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Healthcare-Associated Pneumonia among United States Combat Casualties, 2009–2010

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Abstract

Although there is literature evaluating infectious complications associated with combat-related injuries from Iraq and Afghanistan, none have evaluated pneumonia specifically. Therefore, we assessed a series of pneumonia cases among wounded military personnel admitted to Landstuhl Regional Medical Center, and then evacuated further to participating U.S. military hospitals. Of the 423 casualties evacuated to the U.S., 36 developed pneumonia (8.5%) and 30 of these (83.3%) were ventilator-associated. Restricting to 162 subjects admitted to intensive care, 30 patients had pneumonia (18.5%). The median Injury Severity Score was higher among subjects with pneumonia (23.0, versus 6.0; $p<0.01$). There were 61 first-isolate respiratory specimens recovered from 31 pneumonia subjects, of which 56.1% were gram-negative, 18.2% were gram-positive, and 18.2% were fungal. *Staphylococcus aureus* and *Pseudomonas aeruginosa* were most commonly recovered (10.6%, and 9.1%, respectively). Thirteen bacterial isolates (26.5%) were multidrug-resistant. Outcome data were available for 32 patients, of which 26 resolved their infection without progression, 5 resolved after initial progression, and 1 died. Overall, combat-injured casualties suffer a relatively high rate of pneumonia, particularly those requiring mechanical ventilation. Although gram-negative pathogens were common, *S. aureus* was most frequently isolated. Continued focus on pneumonia prevention strategies is necessary for improving combat care.

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Keywords

ventilator-associated pneumonia; nosocomial infections; military medicine; multidrug resistance; gram-negative bacteria; trauma

INTRODUCTION

Infections are among the most common complications of combat trauma, with 27% of casualties experiencing at least one infectious complication by the time of discharge. If the population is restricted to intensive care unit (ICU) patients, the number increases to 50%.[1] Infecting pathogens recovered from injured casualties evacuated from Iraq and Afghanistan have been notable both for their wide spectrum (e.g., from gram-positive to gram-negative bacteria along with invasive molds), as well as for their drug resistance profiles.[2–8] During the recent conflicts, infections produced by multidrug-resistant organisms (MDROs) have been the rule, rather than the exception, with the epidemiology of the principal MDROs changing over time and between theaters of conflict. Regarding military personnel injured in Iraq, colonization and infection with multidrug-resistant *Acinetobacter baumannii-calcoaceticus* complex (ABC) was a major concern; while in recent years, as the proportion of casualties from Afghanistan increased, extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacteria became predominant.[9,10]

Pneumonia complicating civilian traumatic injuries has been described in a variety of settings, and this particular complication has substantial impact on morbidity, hospital length of stay, additional costs, and in some studies, mortality.[11–14] The National Healthcare Safety Network (NHSN) reports a pooled mean rate of ventilator-associated pneumonia (VAP) in trauma ICUs of 3.6 cases per 1000 ventilator days, which is higher than in any other specific surgical ICU except burn units.[15] Trauma patients are at particular risk for pneumonia, which may relate directly to the effects of chest or abdominal injuries, blast lung and pulmonary contusions, and paralysis of respiratory or oropharyngeal muscles following central nervous system or neck injuries. Moreover, trauma patients may also be more likely than other surgical patients to have numerous scheduled and unscheduled operative returns, with or without repeated intubations; and to require massive transfusions of blood products, total parenteral nutrition, and antimicrobial prophylaxis, which may potentiate an immunosuppressed state increasing the likelihood of infectious complications, particularly pneumonia.[16] Combat trauma patients evacuated from the theater of operation have the additional risk factor of being transported several thousand miles to military treatment facilities (MTFs) while in a supine position.

Epidemiologic data from combat casualties suggest that while pneumonia is less common than skin/wound infections, it does impact the population. Specifically, 3.7% of wounded personnel were affected in one evaluation using NHSN definitions and 8.5% in a retrospective registry study.[1,17] The duration from injury to diagnosis of pneumonia (median 3 days) is also short compared to bloodstream infections (6 days) and skin/soft tissue infections (12 days).[1] Due to this short latency, pneumonia is more likely to present and require treatment prior to the patient's evacuation back to a U.S. MTF, and potentially prior

