Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

HHS Public Access
Author manuscript
*J Trauma Acute Care Surg*. Author manuscript; available in PMC 2021 April 01.

Published in final edited form as:
*J Trauma Acute Care Surg*. 2020 April ; 88(4): 491–500. doi:10.1097/TA.0000000000002562.

# Effects of Hospital-Acquired Pneumonia on Long-Term Recovery and Hospital Resource Utilization Following Moderate to Severe Traumatic Brain Injury

**Raj G. Kumar, PhD MPH**[1,2], **Matthew R. Kesinger, MS**[2,3], **Shannon B. Juengst, PhD**[4,5], **Maria M. Brooks, PhD**[1], **Anthony Fabio, PhD**[1], **Kristen Dams-O'Connor, PhD**[6,7], **Mary Jo Pugh, PhD**[8], **Jason Sperry, MD MPH**[3], **Amy K. Wagner, MD**[2,9,10,*]

[1]Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA

[2]Department of Physical Medicine and Rehabilitation, University of Pittsburgh, Pittsburgh, PA

[3]Department of Surgery, University of Pittsburgh, Pittsburgh, PA

[4]Department of Physical Medicine and Rehabilitation, UT Southwestern, Dallas, TX

[5]Department of Rehabilitation Counseling, UT Southwestern, Dallas, TX

[6]Department of Rehabilitation Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

[7]Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY

[8]Department of Internal Medicine Epidemiology Division, University of Utah, Salt Lake City, UT

[9]Center for Neuroscience, University of Pittsburgh, Pittsburgh, PA

[10]Safar Center for Resuscitation Research, University of Pittsburgh, Pittsburgh, PA

## Abstract

**Background:** Individuals with Traumatic Brain Injury (TBI) have extended inpatient hospital stays that includes prolonged mechanical ventilation, increasing risk for infections, including pneumonia. Studies show the negative short-term effects of hospital-acquired pneumonia (HAP) on hospital-based outcomes; however, little is known of its long-term effects.

**Methods:** Prospective cohort study. National Trauma Databank (NTDB) and Traumatic Brain Injury Model Systems (TBI-MS) were merged to derive a cohort of n=3717 adults with moderate-to-severe TBI. Exposure data were gathered from the NTDB, and outcomes were gathered from

*Corresponding Author: Amy K. Wagner, MD, Professor of Physical Medicine and Rehabilitation and Neuroscience, University of Pittsburgh, 3471 Fifth Ave, Suite 202, Pittsburgh, PA, USA 15213, T: 412-648-6666, F: 412-692-4354, wagnerak@upmc.edu.
**Author Contributions:** Dr. Raj Kumar was involved in conceptualizing study design, creating the merged data set, data analysis, interpretation, and writing; Mr. Matthew Kesinger was involved with conceptualizing study design, creating the merged data set, data interpretation, and critical revision; Dr. Shannon Juengst was involved with data interpretation, writing, and critical revisions; Dr. Anthony Fabio and Dr. Kristen Dams-O'Connor were involved with data interpretation and critical revisions; Dr. Mary Jo-Pugh was involved in data interpretations and critical revisions; Dr. Jason Sperry was involved in conceptualizing study design, data interpretation, writing, and critical revision; Dr. Maria Brooks is a senior statistician that reviewed all of the statistics conducted in the study, and ran the power analysis; Dr. Amy Wagner was involved in conceptualizing study design, data interpretation, writing, and critical revision.

Level III Evidence

There are no conflicts of interest for any authors to report.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

the TBI-MS. The primary outcome was the Glasgow Outcome Scale-Extended (GOS-E), which was collected at 1, 2 and 5 years post-injury. GOS-E was categorized as favorable (>5) or unfavorable (≤5) outcomes. A generalized estimating equation model was fitted estimating the effects of HAP on GOS-E over the first five years post-TBI, adjusting for age, race, ventilation status, brain injury severity, injury severity score (ISS), thoracic Abbreviated Injury Scale score ≥3, mechanism of injury, intraventricular hemorrhage, and subarachnoid hemorrhage.

**Results:** Individuals with HAP had a 34% (OR=1.34, 95% CI 1.15, 1.56) increased odds for unfavorable GOS-E over the first five years post-TBI compared to individuals without HAP, after adjustment for covariates. There was a significant interaction between HAP and follow-up, such that the effect of HAP on GOS-E declined over time. Sensitivity analyses that weighted for non-response bias and adjusted for differences across trauma facilities did not appreciably change the results. Individuals with HAP spent 10.1 days longer in acute care and 4.8 days longer in inpatient rehabilitation, and had less efficient functional improvement during inpatient rehabilitation.

**Conclusions:** Individuals with HAP during acute hospitalization have worse long-term prognosis and greater hospital utilization. Preventing HAP may be cost-effective and improve long-term recovery for individuals with TBI. Future studies should compare the effectiveness of different prophylaxis methods to prevent HAP.

### Keywords

Traumatic Brain Injury; Health Services; Hospital-acquired Pneumonia; Rehabilitation; Long-term outcomes

## Background:

An estimated 2.5 million Americans annually have an emergency department visit, are hospitalized with, or die due to traumatic brain injury (TBI).[1] Nearly half of patients hospitalized with TBI experience long-term morbidity, contributing to a large proportion of US citizens living with chronic disability from TBI.[2] To prevent the high disability burden and associated costs, TBI researchers have focused on identifying acute predictors of long-term disability, including injury severity based on the Glasgow Coma Scale (GCS),[3-5] systemic hypotension,[6] intracranial pressure,[7] and post-traumatic hydrocephalus[8,9] among others.

An underemphasized area of TBI research is the contribution of acute non-neurological complications and conditions to long-term recovery. Many patients with moderate-to-severe TBI require mechanical ventilation in the days following their injuries and are susceptible to infection. A common result of mechanical ventilation and susceptibility to infection is hospital-acquired pneumonia (HAP). In observational studies, HAP incidence rates range from 30–61% in TBI populations.[10-12] Variation in incidence estimates arise from heterogeneous, single-center cohorts, including cohorts restricted to only ventilated patients. Ventilation is an important predictor for incident HAP following TBI, with each additional ventilator day conferring a 7% increased risk for infection.[13] Other variables associated with HAP incidence post-TBI include thoracic Abbreviated Injury Scale (AIS) score ≥3 and gastric aspiration.[12] Some individuals with TBI also experience a period of acute

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

lymphocyte dysfunction following injury, known as lymphopenia,[14] resulting in suppressed immunity and a decreased capacity to fight acquired infections, like pneumonia.[14-19]

HAP development leads to direct increases in healthcare utilization and expenditures. Critically ill patients with HAP accrue roughly $40,000 more in acute hospitalization costs, and require approximately twice the intensive care unit and hospital lengths of stay (LOS) compared to critically ill patients without HAP.[10,20] One study evaluating acquired brain injury patients determined that individuals with ventilator-associated pneumonia (VAP) had higher hospital costs, longer LOS, and more readmissions compared to individuals without VAP matched on age, sex, diagnosis, date of admission, and hospital size.[21]

Past TBI studies characterizing HAP have examined short-term associations of HAP with greater cost and worse acute hospital outcomes.[10,13,22,23] A research gap exists in understanding the long-term associations with HAP in this population. Two recent small studies lend preliminary evidence that HAP may negatively impact long-term outcomes following injury.[11,24] To build upon these studies, a large multi-site longitudinal prospective study is necessary to estimate the long-term effects of HAP on disability and hospital resource utilization post-TBI. As an initial step, we leveraged a large probabilistically-merged database of the National Trauma Databank (NTDB) and TBI Model Systems (TBI-MS) National Database. Study objectives included: 1) determining the long-term effects of HAP on disability after moderate-to-severe TBI; and 2) comparing hospital resource utilization metrics between individuals with moderate-to-severe TBI, with/without HAP. We hypothesized that individuals with HAP have significantly poorer long-term outcomes over time, and have longer LOS during acute and rehabilitation inpatient care.

