Male Gender is Associated with Increased Risk for Postinjury Pneumonia.

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Published In/Presented At

Gannon, C. J., Pasquale, M., Tracy, J. K., McCarter, R. J., & Napolitano, L. M. (2004). Male gender is associated with increased risk for postinjury pneumonia. *Shock (Augusta, Ga.)*, *21*(5), 410-414.

SHOCK, Vol. 21, No. 5, pp. 410–414, 2004

MALE GENDER IS ASSOCIATED WITH INCREASED RISK FOR POSTINJURY PNEUMONIA

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Received 5 Dec 2003; first review completed 19 Dec 2003; accepted in final form 24 Feb 2004

ABSTRACT—Nosocomial pneumonia in trauma patients is a significant source of resource utilization and mortality. We have previously described increased rates of pneumonia in male trauma patients in a single institution study. In that study, female trauma patients had a lower incidence of postinjury pneumonia but a higher relative risk for mortality when they did develop pneumonia. We sought to investigate the hypothesis that male trauma patients have an increased incidence of postinjury pneumonia in a separate population-based dataset. Prospective data were collected on 30,288 trauma patients (26,231 blunt injuries, 4057 penetrating injuries) admitted to all trauma centers (n = 26) in Pennsylvania over 24 months (January 1996 to December 1997). Gender differences in pneumonia were determined for the entire dataset. A second analysis examined all blunt injury patients and excluded all patients with a hospital length of stay less than 24 h, eliminating patients who expired early after admission. In trauma patients with minor injury (ISS < 15), there was no significant difference between male and female patients in the rate of postinjury pneumonia (male 1.37%, female 1.11%). In the moderate-injury group (ISS > 15), male trauma patients had a significantly increased incidence of postinjury pneumonia (ISS 15–30, male 8.85%, female 6.45%; ISS > 30, male 24.35%, female 17.30%). Logistic regression analysis of blunt trauma patients revealed that gender, ISS, injury type, admission Revised Trauma Score (RTS), admission respiratory rate, history of cardiac disease, and history of cancer were all independent predictors of pneumonia. Trauma patients with nosocomial pneumonia had a significantly higher mortality rate ($P < 0.001$) than patients without pneumonia. There was no gender-specific difference in mortality among pneumonia patients. Male gender is significantly associated with an increased incidence of postinjury pneumonia. In contrast to our initial study, there was no gender difference in postinjury pneumonia mortality rates identified in this population-based study.

KEYWORDS—Sex, gender, hormone, trauma, pneumonia, infection, pulmonary, outcomes

INTRODUCTION

Traumatic injury induces an early inflammatory and immune response in the host that results in the systemic inflammatory response syndrome (SIRS) (1). The subsequent trauma host response is one of immunosuppression, manifested as the compensatory anti-inflammatory response syndrome (CARS) (2, 3). This predisposes the host to infection, which may lead to late multiple organ failure (4, 5).

A prior study from our institution investigated the prevalence of nosocomial infections in trauma and found that 31% of trauma patients developed postinjury infection (6). Pneumonia was the most common site of postinjury infection, comprising 38% of all infections in trauma patients. Additionally, nosocomial infections were associated with a significant increase in hospital length of stay (HLOS), intensive care unit length of stay (ICU LOS), and mortality in trauma.

Trauma patients are at particularly increased risk for developing pneumonia in the postinjury period, related to multiple risk factors. A recent review of 7503 trauma patients demonstrated a pneumonia incidence of 31% in 1366 ventilated trauma patients (7). Multivariate logistic regression analysis identified age, injury severity, significant traumatic brain injury, blood transfusions, emergent intubation, severe chest injury, spinal cord injury, and need for emergent operation as independent predictors for pneumonia.

We have previously investigated gender differences in postinjury pneumonia rates in a single-institution study with a study cohort of 18,892 blunt trauma patients over a 12-year period (8). In that study, male gender was associated with a greater incidence of nosocomial pneumonia, prolonged need for mechanical ventilation, greater resource utilization, increased HLOS, and increased ICU LOS. Despite an overall lower rate of pneumonia, female patients who developed pneumonia demonstrated a higher mortality rate when compared with age- and ISS-matched male trauma patients.

The purpose of our current study was to validate our prior findings of increased rates of postinjury pneumonia in male patients and increased mortality in female patients with pneumonia by utilizing a statewide population-based dataset of trauma patients. We also sought to elucidate risk factors for pneumonia in trauma.

