998 (15.7)	12563 (15.9)	0.32
Isolated upper extremity fracture	96161 (34.4)	25269 (32.0)	<0.001
Isolated lower extremity fracture	235399 (84.3)	69578 (88.0)	<0.001
AIS (severe)[a], n (%)			
Head	17756 (6.4)	5302 (6.7)	<0.001
Spine	1133 (0.4)	453 (0.6)	<0.001
Abdomen	5257 (1.9)	2108 (2.7)	<0.001
Thorax	12406 (4.4)	4131 (5.2)	<0.001
LOS, days, mean (SD)	8.1 (10.5)	10.1 (12.7)	<0.001
ICU, days, mean (SD)	7.7 (9.3)	7.7 (9.6)	<0.05
Ventilator, days, mean (SD)	7.82 (10.2)	6.9 (9.2)	<0.001

SD = standard deviation, AIS = abbreviated injury scale, LOS = length of stay, ICU = intensive care unit.
[a] = severe (grade>3).

1.57–4.77, $p < 0.001$). None of the long bone shaft fractures analyzed were found to be independent risk factors for acute osteomyelitis ($p > 0.05$). This remained true for both open and closed injuries (Table 6).

4. Discussion

Our study examines a large national database of trauma patients with long bone shaft fractures and provides an analysis for the risk of acute osteomyelitis in trauma. The rate of long bone shaft fractures is 6.5% with most involving the tibia/fibula. The rate of acute osteomyelitis across all patients with long bone shaft fractures is less than 0.1%. The strongest independent risk factor for acute osteomyelitis in trauma patients is *non-pseudomonas* bacteremia. We did not find any long bone (humerus, femur, or tibia/fibula) shaft fracture to increase risk for acute osteomyelitis and this remained true for both open and closed injuries. However, major surgery of the tibia/fibula is associated with over a five-fold increased risk for acute osteomyelitis and major surgery of the humerus is associated with nearly a three-fold increased risk for acute osteomyelitis.

Contrary to our hypothesis, we did not find open or closed long bone shaft fractures to be associated with higher risk for acute osteomyelitis. This association has widely been believed to be true by practicing surgeons since the 1960s, even though the evidence has been poor.[18,19] The pathogenesis of osteomyelitis is likely multifactorial but remains poorly understood. In trauma, it is believed to involve direct inoculation of microorganisms into bone made possible by breakage in skin and/or soft tissue.[4] This is the basis of why open fractures may have higher risk for acute osteomyelitis compared to closed fractures. Only 18 cases of osteomyelitis following any closed bone fracture have been reported in the literature since the 1970s.[20] However, we did not find open (or closed) long bone shaft fractures to be associated with higher risk for acute osteomyelitis in adult trauma patients. One reason for this may be that acute development of osteomyelitis is more related to hematogenous inoculation then direct spread from the wound, evidenced by our finding that non-*pseudomonas* bacteremia has the strongest association with acute development of osteomyelitis in the hospitalized trauma patient. Additional prospective studies to confirm the lack of correlation between long bone shaft fractures and acute osteomyelitis in adults is needed.

Bacteremia has been reported to be associated with the development of acute osteomyelitis.[21,22] Jorge et al. found *Pseudomonas* infection to be associated with nearly a three-fold increased risk for post-traumatic osteomyelitis.[17] However, the most commonly isolated organism in patients with osteomyelitis is reported to be *Staphylococcus*.[23,24] In our study, *Staphylococcus* occurred in nearly 20% of patients and was the most common specified organism. We did not find *Pseudomonas* bacteremia to be associated with increased risk for acute osteomyelitis in trauma patients. In contrast, non-*pseudomonas* bacteremia was the strongest predictor of acute osteomyelitis. Future prospective studies that include intraoperative cultures, as well as the source, organism type and associated sensitivities of the organisms causing bacteremia-associated osteomyelitis appears warranted.

The decision to operate and the timing of the procedure may affect the rate of acute osteomyelitis in patients with long bone fractures. Although the classic teaching has been to debride devitalized and contaminated tissue within six hours of patients arriving with traumatic long bone fractures, previous studies have

Table 3
Outcomes of all adult trauma patients with long bone shaft fractures.

