Infection after penetrating brain injury—An Eastern Association for the Surgery of Trauma multicenter study oral presentation at the 32nd annual meeting of the Eastern Association for the Surgery of Trauma, January 15–19, 2019, in Austin, Texas

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BACKGROUND: Fatality rates following penetrating traumatic brain injury (pTBI) are extremely high and survivors are often left with significant disability. Infection following pTBI is associated with worse morbidity. The modern rates of central nervous system infections (INF) in civilian survivors are unknown. This study sought to determine the rate of and risk factors for INF following pTBI and to determine the impact of antibiotic prophylaxis.

METHODS: Seventeen institutions submitted adult patients with pTBI and survival of more than 72 hours from 2006 to 2016. Patients were stratified by the presence or absence of infection and the use or omission of prophylactic antibiotics. Study was powered at 85% to detect a difference in infection rate of 5%. Primary endpoint was the impact of prophylactic antibiotics on INF. Mantel-Haenszel χ^2 and Wilcoxon's rank-sum tests were used to compare categorical and nonparametric variables. Significance greater than $p = 0.2$ was included in a logistic regression adjusted for center.

RESULTS: Seven hundred sixty-three patients with pTBI were identified over 11 years. 7% (n = 51) of patients developed an INF. Sixty-six percent of INF patients received prophylactic antibiotics. Sixty-two percent of all patients received one dose or greater of prophylactic antibiotics and 50% of patients received extended antibiotics. Degree of dural penetration did not appear to impact the incidence of INF ($p = 0.8$) nor did trajectory through the oropharynx ($p = 0.18$). Controlling for other variables, there was no statistically significant difference in INF with the use of prophylactic antibiotics ($p = 0.5$). Infection was higher in patients with intracerebral pressure monitors (4% vs. 12%; $p = <0.001$) and in patients with surgical intervention (10% vs. 3%; $p < 0.001$).

CONCLUSION: There is no reduction in INF with prophylactic antibiotics in pTBI. Surgical intervention and invasive intracerebral pressure monitoring appear to be risk factors for INF regardless of prophylactic use. (*J Trauma Acute Care Surg.* 2019;87: 61–67. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic, level IV.

KEY WORDS: Penetrating brain injury; infection; antibiotics; intervention.

Over one million Americans are treated for traumatic brain injuries (TBI) annually. Traumatic brain injuries account for nearly 33% of injury-related deaths in the United States.[1,2] The incidence of penetrating TBI (pTBI) continues to rise and was associated with over 34,000 deaths in the United States in 2015[3–6] with mortality rates of pTBIs as high as 85%.[7]

The literature on pTBI has largely separated injury type into civilian and military settings.[8] Historically, military injuries have been associated with high-velocity ballistics as well as shrapnel injuries.[8] Mortality rates from pTBI in the military population are reported to range from 6.8% to 61.1%.[9–13] Civilian injuries were classically lower velocity injuries; however, the use of high-velocity weapons has significantly increased in recent years. Civilian mortality from pTBI ranges from 34% to 88.1%.[14]

The incidence of infection after penetrating brain injury, or penetrating brain injury infections (INF) has also been separated into injury type. In the military population, infection is reported to occur up to 25%,[9] and occurs anywhere from 8% to 23% in the civilian population.[14] INF is hypothesized to be a direct consequence of intracranial exposure to debris, projectile, hair, skin, or bone fragments[4,14] with the most common diagnosis being meningitis, ventriculitis, empyema, brain abscess, osteomyelitis, or superficial wound infections.[4,14]

Jimenez et al.[14] studied low velocity pTBI and the use of antibiotics. This study was limited to 160 patients, all of whom underwent operative intervention. Fifty-nine patients received prophylactic antibiotics while 101 patients did not. Patients had, on average, 3 months of follow-up. There was a 25% postoperative infection rate across the entire population with a 20% infection rate among patients who did not receive prophylactic antibiotics and a 33% infection rate in those who did receive antibiotics.[14] There was no statistical difference in infection rate in patients who received preoperative antibiotics and those who did not. In this study, risk factors for postoperative infection included trajectory through the oropharynx and retained intracranial fragments.[14]