to evacuation from the theater of operations. This poses specific diagnostic and management challenges, since a forward operating base may lack access to bronchoscopy, timely and accurate microbiology results, or methods for monitoring drug levels such as aminoglycosides or vancomycin. Therefore, there is a need to characterize the demographics, microbiology, and outcomes of pneumonia cases in this combat casualty population. Additionally, infection prevention in theater and during the chain of evacuation presents special challenges, and evidence-based prevention interventions must be designed to target high-risk problems.[18] Characterization of the risk of pneumonia, particularly in ventilated patients, and description of the patients at highest risk, may help target future prevention efforts for VAP in war casualties, both in and out of the combat zone. Our objective was to describe demographics, microbiology and outcomes of pneumonia in a cohort of combat trauma patients evacuated from Iraq and Afghanistan and enrolled in the Trauma Infectious Disease Outcomes Study (TIDOS).

MATERIALS AND METHODS

Study Population

The TIDOS project, which has been previously described in detail, is a multicenter, observational cohort of U.S. military members with deployment-related injuries.[1] Participants eligible for inclusion in TIDOS were evacuated out of theater through Landstuhl Regional Medical Center in Germany to one of three U.S. sites: Walter Reed Army Medical Center, National Naval Medical Center, or Brooke Army Medical Center. The study period was defined as June 2009 to January 2010, during which time a pneumonia case evaluation form was temporarily used to capture specific pulmonary infection data on patients. This study was approved by the Infectious Disease Institutional Review Board of the Uniformed Services University of the Health Sciences in Bethesda, MD.

Case Definition

We defined pneumonia by new or progressive infiltrates seen on radiologic examination and evidence of infection (documented body temperature >38°C or <36°C, or peripheral white blood cell count ≥12,000 or <4,000 cells/mm^3), plus one of the following: new onset purulent sputum, change in character of sputum, increase in respiratory secretions, new onset worsening cough, dyspnea or tachypnea, rales/bronchial breath sounds, worsening gas exchange, same organism isolated from both respiratory and blood cultures, positive culture from a minimally contaminated lower respiratory tract specimen, ≥5% bronchoalveolar lavage-obtained cells containing intracellular bacteria on direct microscopy, or laboratory confirmation of infection with an uncommon pathogen. Patients not meeting this *a priori* definition, as outlined by the NHSN, could receive a clinical diagnosis by the treating physician if they met the diagnostic criteria with concurrent directed antimicrobial therapy for more than five days.

Microbiology

Microbiological evaluations were conducted at the clinicians' discretion. Antibiotic susceptibility results were performed by each MTF's clinical microbiology laboratory, and interpreted in accordance with Clinical and Laboratory Standards Institute. We categorized

bacteria as MDRO if it was resistant to ≥3 classes of antibiotics (aminoglycosides, beta-lactams, carbapenems, or fluoroquinolones), produced either ESBL or *Klebsiella pneumoniae* carbapenemase, or if they were methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci. All participating sites used either BD Phoenix (BD Biosciences, Sparks, MD) or Vitek 2 (bioMerieux Inc., Hazelwood, MO) for automatic identification and susceptibility testing of organisms, along with disk diffusion and E-tests for further evaluation of resistance where applicable.

Statistical Analysis

The statistics presented are descriptive and are shown as frequencies (percentages) for categorical variables and medians (interquartile ranges [IQR]) for continuous variables. Comparisons of categorical variables were made with Fisher's exact test or chi-squared, as applicable; nonparametric continuous variables were compared with Mann-Whitney U test. All p-values are two-tailed and statistical significance at $p<0.05$. We performed our analysis with existing software (SPSS, version 19.0, IBM, Armonk, New York).

RESULTS

From June 2009 to January 2010, 842 U.S. casualties were injured and medically evacuated from theater to Landstuhl. Of these, 423 were transitioned to a TIDOS-participating U.S. MTF and 162 of these patients were admitted to an U.S. ICU. Army personnel accounted for 69.4% of the cohort; 27.8% were Marines and 2.8% other. In addition, enlisted personnel comprised 80.6% of the population; 2.8% were officers, 5.5% warrant officers, 2.8% other, and rank data was missing for 8.3%. Overall, 36 patients met criteria for pneumonia for an overall frequency of 8.5% among those evacuated to the U.S. and 4.3% for those admitted to Landstuhl. Thirty of these patients (83.3%) were on mechanical ventilation within 48 hours of diagnosis, and were, thus, defined as VAP. Among the ICU patients evacuated to a U.S. MTF, the proportion diagnosed with pneumonia was 18.5%. Characteristics of the patients admitted with pneumonia (97.2% male; median age of 26.0 years; Table I) were reflective of the entire TIDOS cohort patient population (96.5% male; median age of 24.0 years [IQR: 22.0, 30.0]). In contrast, the median injury severity score (ISS) of the patients diagnosed with pneumonia was 23.0, which was significantly higher than those of the subjects who did not develop pneumonia (median ISS 6.0 [IQR: 4.0, 13.0]; $p<0.01$).