Characteristic	All	Femur		Tibia/fibula		Humerus	
	(n = 358406)	(n = 146685)	p-value	(n = 158749)	p-value	(n = 69856)	p-value
Outcomes							
LOS, days, mean (SD)	8.5 (11)	9.3 (11)	<0.001	8.6 (11)	<0.001	8.5 (12)	<0.001
ICU, days, mean (SD)	7.7 (11)	7.7 (9)	0.23	7.8 (10)	<0.001	7.5 (9)	<0.001
Ventilator, days, mean (SD)	7.6 (6)	4.0 (8)	<0.05	7.7 (10)	<0.001	8.1 (10)	<0.001
Major surgery, n (%)							
All	178486 (49.8)	116047 (79.1)	<0.001	117550 (74.0)	<0.001	36948 (52.9)	<0.001
Application of external fixation device	35123 (9.8)	9109 (6.2)	<0.001	23729 (14.9)	<0.001	1173 (1.7)	<0.001
Reconstructive operation	1433 (0.4)	251 (0.2)	<0.001	962 (0.6)	<0.001	65 (0.1)	<0.001
Internal fixation without reduction	15053 (4.2)	11599 (3.2)	<0.001	8960 (5.6)	<0.001	924 (1.3)	<0.001
Closed reduction without internal fixation	22937 (6.4)	8700 (5.9)	<0.001	1472 (0.9)	<0.001	5991 (8.6)	<0.001
Closed reduction with internal fixation	59853 (16.7)	36251 (24.7)	<0.001	24548 (15.5)	<0.001	2110 (3.0)	<0.001
Open reduction without internal fixation	4301 (1.2)	1326 (0.9)	<0.001	2856 (1.8)	<0.001	502 (0.7)	<0.001
Open reduction with internal fixation	168809 (47.1)	68313 (46.6)	<0.001	79299 (50.0)	<0.001	29658 (42.5)	<0.001
Debridement	60212 (16.8)	13917 (9.5)	<0.001	37366 (23.5)	<0.001	5520 (7.9)	<0.001
Unspecified bone surgery	71 (0.02)	57 (0.1)	<0.001	39 (0.02)	<0.001	7 (0.01)	<0.001
Complications, n (%)							
Amputation through bone	5017 (1.4)	1862 (1.3)	<0.001	2436 (1.5)	<0.001	594 (0.9)	<0.001
Acute kidney injury	3916 (1.1)	1954 (1.3)	<0.001	1486 (0.9)	<0.001	918 (1.3)	<0.001
ARDS	6039 (1.7)	3262 (2.2)	<0.001	2238 (1.4)	<0.001	1421 (2.0)	<0.001
Myocardial infarction	1044 (0.3)	504 (0.3)	<0.001	376 (0.2)	<0.001	240 (0.3)	<0.05
Pulmonary embolism	3188 (0.9)	1917 (1.3)	<0.001	1165 (0.7)	<0.001	432 (0.6)	<0.001
Unplanned ICU	1742 (0.5)	802 (0.5)	<0.001	768 (0.5)	0.86	349 (0.5)	0.57
Unplanned intubation	2468 (0.7)	1152 (0.8)	<0.05	1057 (0.7)	0.14	537 (0.8)	<0.05
Osteomyelitis	177 (0.05)	59 (0.01)	<0.05	115 (0.1)	<0.001	24 (0.03)	<0.05
Pneumonia	11975 (3.3)	5785 (3.9)	<0.001	4783 (3.0)	<0.001	2969 (4.3)	<0.001
Mortality, n (%)	16152 (4.5)	8889 (6.2)	<0.001	4473 (2.9)	<0.001	4806 (7.1)	<0.001

SD = standard deviation, IQR = interquartile range, LOS = length of stay, ICU = intensive care unit, ARDS = acute respiratory distress syndrome.

Table 4
Patient characteristics of all adult trauma patients with and without osteomyelitis.

Characteristic	- Osteomyelitis	+ Osteomyelitis	p-value
	(n = 4788970)	(n = 833)	
Age, years, mean (SD)	49.6 (21)	47.8 (17)	<0.001
Sex, male, n (%)	3489253 (63.7)	597 (71.7)	<0.001
Blunt mechanism, n (%)	4570498 (95.4)	663 (79.6)	<0.001
ISS, median (IQR)	8.0 (9)	10.0 (7)	<0.001
Injuries, n (%)			
Traumatic brain injury	1687623 (30.7)	187 (22.4)	<0.001
Spine	900861 (16.4)	239 (28.7)	<0.001
Isolated upper extremity fracture	796072 (14.5)	92 (11.0)	<0.05
Isolated lower extremity fracture	1088474 (19.8)	318 (38.2)	<0.001
Upper and lower extremity fracture	196676 (3.6)	135 (16.2)	<0.001