## Methods:

All TBI Model Systems centers represented in this study had approved local Institutional Review Board protocols. Individuals (or their proxies when appropriate) signed informed consent to participate in data collection from the acute and rehabilitation phases of care as well as longitudinal follow-up with the general goal to learn more about TBI outcomes. We used data from two large databases: the NTDB and the TBI-MS National Database. The NTDB is the largest aggregation of trauma registry data in the United States. Participating hospitals contribute information on all trauma patients treated at their institution. Deidentified data are submitted to the NTDB and compiled for hospital benchmarking, data quality reports, and addressing trauma-related research questions. The TBI-MS is a prospective cohort study that includes data collected at up to 20 acute rehabilitation centers. Included patients received acute care within 72 hours of injury at a designated acute care hospital, survived through acute care, and were stable medically to receive rehabilitation. Other TBI-MS inclusion criteria include: a moderate-to-severe TBI (defined by at least one of the following: post-traumatic amnesia>24 hours, trauma-related intracranial neuroimaging abnormalities, loss of consciousness exceeding 30 minutes, or a GCS<13), age 16+ years at time of injury, and presentation to a TBI-MS acute care hospital within 72 hours of injury.[25] Data are collected at enrollment and follow-up interviews occur years 1, 2, and 5, as well as every 5 years afterward until death.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

We used a probabilistic matching algorithm to combine the de-identified NTDB and TBI-MS. The merger of the two databases was possible because participants in the TBI-MS had a trauma record submitted to the NTDB. We developed the algorithm in two sites where exact matches on patient identifiers were available to form a deterministic dataset to quantitatively assess the sensitivity and positive predictive value of our algorithm. We previously published detailed methods used for algorithm development[26] and validation.[27] The final NTDB-TBI-MS cohort contained n=4022 individuals with TBI, injured between 1998–2015. The present study included individuals the TBI-MS National Database, who also were probabilistically merged with NTDB records to derive the current cohort. We further restricted our cohort to participants injured between 1998–2013 to examine five-year outcomes (n=3712). A flow diagram of participant inclusion to the final analytic cohort is shown in Figure 1. There were 21 NTDB trauma facilities across 17 TBI-MS centers represented in the present dataset.

The specific variables used in this study from the NTDB and TBI-MS, along with a detailed description of each variable, are provided in Table 1. The primary exposure was HAP; specifically, cases developed during the acute hospitalization. Individuals were considered to have HAP from either NTDB complication codes or diagnoses codes collected as a part of the TBI-MS. The primary outcome was Glasgow Outcome Scale-Extended (GOS-E) score[28], assessed at 1, 2, and 5 years post-injury. For the purposes of this analysis and direct comparison with prior studies, scores were dichotomized ≤5 (unfavorable outcomes) vs. >5 (favorable outcomes), as reported previously.[11] Secondary descriptive analyses were conducted to examine associations between HAP and variables related to hospital resource utilization: acute care LOS, rehabilitation LOS, and change in Functional Independence Measure (FIM) scores over time (FIM efficiency). FIM efficiency is the change in FIM score during rehabilitation divided by the rehabilitation LOS. For post-hoc analyses, complications other than HAP were extracted from the NTDB complications code to calculate a non-HAP complication burden score.

Though probabilistic matching is common in birth cohorts and life-course studies,[29] its use in merging databases in trauma, surgery, and rehabilitation is novel. To evaluate the integrity of this approach for our purposes, we developed a deterministic cohort from two TBI-MS sites to conduct a post-hoc sensitivity analysis as an internal validation measure to examine the veracity of our primary findings from the probabilistically-derived cohort. This deterministic cohort included n=775 individuals with TBI injured between 2002–2013.

## Statistical Analysis:

Demographic and clinical variables were compared by HAP status and GOS-E. Means and standard errors described continuous variables, and frequency and percentages described categorical variables. Chi-square tests compared categorical variables, and t-tests or Mann Whitney U test, were used to compare continuous variables by HAP status and GOS-E score.

A generalized estimating equation (GEE) model was used for the primary analysis assessing the relationship between HAP and 1, 2 and 5-year GOS-E. GEE models were fit using an unstructured correlation structure, binomial distribution, and logit link. We chose covariates

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

that were associated with HAP and 1-year GOS-E at an $\alpha$=0.20 level. Covariates included: age, race, ventilation status, brain injury severity, injury severity score (ISS), thoracic AIS ≥3, mechanism of injury, intraventricular hemorrhage status, and subarachnoid hemorrhage status. We adjusted for race in our analysis because of its documented associations with unfavorable outcomes in the literature[30] and in our study. The same covariates were included in the primary, secondary, and sensitivity analyses. To observe covariate effects on HAP associations with GOS-E, four models are presented: Model 1 (unadjusted), Model 2 (adjusts for age effects), Model 3 (adjusts for age and race only), and Model 4 (fully adjusted for all chosen demographic and clinical variables). A HAP*follow-up interaction was also tested in the primary cohort to test if the effect of HAP on GOS-E varies across follow-up period (1, 2, and 5 years). Primary results are reported with moderate and severe injury groups combined, and a HAP*injury severity interaction was tested.

Given our fixed sample size, an alpha=0.05, 1/3 rate of HAP, and 50% of non-HAP patients having unfavorable outcomes, we have 80% power to detect an OR of 1.24 for the unadjusted analyses. For multivariable analyses, if we assume the fully-adjusted covariate model explains as much as 50% of the variability in HAP occurrence we will still have 80% power to detect an OR of 1.35. Of note, power analyses were based on a logistic regression model, but we believe our sample size is sufficiently powered for a GEE model, which considers multivariable effects on binary outcomes over time.

In order to determine HAP effects on hospital resource utilization, analysis of covariance (ANCOVA) models were used to compute covariate-adjusted mean scores for acute LOS, rehabilitation LOS, and FIM efficiency by HAP status. SAS 9.4 was used for all statistical analysis (Cary, NC).[31]

A post-hoc analysis was tested using a HAP-associated complication score developed for this report. The score represents hospital complications that are significant associated with both HAP and GOS-E at 1 year. The percentage change in the beta of the HAP variable was noted before/after inclusion of the complication score to determine if this score confounded the relationship between HAP and GOS-E. We also assessed the post-hoc association between tracheostomy status, time to tracheostomy placement, and HAP status, as one potential modifiable procedure that could influence HAP risk. Specifically, we examined whether time to tracheostomy was associated with acute care LOS and FIM efficiency among HAP patients who were ventilated. We conducted a post-hoc analysis where we adjusted the primary model for trauma facility to assess whether the primary association was confounded by acute care trauma hospital. Finally, to address potential nonresponse selection bias, we weighted the primary model for factors associated with nonresponse for GOS-E measured at year 1, 2, and 5 years using inverse probability weighting methods,[32] such that the IPW-model was based on a pseudo-population balanced on factors associated with follow-up at each timepoint.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

## Results:

### Demographic and Clinical Variables by HAP Status:

The cohort included n=1212 (32.7%) individuals with HAP and n=2500 (67.3%) individuals without HAP. The demographic and clinical variables by HAP status are presented in Table 2. Individuals with HAP were more likely to be younger men when compared to individuals without HAP (p<0.001 both comparisons). ISS score and non-head ISS were significantly higher among individuals with HAP (p<0.001 both comparisons). A greater proportion of individuals with HAP had a thoracic AIS score ≥3, were more frequently on a ventilator, spent more days on a ventilator, and had longer acute and rehabilitation LOS compared to individuals without HAP (p<0.001 all comparisons). A greater proportion of individuals with HAP had an interruption during rehabilitation (p=0.027). A greater proportion of individuals with HAP had an intraventricular hemorrhage (IVH) and subarachnoid hemorrhage (SAH) compared to no HAP (p<0.01 both comparisons). Injury mechanism also varied by HAP status (p<0.001), with a greater proportion of MVC and a lower proportion of falls in the HAP group.