MATERIALS AND METHODS

Prospective data were collected on 30,288 trauma patients (26,231 blunt injuries, 4057 penetrating injuries) admitted to all trauma centers (n = 26) in Pennsylvania over 24 months (1/1996–12/1997, see Acknowledgment). Age, gender, and race were evaluated as demographic variables. Injury severity was assessed by injury severity score (ISS). Gender differences in mortality were determined for the entire dataset and separately for blunt and penetrating injury patients. Pneumonia was defined by the Pennsylvania Trauma Systems Foundation and required all of the following to be present: fever (≥38°C), leukocytosis, Gram stain of sputum with predominant pathogenic organism and white blood cells, and chest radiograph with pneumonic infiltrate. These criteria match the Centers for Disease Control (CDC)

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Presented, in part, at American College of Surgeons Surgical Forum, October 2001.

DOI: 10.1097/01.shk.0000125477.37219.ac

clinical definition of pneumonia (9). A second analysis examined all blunt injury patients and excluded all patients with a hospital length of stay less than 24 h, eliminating patients who expired early after admission.

Study cohort: inclusion and exclusion criteria

All trauma patients admitted to all trauma centers in Pennsylvania over a 2-year period (January 1996 to December 1997) were included as the study cohort. Age less than 18 years was an exclusion criterion. This study was approved by our Institutional Human Use Committee and informed consent was obtained. The ISS was used to quantify the extent and severity of an individual's injuries (10, 11). To further investigate the effect of gender on trauma outcomes, the study cohort was stratified into three groups by ISS (ISS <15, 15–29, ≥30) and into two groups by age (18–45, >45).

Definition of preinjury diseases

The definitions of preexisting diseases were based on physician documentation in the medical record, including admission history and physical, consultations, operative reports, laboratory reports, radiology reports, and autopsy reports. The following definitions were used:

Cardiac disease: diagnoses of previous cardiac surgery, coronary artery disease, congestive heart failure, cor pulmonale, myocardial infarction, or hypertension.
Immunosuppression: diagnoses of HIV, AIDS, routine steroid use, transplants (solid organ or cellular), and active chemotherapy.
Malignancy: current oncologic therapy or existence of concurrent metastasis.
Diabetes mellitus: history of insulin dependence or need for oral hypoglycemic therapy.

Statistical analysis

Discrete variables were compared using Pearson's chi-square analysis. Continuous variables were compared using Student's *t* test. Differences were considered significant when $P < 0.05$. Logistic regression analysis was used to identify significant independent risk factors associated with the dependent variable mortality. Binary covariates, along with the main effect of gender and each interaction effect with gender, were entered into regression models for the outcome of mortality: race, respiratory rate, systolic blood pressure, revised trauma score (RTS), cardiac disease, cancer, and injury type. Relationships between variables were tested using Pearson's correlation coefficients and multiple regression analysis.

A second analysis included only blunt trauma patients and excluded all patients with a hospital length of stay < 24 h (n = 24,583), eliminating patients who expired early after admission. This analysis was performed to exclude all nonpreventable deaths related to hemorrhage and severe traumatic brain injury. Pearson's chi-square and logistic regression analysis were performed in a manner duplicating the initial analysis.

RESULTS

The study population included 30,288 trauma patients (26,231 blunt, 4057 penetrating). The study cohort had a mean age of 47 ± 21 and a mean ISS of 13 ± 11 (Table 1). The mean ICU LOS was 2.4 ± 6.9 days with men having a higher admission rate than women (34% vs. 26%). Average admission values included Glasgow coma scale (GCS) 13.5, respiratory rate of 18.9 breaths/min, systolic blood pressure of 137 mmHg, and revised trauma score (RTS) of 7.31. The overall mortality rate was 7.95%. As we have previously reported, logistic regression analysis of the entire dataset identified no significant gender-based differences in outcome once patients had been appropriately stratified for injury severity as measured by ISS and age (Table 2) (12).

TABLE 1. **Clinical characteristics of entire trauma patient cohort (n = 30,288)**

Age	47 ± 21
Injury Severity Score (ISS)	13 ± 11
Revised Trauma Score (RTS)	7.3 ± 1.4
Admission Glasgow Coma Score (GCS)	13.5 ± 3.6
Admission systolic blood pressure	137 ± 31
Mortality rate	7.95%

All data are mean ± standard deviation.