SD = standard deviation, ISS = injury severity score, IQR = interquartile range.

demonstrated that this is accomplished less than 50% of the time.[7,25] Regardless, debridement was the second most common major bone surgery performed in all patients with long bone shaft fractures in our study. Hull et al. studied nearly 500 patients with open extremity fractures, excluding open hand fractures, and found that timing of debridement does not correlate with the rate of deep infections in patients with Gustilo-Anderson grade I open fractures, but did increase the rate of deep infection in patients with grade II or III injuries.[26] However, a large systematic review of nearly 3600 open long bone fractures found no correlation with delayed operative debridement and rates of deep infection.[2] It is important to note that the "six-hour rule" was coined before the era of modern antibiotics, which may play a more important role than the timing of surgical intervention.

Aside from the timing, surgery itself may be a risk factor for the development of post-operative infection. Merritt et al. studied trauma patients with open fractures undergoing operative intervention with or without fixation devices.[8] Bacterial counts taken of debrided tissue in the beginning of the case did not significantly correlate with the development of post-operative infection while bacterial counts taken at the end of the case had a strong correlation. Furthermore, patients receiving external or internal fixation devices had a higher rate of post-operative infection compared to those with no implants. This may be due to concomitant soft tissue injury and colonization of implants. In contrast, Patzakis et al. studied over 1100 open extremity fractures and did not find a correlation between primary internal fixation and subsequent infection.[10] Our study suggests that the correlation between major bone surgery and infection in patients with long bone shaft fractures may be location specific. We did not find major bone surgery on the femur to increase risk of acute osteomyelitis but operating on the tibia/fibula or humerus did increase the risk by five-fold and three-fold, respectively. This may be a function of the increased soft tissue coverage preventing direct inoculation of the bone as well as the excellent blood supply to the shaft of the femur. Compared to the femur, the tibia/fibula does not have the extra layers of subcutaneous tissue and musculature protecting it from trauma, particularly on the anteromedial face, where open injuries are most

Table 5
Univariable analysis of risk factors for osteomyelitis in adult trauma patients.

Risk factor	OR	CI	p value
Closed femur shaft fracture	2.07	1.49–2.88	<0.001
Open femur shaft fracture	5.69	3.76–8.62	<0.001
Femur major surgery	2.27	1.88–2.75	<0.001
Closed tibia/fibula shaft fracture	3.59	2.74–4.70	<0.001
Open tibia/fibula shaft fracture	9.30	7.26–11.92	<0.001
Tibia/fibula major surgery	5.77	4.99–6.67	<0.001
Closed humerus shaft fracture	1.38	0.78–2.45	0.27
Open humerus shaft fracture	6.92	4.00–11.97	<0.001
Humerus major surgery	3.12	2.31–4.20	<0.001
Age ≥65	0.53	0.44–0.63	<0.001
Steroid use	1.19	0.44–3.17	0.73
Positive BAC on admission	1.26	1.03–1.53	<0.05
Positive illegal drug screen on admission	1.93	1.49–2.49	<0.001
Hypotension on admission	2.82	2.20–3.61	<0.001
Smoker	2.19	1.87–2.56	<0.001
Diabetes	2.45	2.08–2.88	<0.001
ESRD	3.17	2.03–4.94	<0.001
ISS≥25	3.46	2.90–4.14	<0.001
Blood transfusion	5.56	4.79–6.46	<0.001
Peripheral arterial disease	11.14	7.59–16.35	<0.001
Pseudomonas bacteremia	5.45	0.27–8.59	0.98
Non-*pseudomonas* bacteremia	41.85	28.49–61.48	<0.001

BAC = blood alcohol concentration, ESRD = end-stage renal disease, ISS = injury severity score.

Table 6
Multivariable analysis[a] for risk of osteomyelitis in adult trauma patients.