The role of prophylactic antibiotics in pTBI has been strongly advocated, but there is no consensus on the efficacy.[8,15,16] The Working Party of British Society for Antimicrobial Chemotherapy recommends 5 days of antibiotic prophylaxis, but admits there is not sufficient evidence to support the recommendation.[8] The Brain Trauma Foundation does not make recommendations about antibiotic prophylaxis use in pTBI outside of the perioperative setting.[17]

The purpose of this study is to determine the incidence of infection after penetrating brain injury and to identify predictive factors for infection after penetrating brain injury. Our

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TABLE 1. Demographics of All Patients

N = 763	N	%
Age, y		
Range	(18–90)	
Mean	35	
Median	31	
ISS		
Range	(1–75)	
Mean	24	
Median	25	
Sex		
Female	115	15%
Male	648	85%
Race		
Asian	8	1%
Black	322	42%
Hispanic	38	5%
White	345	45%
Other	50	7%
Mechanism		
Gunshot wound	685	90%
Stab	47	6%
Other	31	4%
Degree of dural penetration		
Diffuse	455	60%
Local	309	40%
Trajectory through the oropharynx		
Yes	306	40%
No	457	60%
Retained foreign body		
Yes	479	63%
No	284	37%
Operative intervention*		
Yes	365	48%
No	396	52%
ICP monitor**		
Yes	223	29%
No	539	71%
Prophylactic antibiotics		
Yes	475	62%
No	287	38%
Any antibiotics during admission		
Duration of antibiotics		
None	272	36%
<24 h	107	14%
24–72 h	164	21%
3–7 d	141	19%
>7 d	78	10%
Infection		
Yes	51	7%
No	712	93%
LOS		
Range		
Mean		
Median		

*Craniotomy or craniectomy.
**Intraparenchymal or intraventricular.

hypothesis is that the use of prophylactic antibiotics does not impact the rate of infection.

METHODS

The Eastern Association of Surgeons Trauma Multicenter trial committee approved this study and participating centers were drawn from the membership of the Eastern Association of Surgery and Trauma. All participating centers obtained local Institutional Review Board (IRB) approval. This was a retrospective review of adult patients (age >17 years) with pTBI and survival longer than 72 hours, admitted between 2006 and 2016 from 17 trauma centers. All patients had to have evidence of dural penetration either confirmed by computed tomography scan or operative report. This study was not limited to isolated head trauma but included all patients with dural penetration irrespective of other organ system injury. Participating centers included: R Adams Cowley Shock Trauma Center, University of Maryland- Baltimore MD (Level 1), St Mary's Medical Center- West Palm Beach FL (Level 1), Carolinas Medical Center- Charlotte NC (ACS verified-Level 1), Rutgers, The State University of New Jersey- New Brunswick NJ (Level 1), Eastern Virginia Medical School- Norfolk VA (Level 1), Wright State Research Institute- Beaver Creek OH (Level 1), Allegheny General Hospital- Pittsburg PA (Level 1), Methodist Hospital- Dallas TX (ACS verified-Level 1), Cooper Health- Camden NJ (ACS verified- Level 1), Banner Health System- Phoenix AZ (ACS verified- Level 1), Indiana University School of Medicine- Indianapolis IN (ACS verified- Level 1), University of California Irvine- Irvine CA (ACS verified- Level 1), Loma Linda Medical Center- Loma Linda CA (ACS verified- Level 1), LA County Harbor-UCLA Medical Center- Los Angeles CA (ACS verified- Level 1), UC Health Northern Colorado- Loveland CO (ACS verified-Level 2), Medical City Plano Hospital- Plano TX (ACS verified-Level 1), University of Colorado Health- Colorado Springs CO (ACS verified-Level 1).