In evaluation of the entire study cohort, including blunt and penetrating trauma patients, men had a significantly higher incidence of pneumonia than women (5.1% vs. 3.1%, $P < 0.001$). In trauma patients with minor injury (ISS < 15), there was no significant difference between male and female patients in the rate of postinjury pneumonia (male 1.37%, female 1.11%). In patients with ISS > 15, men had a significantly higher incidence of postinjury pneumonia than women (ISS 15–30, male 8.85%, female 6.45%; ISS > 30, male 24.35%, female 17.30%; Fig. 1).

A similar pattern was observed in blunt trauma patients with > 24 h LOS stratified by age and ISS (n = 24,583). Men had a significantly higher incidence of postinjury pneumonia in all groups, except for the age 18–45 group with minor injury (ISS < 15) (Fig. 2). Respectively, the rates were: age 18–45, ISS <15, male 0.8%, female 0.6%, $P = 0.254$; age 18–45, ISS 15–29, male 8.0%, female 5.7%, $P = 0.039$; age 18–45, ISS 30–75, male 23.8%, female 18.0%, $P = 0.04$; age > 45, ISS < 15, male 2.2%, female 1.2%, $P < 0.001$; age > 45, ISS 15–29, male 9.9%, female 7.1%, $P = 0.008$; age > 45, ISS 30–75, male 32.5%, female 17.0%, $P < 0.001$.

Logistic regression analysis of blunt trauma patients confirmed that female gender [odds ratio 0.68, 95% confidence interval (CI) 0.55–0.83, $P < 0.001$] and increased admission RTS (odds ratio 0.76, 95% CI 0.71–0.82, $P < 0.001$) are both protective in postinjury pneumonia risk (Table 3). In contrast, increased admission respiratory rate (odds ratio 1.03, 95% CI 1.01–1.04, $P < 0.001$), increasing ISS (odds ratio 1.06, 95% CI 1.05–1.07, $P < 0.001$), and preexisting cardiac disease (odds ratio 1.34, 95% CI 1.04–1.72, $P < 0.022$) were identified as independent risk factors for pneumonia after blunt trauma.

Trauma patients with nosocomial pneumonia had a significantly increased (13.5% vs. 7.8%, $P < 0.001$) mortality rate when compared with patients without pneumonia (Fig. 3). There was no significant gender-specific difference in mortality among pneumonia patients (male 13.1%, female 14.9%, $P = 0.56$) (Fig. 4).

DISCUSSION

Pneumonia is the most common pulmonary complication in trauma, the most common infection in trauma, and the leading cause of death in nosocomial infections (13, 14). The European Prevalence of Infection in Intensive Care (EPIC) study investigated ICU-acquired infections in a 1-day point prevalence study of over 10,000 patients (15). They identified a 45% infection rate and confirmed the importance of pneumonia and lower respiratory tract infections, which accounted for more than 50% of all infections. The diagnosis of traumatic injury

TABLE 2. **Gender-related differences in mortality**

Group		ISS < 15	ISS 15–29	ISS ≥30
Male	N	4707/182	4997/430	1337/434
	Mortality	(1.9%)	(10.8%)	(32.5%)
Female	N	6941/124	2020/248	581/214
	Mortality	(1.8%)	(12.3%)	(36.8%)

No differences were statistically significant.

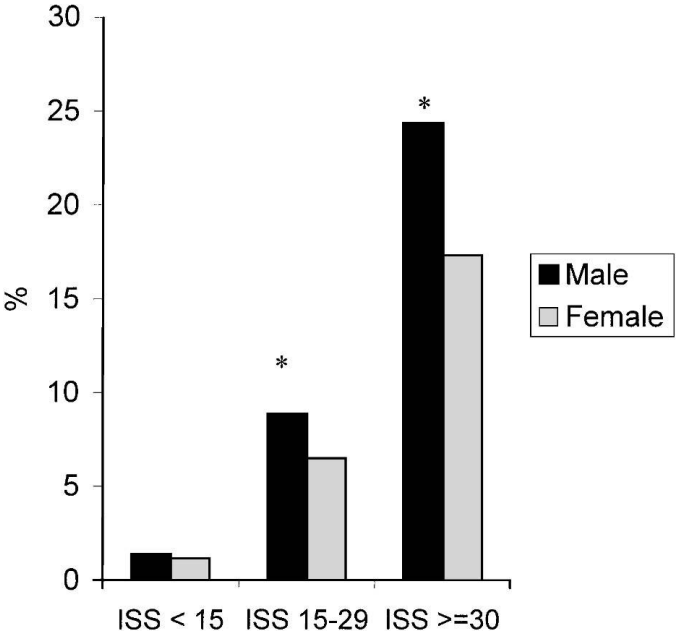

FIG. 1. **Pneumonia rates by ISS for penetrating and blunt injury.** *P < 0.001.