Among the pneumonia patients, there was a predominance of head trauma (38.9%), followed by injuries to the lower extremities (22.2%; Table I). In general, trauma was largely sustained as a result of a blast mechanism (66.7%). Transfusion data from the first 24 hours after injury revealed a median of 6 units of packed red blood cells; all patients for whom transfusion data were available (31 patients) received at least one unit of blood. The median time between injury and diagnosis of pneumonia was 4.0 days (IQR: 3.0, 7.5).

The criteria used to determine the diagnosis of pneumonia, and their respective frequencies of use, are represented in Table II. As defined by the NHSN, 55.6% met the *a priori* case definition for pneumonia, while the remaining 44.4% met the clinical definition of being diagnosed by the treating physician with concurrent directed antimicrobial therapy (≥5 days). Despite the overall injury severity and complicating pneumonia, there was only one

death, for an overall rate of 3.1% (3.3% among ventilated ICU patients with pneumonia), and this was not considered to be related to the pneumonia diagnosis. Among the VAP subjects, there were no deaths and 76.7% resolved their infection without progression (i.e. without significant clinical change related to the infection such as worsening vital signs).

Overall, gram-negative rods (GNR) were the most commonly isolated organisms from respiratory specimens and associated with a concurrent clinical diagnosis of pneumonia, accounting for 56.1% of all first-isolate positive cultures (Table III). Of these, *Pseudomonas aeruginosa* was the most frequent, followed by *Enterobacter aerogenes*, ABC, *Haemophilus influenzae*, and *Serratia marcescens. Escherichia coli* was only isolated from the respiratory specimens of three subjects. In addition, 21.6% of the GNR isolated met the definition of MDRO. Regarding gram-positive bacteria, which represented 18.2% of the organisms, *S. aureus* was predominant and 57.1% of the isolates were methicillin-resistant. Fungi accounted for remaining 18.2% of organisms isolated with *Aspergillus* and *Candida* spp. as the most frequent.

Antimicrobial use data (not specific to therapy for pneumonia) was available for 31 subjects (Table IV). The most commonly received systemic antimicrobials were meropenem, vancomycin, and amikacin, which were administered to 80.6, 67.7, and 45.2% of subjects, respectively. Subjects received a median of three antimicrobials (IQR: 2, 4; range: 1–10). Excluding two patients who received prolonged antimicrobials (individual total antimicrobial dose-days of 1173 and 299, respectively), the mean total antimicrobial dose-days per individual was 24.8. Nebulized colistin and tobramycin were each utilized in two subjects, while fluconazole was administered to one.

DISCUSSION

These data represent a systematic evaluation of clinical pneumonia in combat trauma patients evacuated from Iraq and Afghanistan as a substudy of the larger TIDOS cohort. Overall, our data showed a relatively high rate of pneumonia (8.5%), of which 83.3% of the cases were ventilator-associated. Among non-combat trauma patients, VAP rates in similarly performed prospective studies have ranged from 12 to 40%, comparable to the approximately 18% in this study's ICU population.[19–24] These studies have generally involved an older trauma population with a greater number of medical comorbidities compared to the TIDOS cohort, which has been previously well characterized to have predictably young and otherwise healthy patients.[1] The severity of injury, as defined by average ISS in civilian trauma studies of pneumonia, has ranged from 23 to 25 as well,[21,22,24] which is concordant with the data described herein. Notably, primary chest and abdominal injuries were relatively uncommon in this cohort, most likely due to the widespread use of body armor.[25] Nevertheless, the 8.5% rate of pneumonia is consistent with that described in civilian studies, and likely related to injury severity, large-volume blood product transfusion requirements, and a relative predominance of head injuries.[19–24] Although this small case series was not designed to evaluate factors associated with outcomes or attributable morbidity, based on the rate data presented here, VAP in the war wounded population is a problem of no less importance than that of the civilian trauma population. The TIDOS database captures only trauma patients who are evacuated to a

participating MTF in the U.S., accounting for 54% of Landstuhl admissions, and arguably represent a more seriously injured subset than those who are evacuated to other facilities.[1] However, even with an assumption of pneumonia and VAP rates half of those demonstrated here, with the casualty count from Operations Iraqi Freedom and Enduring Freedom up to 51,567,[26] this would represent >2000 cases of pneumonia and >1700 cases of VAP.