### Demographic and Clinical Variables by GOS-E at 1 year:

Demographic and clinical variables by unfavorable/favorable 1-year GOS-E status are presented in Table 3. There were 1491 (47.5%) individuals with unfavorable GOS-E scores and n=1651 (52.5%) individuals with favorable GOS-E scores. There were significant differences in GOS-E by race and payor status and mechanism of injury (p<0.001 all comparisons). Individuals with unfavorable GOS-E scores were older, more often on a ventilator, had more ventilator days, longer acute care and rehabilitation LOS, and a greater proportion of interruptions in rehabilitation care compared to individuals with favorable GOS-E scores (p<0.001 all comparisons). Individuals with unfavorable outcomes more often experienced SDH, IVH, and SAH injuries (p<0.01 all comparisons).

### Primary analysis: GEE Model of GOS-E at 1, 2, and 5 years post-TBI using NTDB probabilistic cohort

The GEE models for the GOS-E primary analysis are provided in Table 4. In the unadjusted model, individuals with HAP had a 28% increased odds for unfavorable GOS-E scores compared to individuals without HAP (OR=1.28, 95% CI (1.14, 1.45), p<0.001). After adjustment for age only, individuals with HAP had a 48% increased odds for unfavorable GOS-E scores compared to individuals without HAP (OR=1.48, 95% CI (1.29, 1.69), p<0.001). After adding race, individuals with HAP had a 51% increased odds for unfavorable GOS-E scores compared to individuals without HAP (OR=1.51, 95% CI (1.32, 1.73), p<0.001). In the fully adjusted model, individuals with HAP had a 34% increased odds for unfavorable GOS-E scores compared to individuals without HAP (OR=1.34, 95% CI (1.15, 1.56), p<0.001). The interaction between HAP and follow-up period on GOS-E over time was significant (p=0.018), indicating that the effect of HAP on GOS-E tends to decrease each follow-up period over the first five years post-injury. The interaction term between HAP*injury severity was tested, but was not significant (p=0.728); therefore, the interaction term was dropped from the model. The estimates for the full model and all covariates are provided in Supplemental Table 1.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

### Sensitivity analysis: GEE Model of GOS-E at 1, 2, and 5 years post-TBI using Deterministic cohort

Using only the deterministic cohort, the unadjusted analysis showed individuals with HAP were at a 44% increased odds for unfavorable GOS-E scores compared to individuals without HAP (OR=1.44, 95% CI (1.05, 1.98), p=0.022) (Table 5). After adjusting for age, individuals with HAP had a 69% increased odds for unfavorable GOS-E (OR=1.69, 95% CI (1.22, 1.34), p=0.002). After adding race, individuals with HAP had a 72% increased odds for unfavorable GOS-E (OR=1.72, 95% CI (1.23, 2.39), p=0.001). In the full adjusted model, individuals with HAP had a 63% increased odds for unfavorable GOS-E compared with individuals without HAP (OR=1.63, 95% CI (1.16, 2.30), p=0.005).

### Secondary analysis: Hospital utilization variables by HAP status

After covariate adjustment, individuals with HAP, had on average 10.1 more days in acute care LOS and 4.8 more days in rehabilitation LOS (p<0.001 both comparisons), which negatively impacted FIM efficiency for those with HAP. The unadjusted FIM efficiency for individuals with HAP was 2.02 compared to 2.31 for individuals without HAP. After adjustment for covariates, individuals with HAP, had 0.29 reduced FIM efficiency during rehabilitation (p<0.001).

### Post-hoc Analyses:

As a post-hoc analysis, a HAP-associated complication score was added as a covariate in the primary model, and the beta estimate for the HAP variable did not significantly change (% change $\beta_{HAP}$=1.028%); therefore, this burden score was dropped as a covariate. We also descriptively observed a 44.7% rate of tracheostomy in the HAP group and 27.9% in the no HAP group ($\chi^2$=84.8, p=<0.001). When examining timing of tracheostomy placement, time to tracheostomy was not associated with HAP. Among individuals with HAP, greater time to tracheostomy placement was associated with a longer acute care LOS, but not associated with FIM efficiency. The association between HAP and outcome remained significant after adjustment for trauma facility (aOR=1.45; 95% CI: 1.24, 1.70, p<0.001). Finally, there were n=563 with missing follow-up data at year 1, n=626 with missing follow-up data at year 2, and n=733 with missing follow-up at year 5. Demographic and injury characteristics associated with loss to follow-up are provided in Supplemental Tables 2-4. When we applied the IPW to the primary model (Supplemental Tables 5), the relationship between HAP and GOS-E did not appreciably change (aOR=1.34, 95% CI: 1.14, 1.57).

## Discussion:

Our findings highlight HAP as a potential early modifiable risk factor impacting TBI recovery and hospital resource utilization. We observed a HAP incidence rate of 32.7%, which is similar to past estimates.[11] The present study provides evidence that HAP effects may extend beyond the infection period itself and persist for years post-injury, perhaps through the propagation of a chronic inflammatory milieu[33] and decreased or delayed rehabilitation gains. In addition to poorer long-term prognosis, individuals with HAP had longer LOS and decreased efficiency in attaining functional rehabilitation gains compared to those without HAP.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Recent work by Esnault[12] examined the effects of early-onset VAP among 175 individuals with severe TBI and observed an elevated odds (OR=2.71, 95% CI: 1.01–7.25) for more unfavorable GOS scores at 1-year. Similarly, a small pilot study (n=141) led by our research group[11] used a similar design as the present study. To avoid duplicity in reporting, no individuals in our prior study were included in our present analysis. We previously showed HAP carried a 4.6 times (95% CI: 1.80–11.60) increased odds for unfavorable outcomes in a longitudinal model.[11] The small sample size and single-site design by Esnault et al.[12] and Kesinger et al.[11] likely account for the inflated effect sizes and wide confidence intervals compared to the present larger study. Importantly, we also observed that HAP effects attenuate modestly (~5%) over the 5-year time period. Additionally, we observed that HAP effects were similar when GOS-E was analyzed as a multinomial variable (data not shown).