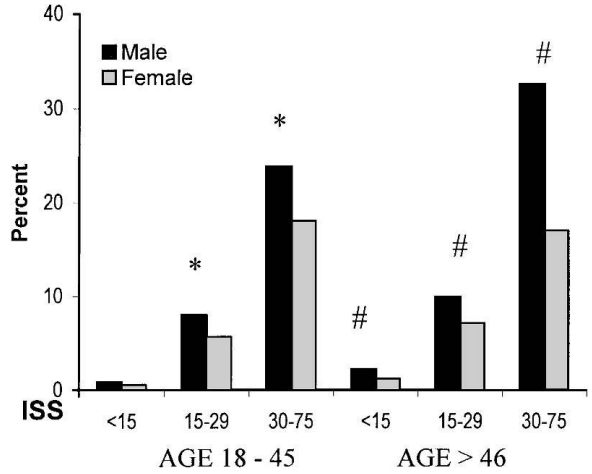

FIG. 2. **Pneumonia incidence in blunt Injury.** *P < 0.05, #P < 0.01.

TABLE 3. **Independent predictors of pneumonia after blunt trauma (logistic regression analysis)**

Variable	Odds ratio	95% Confidence intervals	P
Female gender	0.68	0.55–0.83	<0.001
Admission Revised Trauma Score	0.76	0.71–0.82	<0.001
Admission respiratory rate	1.03	1.01–1.04	<0.001
Injury Severity Score	1.06	1.05–1.07	<0.001
Cardiac disease	1.34	1.04–1.72	<0.022

was determined to be an independent risk factor for ICU-acquired infections in that study.

Cook and colleagues examined the incidence and risk factors for ventilator-associated pneumonia in mechanically ventilated critically ill patients (n = 1014) (16). Multivariate analysis confirmed that a primary admitting diagnosis of trauma (risk ratio 5.00, CI 1.05–7.01) and burn injury (risk ratio 5.09, CI 1.52–17.03) were independent predictors of ventilator-

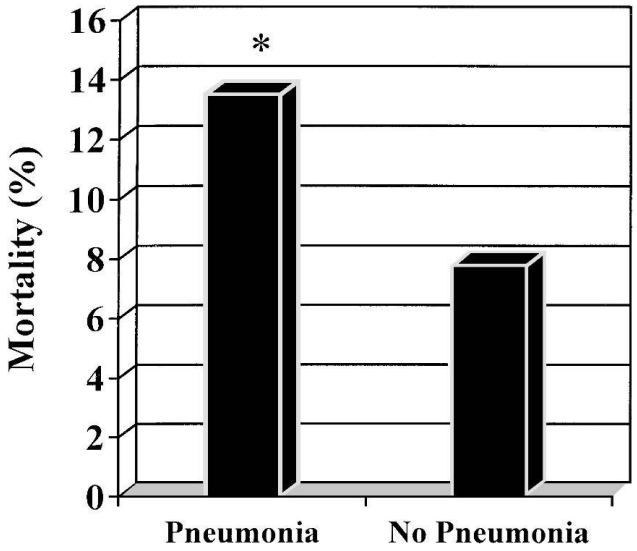

FIG. 3. **Increased mortality in trauma patients with postinjury pneumonia.** *P < 0.001.