Numerous strategies have been proposed for generalized VAP prevention, though not all have been specifically evaluated in high-risk trauma patients. Per the personal experience and dedicated observations made on three separate infection prevention deployments to Iraq and Afghanistan by our authors, VAP bundle implementation is widespread, even in combat support hospitals. Their use is also recommended in Joint Theater Trauma System (JTTS) Clinical Practice Guidelines (CPG);[27] however, their efficacy in trauma populations is debated. One recent prospective evaluation demonstrated that while male gender and chest injury severity were associated with VAP development, time-dependent compliance with the Institute for Healthcare Improvement ventilator bundle was not.[22] Another practice, chlorhexidine bathing, is also gaining traction as data supporting its role in decreasing infectious complications in ICU patients accumulate. Chlorhexidine bathing has been used in the ICUs at combat support hospitals and Landstuhl for several years, and is now formally recommended in the JTTS CPG.[28] This practice has been evaluated in a trauma population, resulting in no overall reduction in VAPs; however, the subset of VAP caused by MRSA showed a statistically significant decrease. Nonetheless, a shift toward recovery of GNR associated with VAP, despite a trend toward a reduction in *Acinetobacter* spp. incidence, was also reported.[29] Other evaluations of chlorhexidine bathing either do not report data for infection or colonization with GNR or show no reduction.[30,31] In a population where gram-negative bacterial pathogens predominate, not just for VAP but for infectious complications in general, and where 15–16% of subjects become colonized with gram-negative MDROs, the utility of chlorhexidine bathing as an effective prevention strategy for healthcare-associated infections cannot be taken for granted and merits a dedicated investigation.[1,10] Other interventions, such as selective digestive and/or oral decontamination, silver-coated endotracheal tubes, or short-wavelength ultraviolet radiation disinfection of the healthcare environment, could be areas for targeted study in this population if a means of real-time active surveillance for VAP inclusive of all echelons of care is introduced.

The microbiologic incidence of pathogens isolated from respiratory specimens in patients with VAP herein reflects an overall predominance of GNR, which is not surprising based on the general prevalence of such organisms in any study of VAP, or in infectious complications resulting from combat trauma. However, we feel that the distribution of pathogens from our pneumonia patients presents some unexpected findings. During the time frame of our analysis, organisms isolated through active surveillance of combat casualties were largely ESBL-producing *E. coli*, followed by *K. pneumoniae* and *E. aerogenes*.[10] In our evaluation, we commonly recovered *S. aureus*, *P. aeruginosa* and *Enterobacter* spp., but potential ESBL-producers, *E. coli* and *K. pneumoniae*, were less frequently isolated, found in only 16% of subjects. Empiric meropenem use for suspected infection is currently routine in this population and is driven by the known prevalence of ESBL-producers. Correspondingly, meropenem was the most commonly used antibiotic in our cohort;

although, not entirely for pneumonia, as some patients had other infectious complications. The predominance of relatively drug-susceptible GNR may be reflective of the early-onset nature of this infectious complication, amidst the background time-dependent nature of incident colonization with MDROs. Contemporaneous colonization data from redeployed, combat casualties for *P. aeruginosa* showed that none were MDR, and only 2% demonstrated resistance to antipseudomonal beta-lactams.[10] Potentially, empiric carbapenem use may be unnecessary in the combat casualty with early-onset VAP alone, though this bears confirmation in a larger study before a change in clinical practice can be recommended. The utility of vancomycin was also seen in two-thirds of the subjects, while only 11% of the subjects had a respiratory specimen positive for MRSA. Limiting empiric vancomycin use for VAP, except in patients with unusual clinical features, sepsis, or known colonization, might be an additional means of safely exercising antimicrobial stewardship. Fungal organisms were recovered in a minority of patients, of which most were likely not pathogens, thus, antifungal use was rare.