The primary endpoint was the incidence of central nervous system (CNS INF) infection after penetrating brain injury. The study was powered at 85% to detect a difference in infection rate of 5%. Patients were stratified on the presence or absence of infection and the use or omission of prophylactic antibiotics. Infection was defined by microbiology cultures, imaging and clinical presentation. Clinical diagnosis of CNS infection was based on clinical findings indicative of CNS infection. The CNS infections included cerebral abscess, empyema, meningitis or ventriculitis. Extracalvarial infections such as soft tissue cellulitis or abscess and sinusitis were not included.

Antibiotic type and duration were identified. Prophylactic antibiotics were defined as any antibiotics given within the first 24 hours of admission. Demographics, injury pattern, and outcomes pertaining to mortality and LOS were also obtained. Additional factors analyzed for their association with infection included retained foreign body, surgical intervention, intracerebral pressure (ICP) monitoring, natural orifice involvement and degree of penetration. Pearson's χ^2 and Wilcoxon rank-sum tests were used to compare categorical and nonparametric variables in bivariate analysis with infection rate. Ordinal data were analyzed using the Mantel-Haenszel χ^2 statistic. Statistical significance was indicated by a probability (p) value below

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TABLE 2. Bivariate Analysis of Factors Impacting Infection Rate After Penetrating Brain Injury

	CNS Infection	No CNS Infection	*p*
Sex			0.49
Male	45 (7%)	603 (93%)	
Female	6 (5%)	109 (95%)	
Race			0.8
Black	23 (45%)	299 (42%)	
White	23 (45%)	322 (45%)	
Other	5 (10%)	91 (13%)	
Age, y			0.79
18–30	24 (47%)	352 (55%)	
31–40	11 (22%)	143 (20%)	
41–50	9 (18%)	89 (13%)	
51–60	5 (10%)	70 (10%)	
61+	2 (3%)	58 (8%)	
Mechanism			0.35
Gunshot wound	47 (92%)	638 (90%)	
Stab	1 (2%)	46 (6%)	
Other	3 (6%)	28 (4%)	
ISS			0.38
≤ 8	1 (2%)	19 (3%)	
9–15	5 (10%)	96 (13%)	
16–24	20 (39%)	203 (29%)	
≥25	23 (45%)	379 (53%)	
Unknown	2 (4%)	15 (2%)	
Head AIS score			0.33
0–2	1 (2%)	35 (5%)	
≥ 3	50 (98%)	677 (95%)	
Face AIS score			0.80
0–2	42 (82%)	596 (84%)	
≥3	9 (18%)	116 (16%)	
Prophylactic antibiotics	34 (7%)	441 (93%)	0.50
No prophylactic antibiotics	17 (6%)	271 (94%)	
Duration of total antibiotics			0.37
≤24 h	13 (25%)	261 (37%)	
1–3 d	8 (16%)	98 (14%)	
3–5 d	10 (20%)	154 (22%)	
5–7 d	12 (24%)	129 (18%)	
>7 d	8 (16%)	70 (10%)	
Degree of dural penetration			0.10
Local	15 (5%)	293 (95%)	
Extensive	36 (8%)	419 (92%)	
Trajectory			0.18
Includes oropharynx	25 (8%)	281 (91%)	
Excludes oropharynx	26 (6%)	431 (94%)	
Retained foreign body	444 (93%)	35 (7%)	0.37
No retained foreign body	268 (95%)	16 (5%)	
ICP monitor*	27 (12%)	196 (88%)	<0.0001
No ICP monitor	24 (4%)	516 (96%)	
Operative intervention**	37 (10%)	328 (90%)	<0.0001
No operative intervention	13 (3%)	383 (97%)	

*Intraparenchymal or intraventricular.
**Craniotomy or craniectomy.
AIS, Abbreviated Injury Scale.