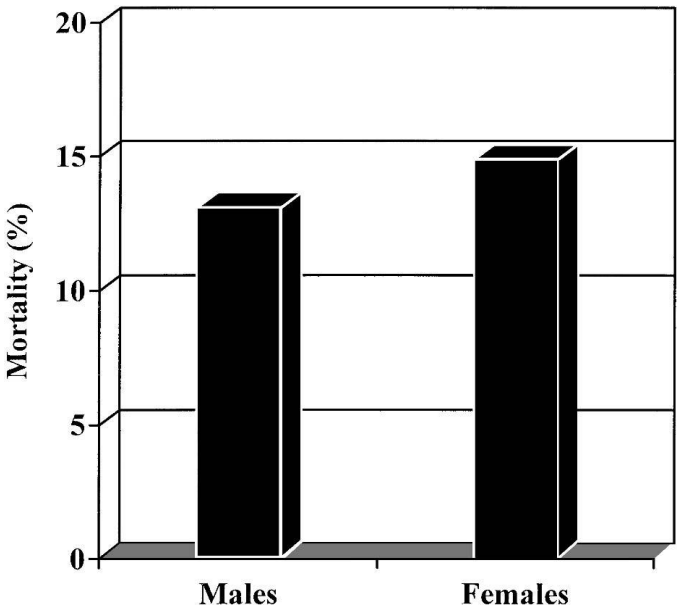

FIG. 4. **Gender-related mortality in trauma patients with postinjury pneumonia.** No significant difference identified (P = 0.56).

associated pneumonia. A more recent study that examined risk factors for ventilator-associated pneumonia also found that trauma admission was an independent risk factor (adjusted odds ratio 1.75, 95% CI 1.41–2.18) (17).

Male gender has also been identified as an independent risk factor for both ICU-acquired and ventilator-associated pneumonia (18). Kollef et al. confirmed that male gender (OR 2.02, 95% CI 1.50–2.71, P = 0.017) was an independent predictor of ventilator-associated pneumonia in a prospective cohort study of 521 ICU patients requiring mechanical ventilation for > 12 h (19). Rello and colleagues examined 842 patients who developed ventilator-associated pneumonia and documented that there was a significantly greater incidence in men (male 64.1%, female 35.9%) (17). Multiple logistic regression analysis confirmed that male gender (adjusted OR 1.58, 95% CI 1.36–1.83, P < 0.001) was independently associated with the development of ventilator-associated pneumonia.

In contrast, no gender-related difference in pneumonia incidence was identified in a single-institution study of 7438 trauma patients (male 4.4% vs. female 3.6%, $P = 0.13$) (20). It should be noted, however, that injury severity was lower (median ISS 6–8) in this patient cohort than in the current study cohort, with lower rates of pneumonia overall. Logistic regression analysis in this study indicated that male blunt trauma patients under 50 years old had a 2.5-fold increased risk of death compared with women (95% CI 1.3–4.9). Similarly, no gender-related difference in pneumonia incidence was identified in a single-institution study of 1611 burn patients. Interestingly, in this study women had a significantly higher in-hospital mortality (13.4%) than men (7.2%, $P = 0.0002$), but the cause of death was organ system failure and not sepsis (21).

Differences in hormonal influence at the cellular level have been postulated as a possible mechanism for divergence in male and female trauma outcomes (22, 23). Sex hormones have been shown to regulate cellular immunity through the alteration of T-helper cell populations (24). A murine trauma-hemorrhage model has shown enhanced immune responses in female as opposed to a decreased immune response in male mice (25). Other animal studies have documented that high testosterone and low estradiol levels in male mice may be responsible in part for immunosuppression after traumatic injury. For example, androgen depletion studies in male mice, either through castration or by blocking testosterone receptors with flutamide, has been shown to improve the function of splenocytes, peritoneal macrophages, and Kupffer cells. Animal studies have documented that androgen depletion prevented or reversed immune depression after trauma-hemorrhage (26, 27). It has also been demonstrated that testosterone is involved in other physiologic events such as enhancing vasoconstriction, which may play a role in producing organ dysfunction following trauma-hemorrhage (28, 29). This effect is also inhibited by flutamide administration.

In humans, the effect of gender on morbidity and mortality following trauma has yielded conflicting results in the past. Two recent clinical studies have shown sex-specific differences in the development of sepsis and multiple organ failure in severely injured patients. Oberholzer et al. (30) demonstrated in a trauma population that the incidence of posttraumatic sepsis and multiple organ dysfunction syndrome was significantly increased in severely injured men with ISS $\geq$ 25 when compared with an equivalent female group. No gender-based differences in trauma mortality were identified, however. Majetschak et al. (31) also examined trauma patients with blunt injuries and ISS > 16 and discovered no sex differences in posttraumatic cytokine release. However, male trauma patients developing severe sepsis were noted to have significantly increased cytokine-producing capacity in the early posttraumatic period. Despite these complications following severe trauma, no significant gender differences in mortality were determined in either study group.