The limitations of our study include its small size, both in terms of number of subjects, and narrow temporal range of six months, related to the temporary use of a specific case report form designed to capture intrathoracic complications during that time period. Microbial ecology, in particular, may change rapidly over time based on a number of factors, and clearly has changed in combat casualties since 2003–2004 when ABC predominated, and pneumonia rates may change quickly as well. Ideally, real-time, active surveillance for common healthcare-associated infections, such as VAP, across the echelons of care could be implemented to ascertain better data and inform prevention interventions. Uncertainty continues regarding the optimal means of diagnosing VAP, particularly in trauma patients who universally have noninfectious systemic, and often pulmonary-specific, inflammation. In our study, we used a clinically-focused approach to capturing VAP based upon NHSN criteria or physician diagnosis accompanied by targeted antimicrobial therapy exceeding or equal to five days. Clearly, there will have been some cases included who would not have been diagnosed with VAP using a more stringent definition. Nonetheless, we felt that a five day antibiotic treatment period would limit the number of such cases, since in unclear cases antibiotics are often deescalated within 48–72 hours if an alternative diagnosis presents itself or the diagnosis of VAP is felt to be less likely. Additionally, since in the clinical care of patients there is frequently uncertainty around the diagnosis of VAP, and given the clinical focus of this study, we felt that this definition was likely sufficient for the outcomes evaluated here. However, obviously the means used to diagnose VAP will impact both rate data as well as attributable microbiological data.

In summary, healthcare-associated pneumonia in the combat casualty population evacuated from the theater of operation was overwhelmingly ventilator-associated, and was seen predominantly in subjects with head injuries with a higher ISS after sustaining a blast injury, and moderate blood product transfusion requirements in the first 24 hours following injury. This complication developed early in the hospital course after injury, and microbial incidence reflected a high proportion of gram-negative organisms. Despite the known high prevalence of MDR gram-negatives infecting combat casualties, only 21.6% of first-isolate GNR were MDR in this case series. We believe that these data have implications for

prioritizing targeted research and ongoing efforts at VAP prevention in this population, and may suggest a limited requirement for empiric carbapenems and vancomycin in combat-injured patients with VAP.

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REFERNCES

1. Tribble DR, Conger NG, Fraser S, Gleeson TD, Wilkins K, Antonille T, et al. Infection-associated clinical outcomes in hospitalized medical evacuees after traumatic injury: Trauma Infectious Disease Outcome Study. J Trauma. 2011; 71(Suppl 1):S33–42. [PubMed: 21795875]
2. Centers for Disease Control and Prevention. Acinetobacter baumannii infections among patients at military medical facilities treating injured U S service members, 2002–2004. MMWR Morb Mortal Wkly Rep. 2004; 53(45):1063–6. [PubMed: 15549020]
3. Paolino KM, Henry JA, Hospenthal DR, Wortmann GW, Hartzell JD. Invasive fungal infections following combat-related injury. Mil Med. 2012; 177(6):681–5. [PubMed: 22730844]
4. Murray CK, Wilkins K, Molter NC, Li F, Yu L, Spott MA, et al. Infections complicating the care of combat casualties during operations Iraqi Freedom and Enduring Freedom. J Trauma. 2011; 71(Suppl 1):S62–73. [PubMed: 21795880]
5. Keen EF 3rd, Robinson BJ, Hospenthal DR, Aldous WK, Wolf SE, Chung KK, et al. Incidence and bacteriology of burn infections at a military burn center. Burns. 2010; 36(4):4618.
6. Keen EF 3rd, Robinson BJ, Hospenthal DR, Aldous WK, Wolf SE, Chung KK, et al. Prevalence of multidrug-resistant organisms recovered at a military burn center. Burns. 2010; 36(6):819–25. [PubMed: 20080354]
7. Yun HC, Branstetter JG, Murray CK. Osteomyelitis in military personnel wounded in Iraq and Afghanistan. J Trauma. 2008; 64(Suppl 2):S163–8. discussion S168. [PubMed: 18376160]
8. Calhoun JH, Murray CK, Manring MM. Multidrug-resistant organisms in military wounds from Iraq and Afghanistan. Clin Orthop Relat Res. 2008; 466(6):1356–62. [PubMed: 18347888]
9. Hospenthal DR, Crouch HK, English JF, Leach F, Pool J, Conger NG, et al. Multidrug-resistant bacterial colonization of combat-injured personnel at admission to medical centers after evacuation from Afghanistan and Iraq. J Trauma. 2011; 71(Suppl 1):S52–7. [PubMed: 21795879]
10. Weintrob AC, Murray CK, Lloyd B, Li P, Lu D, Miao Z, et al. Active surveillance for asymptomatic colonization with multidrug-resistant gram negative bacilli among injured service members--A three year evaluation. MSMR. 2013; 20(8):17–22. [PubMed: 24011372]
11. Brown DL, Hungness ES, Campbell RS, Luchette FA. Ventilator-associated pneumonia in the surgical intensive care unit. J Trauma. 2001; 51(6):1207–16. [PubMed: 11740281]
12. Bouadma L, Wolff M, Lucet JC. Ventilator-associated pneumonia and its prevention. Curr Opin Infect Dis. 2012; 25(4):395–404. [PubMed: 22744316]

13. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: A meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis. 2013; 13(8):665–71. [PubMed: 23622939]
14. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest. 2002; 122(6):2115–21. [PubMed: 12475855]
15. Dudeck MA, Weiner LM, Allen-Bridson K, Malpiedi PJ, Peterson KD, Pollock DA, et al. National Healthcare Safety Network (NHSN) report, data summary for 2012, Device-associated module. Am J Infect Control. 2013; 41(12):1148–66. [PubMed: 24274911]
16. Minei JP, Nathens AB, West M, Harbrecht BG, Moore EE, Shapiro MB, et al. Inflammation and the Host Response to Injury, a large-scale collaborative project: Patient-oriented research core--standard operating procedures for clinical care. II. Guidelines for prevention, diagnosis and treatment of ventilator-associated pneumonia (VAP) in the trauma patient. J Trauma. 2006; 60(5): 1106–13. discussion 1113. [PubMed: 16688078]
17. Murray CK, Wilkins K, Molter NC, Yun HC, Dubick MA, Spott MA, et al. Infections in combat casualties during Operations Iraqi and Enduring Freedom. J Trauma. 2009; 66(Suppl 4):S138–44. [PubMed: 19359957]
18. Hospenthal DR, Green AD, Crouch HK, English JF, Pool J, Yun HC, et al. Infection prevention and control in deployed military medical treatment facilities. J Trauma. 2011; 71(2 Suppl 2):S290–8. [PubMed: 21814095]
19. Blot S, Koulenti D, Dimopoulos G, Martin C, Komnos A, Krueger WA, et al. Prevalence, risk factors, and mortality for ventilator-associated pneumonia in middle-aged, old, and very old critically ill patients. Crit Care Med. 2014; 42(3):601–9. [PubMed: 24158167]
20. Magret M, Amaya-Villar R, Garnacho J, Lisboa T, Diaz E, Dewaele J, et al. Ventilator-associated pneumonia in trauma patients is associated with lower mortality: Results from EU-VAP study. J Trauma. 2010; 69(4):849–54. [PubMed: 20938271]
21. Patel CB, Gillespie TL, Goslar PW, Sindhwani M, Petersen SR. Trauma-associated pneumonia in adult ventilated patients. Am J Surg. 2011; 202(1):66–70. [PubMed: 21497790]
22. Croce MA, Brasel KJ, Coimbra R, Adams CA Jr, Miller PR, Pasquale MD, et al. National Trauma Institute prospective evaluation of the ventilator bundle in trauma patients: Does it really work? J Trauma Acute Care Surg. 2013; 74(2):354–60. discussion 360–2. [PubMed: 23354225]
23. Cook A, Norwood S, Berne J. Ventilator-associated pneumonia is more common and of less consequence in trauma patients compared with other critically ill patients. J Trauma. 2010; 69(5): 1083–91. [PubMed: 21068613]
24. Cavalcanti M, Ferrer M, Ferrer R, Morforte R, Garnacho A, Torres A. Risk and prognostic factors of ventilator-associated pneumonia in trauma patients. Crit Care Med. 2006; 34(4):1067–72. [PubMed: 16484918]
25. Belmont PJ, Schoenfeld AJ, Goodman G. Epidemiology of combat wounds in Operation Iraqi Freedom and Operation Enduring Freedom: Orthopaedic burden of disease. J Surg Orthop Adv. 2010; 19(1):2–7. [PubMed: 20370999]
26. United States Department of Defense. [accessed June 16, 2014] OIF/OEF Casualty Update. Available at http://www.defense.gov/news.casualty.pdf
27. Joint Theater Trauma System. [accessed February 1, 2014] Clinical Practice Guideline. Ventilator associated pneumonia. 2012. Available at http://www.usaisr.amedd.army.mil/assets/cpgs/Ventilator_Associated_Pneumonia_17_Jul_12.pdf
28. Joint Theater Trauma System. [accessed Februar 1, 2014] Clinical Practice Guideline. Guidelines to prevent infection in combat-related injuries. 2012. Available at http://www.usaisr.amedd.army.mil/assets/cpgs/Infection_Control_2_Apr_12.pdf
29. Evans HL, Dellit TH, Chan J, Nathens AB, Maier RV, Cuschieri J. Effect of chlorhexidine whole-body bathing on hospital-acquired infections among trauma patients. Arch Surg. 2010; 145(3): 240–6. [PubMed: 20231624]
30. Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, et al. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med. 2013; 368(24):2255–65. [PubMed: 23718152]