Previously, Zygun[10] showed a VAP incidence rate of 45% among 134 individuals with severe TBI, which the authors report is nearly three times the rate reported for all general trauma patients, according to the National Nosocomial Infections Surveillance program report.[34] This observation supports the possibility that individuals with severe TBI may be particularly vulnerable to hospital infections. Some individuals with TBI experience a period of lymphopenia beginning early post-injury.[14] Persistent lymphopenia, which has been documented in trauma populations[15-19] and shown with preliminary observations in TBI populations,[14] may reflect a decreased capacity to fight exposure to pathogens. Clinical and injury factors, like prolonged mechanical ventilation, concurrent polytrauma and specifically thoracic injuries, and pulmonary aspiration also are HAP risk factors. More severely injured patients are at greater risk for developing both HAP and poor outcomes. HAP was associated with GOS-E in unadjusted models indicating that it is a strong marker for poor outcomes. Moreover, adjustment for several potential confounders, including injury severity, extra-cerebral injury severity, and mechanism of injury, shows that the harmful effects of HAP on GOS-E are still evident after adjusting for standard risk covariates. In addition, our post-hoc analysis adjusting for the HAP-associated complication score, provided some evidence that HAP remains significant to long-term outcomes even after adjusted for other hospital complications. However, we cannot rule out other unmeasured confounders that could impact the effect of HAP on GOS-E.

In our study, we documented a modest negative confounding of the effect of HAP on outcome driven by age. Younger age was associated with a greater incidence of HAP, but is protective against unfavorable outcomes post-TBI. Though this association may seem counterintuitive, the negative association between age and HAP has been previously documented in the TBI-MS[35] and aligns with the mechanism of injuries experienced by older vs. younger individuals. Recent epidemiological data have observed that older individuals more often sustain isolated brain injuries from falls,[36] whereas, younger individuals are more likely to suffer polytrauma injuries resulting from motor vehicle accidents.[36] These findings highlight that HAP prevention efforts should be directed across the age span, particularly among younger ages, where HAP is more common. Though, it is important to consider that because the present cohort is restricted to those individuals with TBI who survived their initial injury and also received inpatient rehabilitation, the observed negative relationship between age and HAP may be subject to some survival selection bias. Specifically, older individuals, particularly those with pre-injury anticoagulation, are more

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

likely to die from their injuries compared to those with similar age/injury type who are not on anticoagulants.[37-40]

HAP occurrence after TBI has significant implications for hospital resource utilization. Our results showed that individuals with HAP had longer acute and rehabilitation LOS compared to individuals without HAP. This may not be a causal relationship between HAP and LOS. Rather, there may be a bidirectional relationship between LOS and HAP wherein individuals with longer hospitalizations more often develop HAP, and HAP leads to longer LOS. Future studies should prospectively and systematically collect time of infection to better understand how a longer LOS influences HAP risk. We also determined that HAP is associated with rehabilitation interruptions. Also, individuals with HAP had decreased FIM efficiency by a factor of 0.29. In other words, patients with HAP require roughly 30% more days in rehabilitation to achieve similar functional gains as patients without HAP. This finding suggests that preventing HAP after TBI may yield substantial cost-related benefits.[41]

This study highlights the potential importance of infection prophylaxis in TBI populations; HAP is extremely common and often preventable. Given the high morbidity and mortality associated with TBI across the lifespan, identifying potentially modifiable factors that can result in improved outcomes cannot be underemphasized. The recent 2016 4$^{th}$ edition Guidelines for the Management of Severe Traumatic Brain Injury[42] recommends Level IIA evidence for early tracheostomy as a method for infection prophylaxis. In our study we observed a strong association between tracheostomy and HAP, however, did not observe an association between time to tracheostomy with HAP incidence in our cohort. Others have also suggested early extubation is important.[43] A potentially cost-effective intervention is early mobility protocols during acute care, for those who are able, which has been shown to be efficacious in reducing incidence of HAP in neurointensive care unit patients through the increased clearance of secretions.[44] Work by Mendez-Tellez and Needham[45] shows that physical rehabilitation for ventilated patients in particular has positive impact on ICU-acquired complications and functional status at hospital discharge.Another study in an acute stroke population found that early dysphagia screening and treatment was associated with decreased HAP rates.[46] Another study found an association between no functional oral intake and HAP incidence after TBI.[47] Chlorhexidine oral disinfectants have also been documented as effective for HAP prophylaxis.[48] Additionally, targeted temperature management and conjugate short-term antibiotic therapy showed some evidence for prevention of HAP in populations with cardiac arrest,[49] but needs to be evaluated further in TBI populations.

HAP presents a significant public health problem in TBI populations. Despite some promising interventions that have shown efficacy, there may be issues with clinical implementation such as non-compliance, non-modifiable patient factors, and insufficient institutional priorities placed on pneumonia prevention. Future TBI studies would benefit from conducting pragmatic trials for HAP prevention in real-world settings.

There are limitations of this work that warrant consideration. We assessed HAP instead of VAP because there was no clear information on time until infection in the NTDB. Despite this, our results indicate that HAP is a significant predictor of GOS-E, despite adjusting for

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

ventilation status and other factors shown to contribute to both HAP and GOS-E scores. Furthermore, because timing of infection was not readily available, exposed cases included those with both early- and late-onset HAP. The etiology of early vs. late-onset HAP is likely different, with the former commonly the result of aspiration pneumonia, and the latter potentially related to prolonged ventilation. Future studies would be useful in distinguishing temporal dynamics of HAP etiology and onset during acute care hospitalization. Additionally, NTDB complication codes are subject to underreporting, which could result in an underestimation of HAP incidence and bias the effect towards the null. The NTDB definition of HAP does not distinguish what set of criteria were met for individuals to be classified as cases. Yet the operational definition of HAP, set by the NTDB, could directly influence the observed incidence rate. However, as documented by prior studies, the NTDB definition of pneumonia includes a more liberal criteria of positive chest x-ray and purulent sputum *or* an abnormal physical exam and positive blood culture. The two avenues of positive diagnosis result in greater sensitivity, but lower specificity, of disease classification, compared to a disease definition of only a culture-based criteria.[50] To allay some concerns of underreporting we used all available data sources in this study for our HAP exposure classification. Specifically, through the availability of a second data source we were able to supplement HAP exposure data using diagnosis codes from the TBI-MS National Database. The primary analysis was conducted using a probabilistically-matched cohort; therefore, a small percentage of the pairs may be incorrectly matched. However, based on our previous algorithm development[26] and validation[27] studies, we have empirical evidence to suggest mismatched pairs were likely very rare (<2%). Also, the converging results in our sensitivity analysis from a deterministic dataset support the observation that HAP predicts poor outcomes post-TBI observed in the primary analysis. In our secondary analysis, the data we present is a proxy for hospital resource utilization; however, we do not have claims or cost data that may be a truer measure of utilization. Due to the lack of medication information in the NTDB, we were not able to adjust for potentially important confounding by pharmacological interventions, such as anti-coagulants. We did not account for changes in resuscitation approaches over time, such as crystalloid therapy and component therapy that may lead to some temporal bias. Though the hospital complications by definition occur 48+ hours after admission, it is possible that the findings could be confounded by some community-acquired cases of pneumonia, particularly depending on intubation location (e.g. in the field or ED). Finally, due to the longitudinal nature of the study, there was some degree of lost to follow-up. In our post-hoc analysis when we applied IPW for nonresponse, the association between HAP and GOS-E did not meaningfully change, which suggests that though there are factors associated with follow-up, they are not resulting in major selection bias for the primary effect of HAP on GOS-E.