We have previously examined 18,892 blunt trauma patients (age 18 to 65) from a single institution over a 12-year period (8). No significant gender-based differences in mortality were identified. However, male patients were found to have a higher incidence of pneumonia. Female patients with pneumonia had an increased mortality rate in this group. Croce and colleagues, in their single-institution study (n = 18,133), similarly reported an increased rate of postinjury infections in male trauma patients but a higher mortality in female trauma patients who developed pneumonia, using bronchoalveolar lavage for the diagnosis of pneumonia (32). Despite the large sample size examined in both of these studies, the findings were limited because of the use of trauma patient cohorts from single institutions.

The current study used a statewide population-based dataset to examine gender-based differences in postinjury pneumonia. In evaluation of the entire study cohort, men had a significantly higher incidence of pneumonia. Stratification by ISS revealed a higher pneumonia rate in men in all groups except those with minor injury (ISS < 15). To evaluate a more homogeneous group of patients, a second analysis was performed examining only patients with blunt injuries and LOS greater than 24 h. When this cohort was stratified by age and ISS, a similar pattern to the initial analysis was observed. Men had a significantly higher incidence of postinjury pneumonia in all groups except for age 18–45 with more minor injuries (ISS < 15).

Logistic regression analysis of the homogeneous blunt trauma cohort confirmed that female gender is protective for postinjury pneumonia risk. Independent risk factors identified for postinjury pneumonia were preexisting cardiac disease, tachypnea on trauma admission, and severe injury (low RTS, high ISS).

Overall, development of postinjury pneumonia nearly doubled the mortality rate for trauma patients. In contrast to our prior single-institution study, we identified no significant difference in mortality between male and female trauma patients who developed pneumonia.

This disparate result from our prior study (lack of gender-related mortality difference in postinjury pneumonia) is likely related to multiple factors that ultimately affect pneumonia-related mortality. This may include differences in microbial etiology of pneumonia in this multi-institutional study compared with our prior single-institution study, and bacteriology data were not assessed in either study. Furthermore, interinstitutional variability in the timing of initiation and duration of antibiotic therapy for pneumonia may have existed in this multicenter statewide population-based study. Similarly, differences in duration of mechanical ventilation and strategies for prevention of subsequent secondary episodes of pneumonia likely differed among the many institutions included in this study. Finally, significant differences in genetic polymorphisms (33) and degree of individual patient systemic and lung-specific inflammatory responses (34) may have been present in the two different patient cohorts studied. Further studies investigating gender-related differences in postinjury pneumonia should attempt to evaluate these important variables in pneumonia-associated mortality differences.

An important limitation of this study is that it is a retrospective analysis of trauma registry data that was collected prospectively. Furthermore, the incidence of pneumonia may have been underreported in both studies because one recent study documented that surgeons dedicated to infection control detected significantly more pneumonias and surgical site infections than did infection control practitioners (35).

Evidence from this study and our previous single-institution study, with a cumulative cohort of over 49,000 patients,

confirms that male gender is associated with a greater incidence of pneumonia in trauma after appropriate stratification for other variables (injury severity, age, preexisting disease, admission physiologic parameters) that also affect trauma outcome. Because pneumonia is the most common infectious complication in trauma and is associated with significantly longer ICU and hospital length of stay and with higher hospital cost [estimated attributable cost approximately $12,000 (36)] and mortality rate compared with uninfected patients, continued efforts to examine the mechanism underlying this gender-related difference in trauma are warranted.

ACKNOWLEDGMENT

These data were provided by the Pennsylvania Trauma Systems Foundation, Mechanicsburg, Pennsylvania. The Foundation specifically disclaims responsibility for any analyses, interpretations, or conclusions. The following 26 trauma centers contributed data to the Foundation:

Abington Memorial Hospital
Albert Einstein Medical Center
Allegheny General Hospital
Brandywine Hospital
Children's Hospital of Philadelphia
Children's Hospital of Pittsburgh
Community Medical Center
Conemaugh Memorial Medical Center
Crozer-Chester Medical Center
Frankford Hospital-Torresdale
Geisinger Medical Center
Hahnemann University Hospital
Hershey Medical Center
Lancaster General Hospital
Lehigh Valley Hospital
Medical College of Pennsylvania Hospital
Mercy Hospital of Pittsburgh
The Robert Packer Hospital
St. Luke's Hospital
St. Mary Hospital Center
Temple University Hospital
Thomas Jefferson University Hospital
Tri-State Trauma System
University of Pennsylvania
University of Pittsburgh Medical Center
York Hospital

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