Risk factor	OR	CI	p value
Closed femur shaft fracture	0.82	0.43–1.58	0.55
Open femur shaft fracture	1.54	0.75–3.19	0.24
Femur major surgery	1.37	0.85–2.22	0.19
Closed tibia/fibula shaft fracture	1.28	0.79–2.07	0.32
Open tibia/fibula shaft fracture	1.21	0.71–2.04	0.49
Tibia/fibula major surgery	***5.31***	***3.81–7.41***	***<0.001***
Closed humerus shaft fracture	***0.18***	***0.04–0.79***	***<0.05***
Open humerus shaft fracture	2.03	0.83–4.97	0.12
Humerus major surgery	***2.74***	***1.57–4.77***	***<0.001***
Age ≥65	0.81	0.51–1.29	0.37
Steroid use	0.98	0.77–1.22	0.45
Positive BAC on admission	0.92	0.69–1.23	0.55
Positive illegal drug screen on admission	***1.57***	***1.20–2.08***	***<0.05***
Smoker	***1.94***	***1.44–2.62***	***<0.001***
Hypotension on admission	***2.08***	***1.37–3.14***	***<0.05***
Diabetes	***2.10***	***1.42–3.12***	***<0.001***
ESRD	***3.37***	***1.04–10.90***	***<0.05***
ISS≥25	***2.29***	***1.67–3.14***	***<0.001***
Blood transfusion	***3.74***	***2.74–5.10***	***<0.001***
Peripheral arterial disease	1.88	0.26–13.81	0.54
Pseudomonas bacteremia	*3.45*	*0.34–8.59*	*0.98*
Non-pseudomonas bacteremia	***9.30***	***3.74–23.10***	***<0.001***

BAC = blood alcohol concentration, ESRD = end-stage renal disease, ISS = injury severity score.
[a] = controlled for diabetes, peripheral arterial disease, steroid use, smoker, positive blood alcohol concentration on admission, positive illegal drug screen on admission, age ≥65, end-stage renal disease, blood transfusion, bacteremia, hypotension on admission, major bone surgery and injury severity score ≥25.

common. This may result in considerable associated internal soft tissue loss that may not be obvious on the initial survey. Early fixation of these injuries that appear relatively benign externally, may result in florid infection.[27] Additional prospective studies to confirm the association between location-specific long bone shaft fracture, as well as if the timing of intervention correlates with rates of postoperative acute osteomyelitis, is warranted.

Perioperative blood transfusion may be associated with a higher rate of post-operative infection. Pulido et al. demonstrated that allogenic blood transfusion is associated with more than a two-fold increased risk for periprosthetic joint infection in patients undergoing hip or knee arthroplasty.[28] This association was subsequently confirmed in a large meta-analysis of patients undergoing total joint arthroplasty.[29] We found perioperative blood transfusion to also be associated with increased risk of acute osteomyelitis in trauma patients. However, this may simply be a surrogate for severe injuries, surrounding soft tissue damage and perioperative hemodynamic instability, which may invalidate this finding. Future prospective studies examining the role that intraoperative hemodynamic instability and grade of the extremity fracture have in the development of post-traumatic osteomyelitis is warranted.

As a retrospective database study, our study has several limitations. All data fields in the NTDB are subject to input error. In addition, the difficulty in diagnosing osteomyelitis and the lack of a uniform definition for osteomyelitis used by all participating centers in the NTDB certainly introduced variability in reporting. Furthermore, the NTDB does not track patient outcomes after discharge. As osteomyelitis can develop over several days to weeks, some patients may have developed osteomyelitis after discharge, but were not included in the study. Fields relevant to our study that are missing in the NTDB include units of blood transfusion received, Gustilo-Anderson grade of open fractures, intraoperative hemodynamics, and tissue culture with quantification results. Additionally, many patients had unspecified bacteremia as the NTDB does not require documentation of the organism causing the infection. Thus, in our analysis of *pseudomonas* versus non-*pseudomonas* bacteremia, some cases of *pseudomonas* bacteremia may not have been reported as such and been included in the non-*pseudomonas* group.

5. Conclusion

In adult patients, long bone shaft fracture is not independently associated with increased risk for acute osteomyelitis. Major extremity surgery on the humerus and tibia/fibula, but not femur, are risk factors for osteomyelitis. Additionally, perioperative blood transfusion increases risk for acute osteomyelitis in trauma. However, the most significant risk factor for development of acute osteomyelitis is *non-pseudomonas* bacteremia.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcot.2019.04.003.

Appendix A. ICD-9 diagnosis codes for long bone shaft fractures

Femur	Tibia/fibula	Humerus
821–821.01 (closed)	823.2–823.22 (closed)	812.2–812.21 (closed)
821.1–821.11 (open)	823.3–823.32 (open)	812.3–812.31 (open)

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