TABLE 3. Outcomes and Antibiotic Prophylaxis

	CNS Infection	No CNS Infection	*p*
Hospital LOS, d			<0.001
3	0 (0%)	100 (14%)	
>3–7	5 (10%)	225 (32%)	
8–15	5 (10%)	141 (20%)	
15+	41 (80%)	246 (35%)	
ICU LOS, d			<0.001
0	3 (6%)	116 (16%)	
<3	3 (6%)	108 (15%)	
3–7	9 (18%)	229 (32%)	
8–15	12 (24%)	142 (20%)	
15+	24 (47%)	117 (16%)	
Mortality			0.006
Yes	4 (8%)	537 (75%)	
No	47 (92%)	175 (25%)	

0.05. All variables with p values below 0.20 were included as covariates in a logistic regression model examining the association of prophylactic antibiotics with INF rate following adjustment by clinical center.

RESULTS

Over an 11-year period, from 2006 to 2016, 763 patients met inclusion criteria with penetrating brain injury and confirmed dural violation. Median Injury Severity Score (ISS) was 25. Eighty five percent of patients were male, with age ranging from 18 to 90 years; mean age, 35 years. Primary mechanism of injury was gunshot wound (90%); however, 6% of patients included had a knife stab wound to the head. Nail gun injuries, hammer injuries, arrow injuries were categorized as "other" and made up 4% of all injuries. Forty-eight percent (n = 365) of the patients underwent craniotomy or craniectomy. Sixty-two percent (n = 475) of patients received at least one dose of prophylactic antibiotics (Table 1). Extended penetration (greater than 1 cm of intrusion or involving multiple lobes) constituted 60% of the patients; the remaining patients sustained local dural penetration (classified as less than 1 cm of intrusion limited to one region). Twenty-nine percent of patients had intracranial pressure monitors. Fifty-one (7%) patients had a CNS infection after penetrating brain injury (INF).

When comparing patients who received prophylactic antibiotics and those who did not, there was no significant difference in the rate of secondary infection ($p = 0.50$, Table 2). Additional bivariate analyses indicated that degree of dural penetration ($p = 0.10$) and oropharyngeal trajectory did not impact infection

TABLE 4. Multivariable Analysis of the Factors Contributing to Secondary Infection After Penetrating Brain Injury

	Odds Ratio	CI	*p*
Prophylactic antibiotics	0.76	0.38–1.5	0.43
Institution	0.97	0.89–1.04	0.32
ICP monitor	2.27	1.18–4.4	0.01
Operative intervention	2.60	1.3–5.6	0.01

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TABLE 5. Assessment of Infection

N = 51		
Diagnosis		
Clinical*	13	25%
Culture**	38	75%
Culture data		
Monomicrobial	20	53%
Polymicrobial	8	21%
No growth	10	26%
Microbes		
Enterococcus	12	43%
Staphylococcus	15	54%
Klebsiella	2	7%
Eikenella	1	4%
Streptococcus	1	4%
Proteus	1	4%
Pseudomonas	1	4%
Cornybacterium	1	4%
Parasilosis	1	4%
Achromobacter	1	4%
Escherichia	1	4%
Diagnosis of infection		
1–4 d	4	8%
5–10 d	11	21%
>10 d	32	63%
Unknown	4	8%
Antibiotic choices		
Cefalosporin	29	57%
PCN	14	27%
Vancomycin	10	20%
Flagyl	6	12%

*Clinical diagnosis—based on imaging or clinical constellation of symptoms including meningitis, sinusitis, abscess formation.
**Culture data obtained from cerebrospinal fluid or wound.

rate ($p = 0.18$), nor did retained foreign body ($p = 0.18$). Operative intervention and ICP monitoring were each associated with infection rate ($p < 0.001$).

A multivariable logistic regression model was then constructed to investigate the adjusted effect of prophylactic antibiotic use on the outcome of infection. Adjustment was made by clinical center as well as the following variables having a p value below 0.20 in the bivariate analysis: dural penetration, oropharyngeal trajectory, operative intervention, and ICP monitoring. The adjusted analysis of prophylactic antibiotic use indicated that it did not impact the rate of secondary infection ($p = 0.83$; odds ratio [OR], 0.93; confidence interval [CI], 0.48–1.80). Overall infection rate was consistent across the 17 institutions ($p = 0.14$; OR, 0.95; CI, 0.89–1.02; Table 3). Significantly increased rates of infection were also found in those undergoing operative intervention and ICP monitor placement. Results did not change following removal of the covariate for clinical center.