We demonstrate that HAP increases odds for unfavorable outcomes by 34% up to five years post-TBI. This study provides a meaningful contribution to the field by highlighting the deleterious association between acute care HAP and long-term outcome in a large sample of individuals with TBI. The work supports the need for future studies to expand prospective research on infection prophylaxis during acute hospitalization. TBI populations are particularly vulnerable to incident HAP, and concerted efforts are needed to assess how primary infection prevention might improve long-term recovery.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Funding Acknowledgements:

National Institutes of Health (NIH) R21 HD 089075–01; NIH TL1 TR001858; National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR) TBI Model Systems 90DP0041–02-01, NIDILRR HHSP233201850070A

## References:

1. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Traumatic Brain Injury and Concussion | Basic Information on TBI and Concussion | Traumatic Brain Injury | Injury Center. http://www.cdc.gov/traumaticbraininjury/basics.html. Accessed January 23, 2016.
2. Roozenbeek B, Maas AIR, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol. 2013;9(4):231–236. [PubMed: 23443846]
3. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. The Lancet. 1974;304(7872):81–84.
4. Foreman BP, Caesar RR, Parks J, Madden C, Gentilello LM, Shafi S, Carlili MC, Harper CR, Diaz-Arrastia RR. Usefulness of the abbreviated injury score and the injury severity score in comparison to the Glasgow Coma Scale in predicting outcome after traumatic brain injury. J Trauma. 2007;62(4):946–950. [PubMed: 17426553]
5. Balestreri M, Czosnyka M, Chatfield DA, Steiner LA, Schmidt EA, Smielewski P, Matta B, Pickard JD. Predictive value of Glasgow Coma Scale after brain trauma: change in trend over the past ten years. J Neurol Neurosurg Psychiatry. 2004;75(1):161–162. [PubMed: 14707332]
6. Chesnut RM, Marshall SB, Piek J, Blunt BA, Klauber MR, Marshall LF. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank In: Monitoring of Cerebral Blood Flow and Metabolism in Intensive Care. Springer; 1993:121–125. http://link.springer.com/chapter/10.1007/978-3-7091-9302-0_21. Accessed October 4, 2017.
7. Marmarou A, Anderson RL, Ward JD, Choi SC, Young HF, Eisenberg HM, Foulker MA, Marshall LF, Jane JA. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. Spec Suppl. 1991;75(1S):S59–S66.
8. Kishore PRS, Lipper MH, Miller JD, Girevendulis AK, Becker DP, Vines FS. Post-traumatic hydrocephalus in patients with severe head injury. Neuroradiology. 1978;16(1):261–265. [PubMed: 740188]
9. Mazzini L, Campini R, Angelino E, Rognone F, Pastore I, Oliveri G. Posttraumatic hydrocephalus: a clinical, neuroradiologic, and neuropsychologic assessment of long-term outcome. Arch Phys Med Rehabil. 2003;84(11):1637–1641. [PubMed: 14639563]
10. Zygun DA, Zuege DJ, Boiteau PJ, Lapland KB, Henderson EA, Kortbeek JB, Doig CJ. Ventilator-associated pneumonia in evere traumatic brain injury. Neurocrit Care. 2006;5(2):108–114. [PubMed: 17099256]
11. Kesinger MR, Kumar RG, Wagner AK, Puyana JC, Peitzman AP, Billiar TR, Sperry JL. Hospital-acquired pneumonia is an independent predictor of poor global outcome in severe traumatic brain injury up to 5 years after discharge: J Trauma Acute Care Surg. 2015;78(2):396–402. [PubMed: 25757128]
12. Esnault P, Nguyen C, Bordes J, D'Aranda E, Montcriol A, Contargyris C, Cotte J, Goutorbe P, Joubert C, Dagain A, et al. Early-Onset Ventilator-Associated Pneumonia in Patients with Severe Traumatic Brain Injury: Incidence, Risk Factors, and Consequences in Cerebral Oxygenation and Outcome. Neurocrit Care. 2017;27(2):187–198. [PubMed: 28432539]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript


13. Hui X, Haider AH, Hashmi ZG, Rushing AP, Dhiman N, Scott VK, Selvarajah S, Haut ER, Efron DT, Schneider EB. Increased risk of pneumonia among ventilated patients with traumatic brain injury: every day counts! J Surg Res. 2013;184(1):438–443. [PubMed: 23816243]
14. Calcagno J, Kumar R, Maza A, Awan N, Ferimer S, Nierstedt R, Wagner AK. Lymphopenia After Traumatic Brain Injury Increases Infections, Hospital Resource Utilization, and Worsens Long-Term Outcomes. J Neurotrauma. 2018.
15. Stirling DP, Yong VW. Dynamics of the inflammatory response after murine spinal cord injury revealed by flow cytometry. J Neurosci Res. 2008;86(9):1944–1958. [PubMed: 18438914]
16. Lucin KM, Sanders VM, Popovich PG. Stress hormones collaborate to induce lymphocyte apoptosis after high level spinal cord injury. J Neurochem. 2009;110(5):1409–1421. [PubMed: 19545280]
17. Kasten KR, Goetzman HS, Reid MR, et al. Divergent adaptive and innate immunological responses are observed in humans following blunt trauma. BMC Immunol. 2010;11:4. [PubMed: 20100328]
18. Heffernan DS, Monaghan SF, Thakkar RK, Machan JT, Cioffi WG, Ayala A. Failure to normalize lymphopenia following trauma is associated with increased mortality, independent of the leukocytosis pattern. Crit Care Lond Engl. 2012;16(1):R12.
19. Kopp MA, Druschel C, Meisel C, Liebscher T, Prilipp E, Watzlawick R, Cinelli P, Niedeggen A, Schaser KD, Wanner GA, et al. The SCIentinel study--prospective multicenter study to define the spinal cord injury-induced immune depression syndrome (SCI-IDS)--study protocol and interim feasibility data. BMC Neurol. 2013;13:168. [PubMed: 24206943]
20. Kollef MH, Hamilton CW, Ernst FR. Economic impact of ventilator-associated pneumonia in a large matched cohort. Infect Control Hosp Epidemiol. 2012;33(3):250–256. [PubMed: 22314062]
21. Yang C-C, Shih N-C, Chang W-C, Huang S-K, Chien C-W. Long-term medical utilization following ventilator-associated pneumonia in acute stroke and traumatic brain injury patients: a case-control study. BMC Health Serv Res. 2011;11:289. [PubMed: 22040214]
22. Leone M, Bourgoin A, Giuly E, Antonini F, Duboc M, Viviand X, Albanese J, Claude M. Influence on outcome of ventilator-associated pneumonia in multiple trauma patients with head trauma treated with selected digestive decontamination. Crit Care Med. 2002;30(8):1741–1746. [PubMed: 12163786]
23. Cazzadori A, Di Perri G, Vento S, Bonora S, Fendt D, Rossi M, Lanzafame M, Mirandola F, Concia E. Aetiology of pneumonia following isolated closed head injury. Respir Med. 1997;91(4):193–199. [PubMed: 9156141]
24. Esnault P, Nguyen C, Bordes J, D'Aranda E, Montcriol A, Contargyris C, Cotte J, Goutorbe P, Joubert C, Dagain A, et al. Early-Onset Ventilator-Associated Pneumonia in Patients with Severe Traumatic Brain Injury: Incidence, Risk Factors, and Consequences in Cerebral Oxygenation and Outcome. Neurocrit Care. 2017:1–12.
25. Karpur A A Guide to the Traumatic Brain Injury Model Systems National Database. 2013.
26. Kesinger MR, Kumar RG, Ritter AC, Sperry JL, Wagner AK. Probabilistic Matching Approach to Link Deidentified Data from a Trauma Registry and a Traumatic Brain Injury Model System Center. Am J Phys Med Rehabil. 2017;96(1):17–24. [PubMed: 27088479]
27. Kumar RG, Wang Z, Kesinger MR, Newman MA, Huynh TT, Niemeier JP, Sperry JL, Wagner AK. Probabilistic Matching of Deidentified Data From a Trauma Registry and a Traumatic Brain Injury Model System Center: A Follow-up Validation Study. Am J Phys Med Rehabil. 2018;97(4):236. [PubMed: 29557888]
28. Wilson JL, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma. 1998;15(8):573–585. [PubMed: 9726257]
29. Patterson L, Weiss H, Schano P. Combining multiple data bases for outcomes assessment. Am J Med Qual Off J Am Coll Med Qual. 1996;11(1):S73–7.
30. Shafi S, Marquez de la Plata C, Diaz-Arrastia R, Shipman K, Carlile M, Frankel H, Parks J, Gentilello LM. Racial Disparities in Long-Term Functional Outcome After Traumatic Brain Injury. J Trauma Acute Care Surg. 2007;63(6):1263.
31. SAS Institute Inc. SAS 9.4.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript


32. Hernán MA, Hernández-Díaz S, Robins JM. A Structural Approach to Selection Bias. Epidemiology. 2004;15(5):615–625. [PubMed: 15308962]
33. Kumar RG, Boles JA, Wagner AK. Chronic inflammation after severe traumatic brain injury: characterization and associations with outcome at 6 and 12 months postinjury. J Head Trauma Rehabil. 2015;30(6):369–381. [PubMed: 24901329]
34. NNIS System. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2003, issued August 2003. Am J Infect Control. 2003;31(8):481–498. [PubMed: 14647111]
35. Kumar RG, Juengst SB, Wang Z, Dams-O'Connor K, Dikmen SS, O'Neil-Pirozzi T, Dahdah MN, Hammond F, Felix ER, Arenth PM, Wagner AK Epidemiology of comorbid conditions among adults 50 years and older with traumatic brain injury. J Head Trauma Rehabil. 2018;33(1):15–24. [PubMed: 28060201]
36. Watanitanon A, Lyons VH, Lele AV, et al. Clinical Epidemiology of Adults With Moderate Traumatic Brain Injury. Crit Care Med. 2018;46(5):781–787. [PubMed: 29369057]
37. Harvey LA, Close JCT. Traumatic brain injury in older adults: characteristics, causes and consequences. Injury. 2012;43(11):1821–1826. [PubMed: 22884759]
38. Mina AA, Bair HA, Howells GA, Bendick PJ. Complications of preinjury warfarin use in the trauma patient. J Trauma. 2003;54(5):842–847. [PubMed: 12777897]
39. Batchelor JS, Grayson A. A meta-analysis to determine the effect of anticoagulation on mortality in patients with blunt head trauma. Br J Neurosurg. 2012;26(4):525–530. [PubMed: 22324438]
40. Franko J, Kish KJ, O'Connell BG, Subramanian S, Yuschak JV. Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. J Trauma. 2006;61(1):107–110. [PubMed: 16832256]
41. Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med. 2005;33(10):2184–2193. [PubMed: 16215368]
42. Ullman JS, Hawryluk GW, Bell MJ, et al. Guidelines for the Management of Severe Traumatic Brain Injury. 2016 https://www.braintrauma.org/uploads/07/04/Guidelines_for_the_Management_of_Severe_Traumatic.97250__2_.pdf. Accessed October 18, 2016.
43. Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD. Implications of Extubation Delay in Brain-Injured Patients Meeting Standard Weaning Criteria. Am J Respir Crit Care Med. 2000;161(5):1530–1536. [PubMed: 10806150]
44. Titsworth WL, Hester J, Correia T, Reed R, Guin P, Archibald L, Layon AJ, Mocco J. The effect of increased mobility on morbidity in the neurointensive care unit. J Neurosurg. 2012;116(6):1379–1388. [PubMed: 22462507]
45. Mendez-Tellez PA, Needham DM. Early Physical Rehabilitation in the ICU and Ventilator Liberation. Respir Care. 2012;57(10):1663–1669. [PubMed: 23013903]
46. Hinchey JA, Shephard T, Furie K, Smith D, Wang D, Tonn S. Formal Dysphagia Screening Protocols Prevent Pneumonia. Stroke. 2005;36(9):1972–1976. [PubMed: 16109909]
47. Hansen TS, Larsen K, Engberg AW. The association of functional oral intake and pneumonia in patients with severe traumatic brain injury. Arch Phys Med Rehabil. 2008;89(11):2114–2120. [PubMed: 18996240]
48. El-Rabbany M, Zaghlol N, Bhandari M, Azarpazhooh A. Prophylactic oral health procedures to prevent hospital-acquired and ventilator-associated pneumonia: A systematic review. Int J Nurs Stud. 2015;52(1):452–464. [PubMed: 25443306]
49. François B, Cariou A, Clere-Jehl R, Dequin PF, Renon-Carron F, Daiz T, Guitton C, Deye N, Legriel S, Plantefeve, Quenot JP, et al. Prevention of Early Ventilator-Associated Pneumonia after Cardiac Arrest. N Engl J Med. 2019;381(19):1831–1842. [PubMed: 31693806]
50. Leonard KL, Borst GM, Davies SW, Coogan M, Waibel BH, Poulin NR, Bard MR, Goettler CE, Rinehard SM, Toschlog EA. Ventilator-associated pneumonia in trauma patients: different criteria, different rates. Surg Infect. 2016;17(3):363–368.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