31. Derde LP, Dautzenberg MJ, Bonten MJ. Chlorhexidine body washing to control antimicrobial-resistant bacteria in intensive care units: A systematic review. Intensive Care Med. 2012; 38(6): 931–9. [PubMed: 22527065]

Table I

Demographic Characteristics of United States Combat Casualties with Healthcare-Associated Pneumonia

Characteristics	Pneumonia Subjects (N=36)	VAP Subjects (N=30)
Male, No. (%)	35 (97.2)	29 (96.7)
Age, median (IQR)	26.0 (22.0, 35.0)	26.0 (22.0, 35.0)
Injury Severity Score, median (IQR)	23.0 (17.0, 29.0)	22.0 (17.0, 29.0)
Maximum Abbreviated Injury Scale, median (IQR)	5 (4, 5)	5 (4, 5)
AIS location, No. (%)		
Head	14 (38.9)	12 (40.0)
External	2 (5.6)	2 (6.7)
Neck	1 (2.8)	1 (3.3)
Thorax	2 (5.6)	2 (6.7)
Abdomen	6 (16.7)	5 (16.7)
Spine	3 (8.3)	3 (10.0)
Upper extremity	0	0
Lower extremity	8 (22.2)	5 (16.7)
Blood products transfused within first 24 hours, median units (IQR)[a]		
Packed red blood cells	6 (2, 14)	6 (2, 11)
Fresh frozen plasma	6 (2, 14)	6 (2, 9)
Theater of Operation, No. (%)		
OEF	29 (80.6)	23 (76.7)
OIF	4 (11.1)	4 (13.3)
Missing	3 (8.3)	3 (10.0)
Mechanism of Injury, No. (%)[b]		
Blast	24 (66.7)	20 (62.5)
Gunshot wound	5 (13.9)	4 (12.5)
Motor vehicle collision	6 (16.7)	5 (15.6)
Other[c]	3 (8.3)	3 (9.4)

AIS – Abbreviated Injury Scale; IQR – interquartile range; OEF – Operation Enduring Freedom; OIF – Operation Iraqi Freedom; VAP – ventilator-associated pneumonia

[a] Blood product transfusion data missing for five patients in the overall pneumonia group and four patients in the VAP group

[b] Subjects may have more than one mechanism of injury

[c] No reported cases in burned patients

Table II

Diagnostic Criteria and Outcomes among United States Combat Casualties with Healthcare-Associated Pneumonia, No. (%)

	Pneumonia Subjects (N=36)	VAP Subjects (N=30)
Diagnostic Criteria[a]		
New or progressive infiltrate seen on radiology film	23 (63.9)	19 (63.3)
Evidence of infection[b]	35 (97.2)	29 (96.7)
New onset of purulent sputum	8 (22.2)	8 (26.7)
Change in character of sputum	12 (33.3)	11 (36.7)
Increased respiratory secretions or suctioning requirement	16 (44.4)	15 (50.0)
New onset or worsening cough, dyspnea, or tachypnea	8 (22.2)	5 (16.7)
Rales or bronchial breath sounds	7 (19.4)	6 (20.0)
Worsening gas exchange	20 (55.6)	17 (56.7)
Same organisms growing from respiratory secretions and blood cultures	3 (8.3)	3 (10.0)
Positive culture from minimally contaminated lower respiratory tract	18 (50.0)	18 (60.0)
>5% BAL-obtained cells contain intracellular bacteria	2 (5.6)	2 (6.7)
Laboratory confirmation of infection with uncommon pathogen	4 (11.1)	4 (13.3)
Basis for meeting diagnostic criteria		
Met a priori definition[c]	20 (55.6)	17 (56.7)
Physician clinical diagnosis (in the absence of meeting a priori definition) with directed antimicrobial therapy ≥5 days)	16 (44.4)	13 (43.4)
Mechanical ventilation within 48 hours prior to diagnosis	30 (83.3)	30 (100)
Outcome[d]		
Infection resolved without progression	26 (81.3)	23 (76.7)
Infection resolved with progression	5 (15.6)	3 (10.0)
Treatment ongoing at discharge	1 (3.1)	0
Death	1 (3.1)	0