Data on several outcome measures were also collected to determine their association with infection rate. Mortality was 8% in the INF population and 75% in the non-INF population ($p = 0.06$). This suggests that overall mortality is more likely a result of brain injury or other associated traumatic injuries rather than infection. Patients with INF cohort had significantly longer hospitalization ($p = 0.001$ for both hospital and ICU length of stay (LOS); Table 4).

Microbes and Antibiotic Choices

In evaluating the 51 patients with INF, the diagnosis of infection was made 74% of the time based on culture data (Table 5). Cultures were obtained either from cerebrospinal fluid or tissue. In 26% of cases, clinical diagnosis was not supported by positive culture data, but rather other clinical findings. These findings included new neurological examination findings consistent with meningitis or ventriculitis, persistent fevers, or leukocytosis without other source, purulent drainage from wounds, CSF fluid laboratories suggestive of infection (e.g., high WBC count with low glucose and high protein levels), and computed tomography or magnetic resonance imaging (e.g., rim enhancing lesion suggestive of abscess or increasing pneumocephalus). Many of these patients with no growth from CNS cultures also had antibiotics initiated prior to obtaining culture data, lowering the sensitivity of the cultures. Of the 74% of patients with infection and culture data available, 53% of infections were monomicrobial while 21% were polymicrobial. Twenty-six percent of all cultures obtained had no growth; however, patients had corresponding clinical symptoms to confirm diagnosis of infection.

Most common microbes were Staphylococcus and Enterococcus. Diagnosis of INF most commonly occurred greater than 10 days after injury (63%). Antibiotic utilization varied widely among institution, though cephalosporins appeared to be the most widely utilized agent.

DISCUSSION

Early reports of infection following penetrating brain injury date back to the preantibiotic with infection rate reported to be as high as 58%.[15] Studies looking at infection after penetrating brain injury in the military population showing rates of infection ranging from 6.8% to 61.1%.[10–13] Military morbidities are often associated with longer transport times, time in field, and delay to definitive debridement.[8] Historically, higher-velocity injuries have also been associated with military combat injuries; however, in recent years, there have been an increase in civilian high-velocity penetrating brain injuries.[8] Jimenez at al.[14] cited a 25% infection rate in civilian penetrating gunshot wounds. In Jimenez et al., all patients underwent operative intervention and antibiotic administration was variable.

Our study is the first attempt at a national multi-institutional review of civilian patients with penetrating brain injury. We were very deliberate to only include patients with confirmation of dural penetration to determine if antibiotic prophylaxis impacted infection rate. The study cohort included patients managed both operatively and nonoperatively, those with and without invasive pressure monitors, and those with and without retained fragments. The rate of infection after penetrating brain injury was 7% and antibiotic prophylaxis use had no effect on infection rate when evaluated in both bivariate and multivariable analyses. This would suggest that administration of antibiotics for dural penetration alone does not reduce secondary infection rate.

Patients who underwent operative intervention or had indwelling ICP monitoring did have higher rate of secondary CNS

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infections when compared with those who did not. This remained significant when controlled for other variables. There is extensive literature surrounding the reduction of infection rates in patients with external ventricular drains, including approaches with prolonged prophylactic antibiotics and antibiotic coated ICP monitors. The IDSA guidelines recommend systemic prophylactic antibiotics for up to 24 hours for surgical intervention and ICP monitor placement, but do not specifically address patients with penetrating brain injury in patients undergoing nonoperative management.[18]