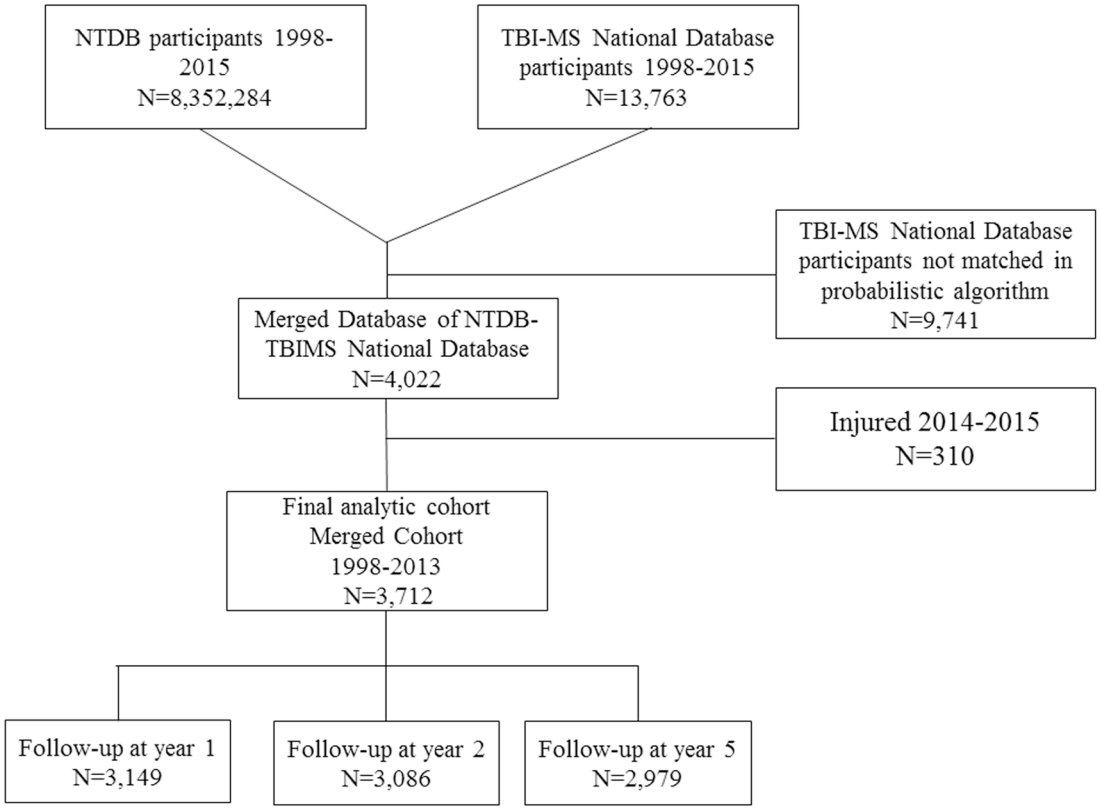


**Figure 1.**

Flow Diagram of Participants in Analytic Sample. N=3712 individuals were in the final analytic cohort. Of those individuals, N=3149 were followed-up at year 1, N=3086 were followed up at year 2, and N=2979 were followed up at year 5 after injury.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Table 1.**

Description of measures

| NTDB measures | Construct | Description of Measure |
|---|---|---|
| HAP | Primary exposure; Pneumonia in hospital | • NTDB complication code: Documentation for HAP was defined as one of two criteria, either:<br>**1.** Rales or dullness on a physical examination of the chest and any of the following: new onset purulent sputum, organism isolated from blood culture, or isolation of pathogen from specimen obtained by transtracheal aspirate or biopsy; OR<br>**2.** positive chest radiographic exam and any of the following: new onset purulent sputum, organism from the blood, isolation of pathogen from specimen isolated from transtracheal aspirate or biopsy, isolation of virus or detection of viral antigen from respiratory secretions, diagnostic single antibody titer (IgM) or 4-fold increase in paired serum sample (IgG) for pathogen, or histopathologic evidence of pneumonia<br>• The complication occurs > 48 hours after hospital admission |
| ISS | Injury Severity-all body regions | • An anatomic trauma severity scale derived from the AIS that quantifies overall injury severity across eight body regions<br>• Scores range from 1-6, with 1 being minor and 6 unsurvivable<br>• ISS is the sum of squares of the 3 most severely injured body regions |
| Non-head ISS | Injury Severity-all non-head body regions | • The Non-head ISS was calculated using AIS region scores<br>• The sum of squares of the 3 most severe non-head body regions |
| Thoracic AIS | Thoracic injury severity | • AIS thoracic region score<br>• Scores range from 1-6, with 1 being minor and 6 unsurvivable<br>• Individuals with no thoracic injuries were assigned a score of 0<br>• Significant thoracic injury was classified as a thoracic AIS score ≥3 |
| Ventilation Status | Ventilation | • ICD-9 Procedure code range from 96.7-96.72 |
| Ventilation days | Number of days on a ventilator | • Number of days on ventilator support among individuals on a ventilator |
| **TBIMS measures** | | |
| HAP | HAP diagnosis code | • ICD-9 Diagnosis codes for HAP: 482-486 |
| Age | Age | • Age at injury |
| Race | Race | • Grouped as White, Black, or Other |

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

| NTDB measures | Construct | Description of Measure |
|---|---|---|
| Brain Injury Severity | Brain Injury Severity based on DoD scale | • Calculated variable consisting of two categories, moderate or severe injuries, which is a function of the Glasgow Coma Scale (GCS), post-traumatic amnesia (PTA), and number of days it takes to follow commands<br>• Moderate injuries are defined by a GCS between 9-12, PTA between 0-7 days, or days to follow commands ≤1 day<br>• Severe injuries were defined as a GCS between 3-8, PTA >8 days, or days to follow commands >1 day |
| MOI | Cause of injury | • Grouped as Motor Vehicle, Fall, Pedestrian, or Other |
| CT scan findings | Nature of TBI | • Trained abstractors review patient electronic medical records to document presence or absence of neuropathology on computed tomography images<br>• Grouped as presence/absence of: SDH, EDH, IVH, and SAH |
| Payor Status | Insurance | • Payor was dichotomized as Medicare or Medicaid vs. all other payment sources |
| Rehabilitation Interruption | Interruption to Rehabilitation Care | • Short-term interruptions during inpatient rehabilitation to acute care |
| Acute care LOS | Number of hospital days in acute care | • Hospital days in acute care |
| Rehabilitation LOS | Number of hospital days in rehabilitation | • Hospital days in rehabilitation |
| FIM efficiency | Rate of change in FIM over the course of Rehabilitation | • Calculated variable from the formula: $(FIM_{discharge}-FIM_{admission})/(\text{Rehab LOS})$ |
| Rehospitalization | 5- year Rehospitalization | • All-cause rehospitalization at any point at 1, 2, or 5 years post-injury |
| GOS-E | Primary outcome; Global disability measure | • A trained research assistant conducts a 20-question structured interview that answers a variety of questions pertaining to patient's current condition, covering the following topics: 1) level of consciousness, 2) independence at home, 3) independence outside home, 4) return to work, 5) participation in social and leisure activities, 6) family and friendships, and their 7) return to normal life.<br>• The range of scores are from 1-8, with higher scores corresponding to better recovery.<br>• Scores were dichotomized ≤5 (unfavorable outcomes) vs. >5 (favorable outcomes) |

Abbreviations: HAP, Hospital-acquired Pneumonia; ISS, Injury Severity Scale; AIS, Abbreviated Injury Scale; DoD, Department of Defense; MOI, Mechanism of Injury; LOS, length of stay, GCS, Glasgow Coma Scale; Post-traumatic Amnesia (PTA); Functional Independence Measure (FIM); GOS-E, Glasgow Outcome Scale-Extended Scale; CT, Computed Tomography; SDH, subdural hematoma, EDH, epidural hematoma, IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Table 2.**