BAL – bronchoalveolar lavage; VAP – ventilator-associated pneumonia

[a] Subjects may have met more than one of the diagnostic criteria

[b] Temperature >38°C or <36°C, or white blood cell count ≥12,000 or <4,000 cells/mm

[c] As defined by National Healthcare Safety Network

[d] Outcome data are missing for four subjects in the overall pneumonia group and the VAP patient group. One pneumonia subject from the overall group (N=36) had two outcomes (infection progression and death). Progression is defined by prior to resolution of the infection, there is a significant clinical change that relates to the infection (e.g., worsening vital signs, need for intubation/ventilation, and change in antimicrobial therapy due to poor response).

Table III

Microbiology of First-Isolates Collected from United States Combat Casualties Diagnosed with Healthcare-Associated Pneumonia, No. (%)[a]

	First-isolate frequency (N=61)	Multidrug-resistant
Gram-negative bacteria	37 (56.1)	8 (21.6)
Acinetobacter calcoaceticus baumannii complex	4 (6.1)	3 (75.0)
Acinetobacter radioresistans	1 (1.5)	0
Elizabethkingia spp.	1 (1.5)	0
Enterobacter aerogenes	5 (7.6)	0
Enterobacter cloacae	2 (3.0)	0
Escherichia coli	3 (4.5)	2 (66.7)
Haemophilus influenzae	4 (6.1)	0
Klebsiella oxytoca	1 (1.5)	0
Klebsiella pneumoniae	2 (3.0)	2 (100.0)
Proteus mirabilis	1 (1.5)	0
Pseudomonas aeruginosa	6 (9.1)	1 (16.7)
Serratia marcescens	4 (6.1)	0
Stenotrophomonas maltophilia	3 (4.5)	0
Gram-positive bacteria	12 (18.2)	5 (41.6)
Enterococcus faecium	1 (1.5)	1 (100.0)
Staphylococcus aureus	7 (10.6)	4 (57.1)
Streptococcus spp.	4 (6.1)	0
Fungi	12 (18.2)	0
Aspergillus spp.	3 (4.5)	0
Candida albicans	3 (4.5)	0
Candida spp. (non-albicans)	3 (4.5)	0
Rhizomucor spp.	1 (1.5)	0
Hansenula anomala	1 (1.5)	0
Yeast, unidentified	1 (1.5)	0

[a] First-isolates were collected from 31 subjects

Table IV

Antimicrobial Therapy in United States Military Personnel Diagnosed with Healthcare-Associated Pneumonia, No. (%)

Antimicrobial	Pneumonia Subjects[a] (N=31)
Amikacin	14 (45.2)
Amoxicillin-clavulanate	1 (3.2)
Cefazolin	1 (3.2)
Cefepime	3 (9.7)
Ceftriaxone	2 (6.5)
Ciprofloxacin	6 (19.4)
Colistin (systemic)	4 (12.9)
Colistin (nebulized)	2 (6.5)
Daptomycin	1 (3.2)
Ertapenem	1 (3.2)
Fluconazole	1 (3.2)
Gentamicin	1 (3.2)
Imipenem	2 (6.5)
Levofloxacin	8 (25.8)
Linezolid	3 (9.7)
Meropenem	25 (80.6)
Minocycline	1 (3.2)
Nafcillin	1 (3.2)
Piperacillin-tazobactam	7 (22.6)
Tigecycline	2 (6.5)
Trimethoprim-sulfamethoxazole	1 (3.2)
Tobramycin (systemic)	6 (19.4)
Tobramycin (nebulized)	2 (6.5)
Vancomycin	21 (67.7)

[a]Subjects often received multiple antimicrobials