Historically it was thought that retained foreign body increased infection rate, however it is now widely accepted that attempted removal of deep fragments cause more tissue damage and the risk far outweighs the benefit.[19] It has become practice to then use antibiotic prophylaxis empirically in patients with retained foreign bodies, though Byrnes et al.[20] published a series with over half of their patients having retained foreign bodies with no subsequent infections.[8,21] This was redemonstrated in Clark et al.[21] with a 3% postinjury infection rate in patients with retained foreign bodies. In all of these cases,[20,21] the primary mechanism of injury was ballistic wound to the head. In our study, there was a small number of patients with stab wounds to the head, hammer or blunt object penetration. Although there did not appear to be a correlation between mechanism and infection, the nonballistic injuries constituted only 10% of the population. Our study showed no association between retained foreign body and infection rate.

The current study has several strengths, including its multicenter nature and the large number of patients screened with penetrating brain injuries. However, our methodology is not without limitations. This is a retrospective review of outcomes for patients with penetrating brain injury. Clinical practice was widely variable among institutions, ranging from no prophylaxis, single-dose prophylaxis and multiple days of antibiotic prophylaxis. Culture practices and diagnosis of infection were also dependent on the individual physician clinical diagnosis at each institution. Additionally, 63% of all CNS INF were diagnosed at greater than 10 days while all-cause mortality was greater than 70%. This begs the question, did patients have long enough survival to acquire a secondary infection. Institutional approach to transtentorial gunshot wounds may also very with some groups being more aggressive with surgical intervention while others consider this a terminal event at the onset. This variation in practice may have impacted inclusion or exclusion of this patient population depending on the centers practice. However we attempted to address this patient population in the exclusion criteria with the assumption that nonsalvagable transtentorial GSW would likely not have survival of a minimum of 72 hours. If patients did have survival more than 72 hours, they would be treated as the general population.

CONCLUSION

The modern rate of infection after penetrating brain injury is 7%. There is no reduction in infection with use of prophylactic antibiotics in penetrating brain injuries not undergoing operative intervention. Surgical intervention and invasive ICP monitoring appear to be risk factors for infection regardless of prophylactic antibiotic use.

AUTHORSHIP

L.A.H., D.J.H., D.M.S. participated in the study conception and design. L.A.H., J.A.K., D.J.H., S.M.A., D.C., L.L., K.W.C., S.B., J.B., J.L.R., G.S., M.R.N., B.N.C., V.A., M.T., J.M., A.G., M.B., N.K., P.M.H., J.T.N., A.G., D.T., V.C., P.L., D.K., T.C., J.D., V.P., T.S. participated in the data collection. L.A.H., J.A.K., D.J.H. participated in the data analysis. L.A.H., D.A.H., J.A.K. participated in the interpretation of data. L.A.H., J.A.K., D.J.H., S.M.A., D.C., L.L., K.W.C., S.B., J.B., J.L.R., G.S., M.R.N., B.N.C., V.A., M.T., J.M., A.G., M.B., N.K., P.M.H., J.T.N., A.G., D.T., V.C., P.L., D.K., T.C., J.D., V.P., T.S., D.M.S. participated in the drafting of article and critical revision.

DISCLOSURE

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EDITORIAL CRITIQUE

The most consistently lethal form of traumatic brain injury (TBI) is from a penetrating mechanism. Often, the penetrating TBI is related to firearms, as was seen in this multicenter pooled data. Not everyone who reaches a trauma center will undergo a neurosurgical procedure, but this work identifies intracranial interventions as the risk factors for infection. Also, a striking epidemiological feature of this work is that less than one in ten patients is afflicted with infection after penetrating TBI. Via this research, the role of prophylactic antibiotics after penetrating TBI remains unclear but perhaps does not influence intracranial infection. Across societal recommendations, there appears to be a broad range of recommendations on prophylactic antibiotics after penetrating TBI, leaving our interdisciplinary neurotrauma teams without clear clinical directions. Given the unfortunate incidence of penetrating TBI in the US, further studying and defining the role (if any) of prophylactic antibiotics could improve the quality of our neurotrauma care.

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