NTDB Demographics and Clinical Variables by HAP Status

| Variable | HAP (n=1212) | No HAP (n=2500) | p-value |
|---|---|---|---|
| Age (mean, SD) | 38.36 (16.56) | 43.45 (20.52) | <0.001* |
| Sex (men, %¥) | 970 (80.03) | 1756 (70.27) | <0.001* |
| Race (n, %¥) | | | 0.170 |
| White | 851 (70.21) | 1678 (67.15) | |
| Black | 209 (17.24) | 473 (18.93) | |
| Other | 152 (12.54) | 348 (13.93) | |
| Brain Injury Severity (n, %) | | | <0.001* |
| Moderate | 77 (6.49) | 696 (28.22) | |
| Severe | 1110 (93.51) | 1770 (71.78) | |
| ISS (median, IQR) | 27 (20-35) | 22 (16-29) | <0.001* |
| ISS Non-Head (median, IQR) | 10 (1-18) | 5 (1-13) | <0.001* |
| Thoracic AIS ≥3 (n,%) | 477 (44.3) | 603 (26.93) | <0.001* |
| Ventilation status (n, %¥) | 795 (65.59) | 972 (38.88) | <0.001* |
| Ventilation days (median, IQR) | 8 (0-16) | 0 (0-3) | <0.001* |
| Cranial surgery status (n, %¥) | 279 (27.30) | 551 (25.94) | 0.418 |
| Payor status (n, %¥) | | | 0.517 |
| Government assistance | 420 (37.80) | 896 (38.96) | |
| Private pay | 691 (62.20) | 1404 (61.04) | |
| Acute care length of stay (median, IQR) | 26 (19-36.5) | 14 (8-22) | <0.001* |
| Rehabilitation length of stay (median, IQR) | 23 (15-36) | 17 (11-28) | <0.001* |
| Rehabilitation Interruptions (n, %¥) | 77 (6.63) | 115 (4.84) | 0.027* |
| CT Injury Type (n, %¥) | | | |
| SDH | 663 (55.02) | 1296 (52.26) | 0.115 |
| EDH | 139 (11.54) | 311 (12.54) | 0.382 |
| IVH | 405 (33.61) | 651 (26.25) | <0.001* |
| SAH | 860 (71.37) | 1661 (66.98) | 0.007* |
| Mechanism of Injury (n, %¥) | | | <0.001* |

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

| Variable | HAP (n=1212) | No HAP (n=2500) | p-value |
|---|---|---|---|
| MVA | 802 (66.23) | 1240 (49.98) | |
| Assault/Violence | 90 (7.43) | 270 (10.88) | |
| Fall | 211 (17.42) | 697 (28.09) | |
| Pedestrian | 80 (6.61) | 172 (6.93) | |
| Other | 28 (2.31) | 102 (4.11) | |

Abbreviations: GCS, Glasgow Coma Scale; ISS, Injury Severity Score; SDH, Subdural hematoma; EDH, Epidural hematoma; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Table 3.**

NTDB Demographic and Clinical Variables by GOS-E Status at 1 Year

| Variable | Unfavorable GOS-E (n=1491) | Favorable GOS-E (n=1651) | p-value |
|---|---|---|---|
| Age (mean, SD) | 44.10 (19.32) | 39.74 (19.41) | <0.001* |
| Sex (men, %¥) | 1099 (73.71) | 1213 (73.47) | 0.880 |
| Race (n, %¥) | | | <0.001* |
| White | 953 (63.92) | 1232 (74.62) | |
| Black | 344 (23.07) | 221 (13.39) | |
| Other | 194 (13.01) | 198 (11.99) | |
| Brain Injury Severity (n, %) | | | <0.001* |
| Moderate | 245 (16.91) | 392 (23.80) | |
| Severe | 1204 (83.09) | 1255 (76.20) | |
| ISS (median, IQR) | 25 (17-34) | 25 (17-33) | 0.182 |
| ISS Non-Head (median, IQR) | 8 (1-13) | 8 (1-14) | 0.675 |
| Thoracic AIS ≥3 (n,%) | 422 (31.24) | 498 (33.56) | 0.187 |
| Ventilation status (n, %¥) | 773 (51.84) | 744 (45.06) | <0.001* |
| Ventilation days (median, IQR) | 1 (0-12) | 0 (0-6) | <0.001* |
| Cranial surgery status (n, %¥) | 411 (32.01) | 334 (22.58) | <0.001* |
| Payor status (n, %¥) | | | <0.001* |
| Government assistance | 662 (48.53) | 437 (28.41) | |
| Private pay | 702 (51.47) | 1101 (71.59) | |
| Acute care length of stay (median, IQR) | 22 (13-33) | 15 (9-23) | <0.001* |
| Rehabilitation length of stay (median, IQR) | 23 (15-38) | 16 (10-25) | <0.001* |
| Rehabilitation Interruptions (n, %¥) | 117 (8.36) | 48 (3.02) | <0.001* |
| CT Injury Type (n, %¥) | | | |
| SDH | 858 (58.13) | 834 (50.73) | <0.001* |
| EDH | 180 (12.20) | 208 (12.65) | 0.699 |
| IVH | 504 (34.15) | 434 (26.40) | <0.001* |
| SAH | 1057 (71.61) | 1104 (67.15) | 0.007* |

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

| Variable | Unfavorable GOS-E (n=1491) | Favorable GOS-E (n=1651) | p-value |
|---|---|---|---|
| Mechanism of Injury (n, %[¥]) | | | <0.001* |
| MVA | 790 (53.27) | 953 (58.00) | |
| Assault/Violence | 176 (6.76) | 111 (6.76) | |
| Fall | 389 (26.23) | 389 (26.23) | |
| Pedestrian | 94 (5.72) | 94 (5.72) | |
| Other | 87 (5.30) | 87 (5.30) | |

Abbreviations: GCS, Glasgow Coma Scale; ISS, Injury Severity Score; CT, Computed Tomography; SDH, Subdural hematoma; EDH, Epidural hematoma; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Table 4.**

Probabilistic Cohort GEE Regression Model for Repeated Measures GOS-E at 1, 2, and 5 years

| | **Model 1**[£] | | **Model 2**[§] | | **Model 3**[¥] | | **Model 4**[€] | |
|---|---|---|---|---|---|---|---|---|
| | Odds ratio (95% CI) | p-value | Odds ratio (95% CI) | p-value | Odds ratio (95% CI) | p-value | Odds ratio (95% CI) | p-value |
| **HAP** | | <0.001 * | | <0.001 * | | <0.001 * | | <0.001 * |
| **No (reference)** | (reference) | | (reference) | | (reference) | | (reference) | |
| **Yes** | 1.28 (1.14, 1.45) | | 1.48 (1.29, 1.69) | | 1.51 (1.32, 1.73) | | 1.34 (1.15, 1.56) | |

*: statistically significant at $p<0.05$

£: Model 1: Unadjusted

§: Model 2: Adjusted for Age only

¥: Model 3: Adjusted for Demographic Variables: Age and Race

€: Model 4: Adjusted Demographic and Clinical Variables: Age, Race, ventilation status, brain injury severity, ISS, Thoracic AIS ≥3, mechanism of injury, intraventricular hemorrhage status, subarachnoid hemorrhage status

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Table 5.**

Deterministic Cohort GEE Regression Model for Repeated Measures GOS-E at 1, 2, and 5 years

| | **Model 1**[£] | | **Model 2**[§] | | **Model 3**[¥] | | **Model 4**[€] | |
|---|---|---|---|---|---|---|---|---|
| | Odds ratio (95% CI) | p-value | Odds ratio (95% CI) | p-value | Odds ratio (95% CI) | p-value | Odds ratio (95% CI) | p-value |
| **HAP** | | 0.022 * | | 0.002 * | | 0.001 * | | 0.005 * |
| **No (reference)** | (reference) | | (reference) | | (reference) | | (reference) | |
| **Yes** | 1.44 (1.05, 1.98) | | 1.69 (1.22, 1.34) | | 1.72 (1.23, 2.39) | | 1.63 (1.16, 2.30) | |

*: statistically significant at $p<0.05$

£: Model 1: Unadjusted

§: Model 2: Adjusted for Age only

¥: Model 3: Adjusted for Demographic Variables: Age and Race

€: Model 4: Adjusted Demographic and Clinical Variables: Age, Race, ventilation status, brain injury severity, ISS, Thoracic AIS ≥3, mechanism of injury, intraventricular hemorrhage status, subarachnoid hemorrhage status