Trauma Surgery & Acute Care Open

From bedside to bedside: how iterative clinical research influenced the diagnosis and management of pneumonia at the Elvis Presley Trauma Center

Jordan A Weinberg [1,2]

[1]Department of Surgery, Dignity Health/St Joseph's Hospital and Medical Center, Phoenix, Arizona, USA
[2]Department of Surgery, Creighton University School of Medicine Phoenix Regional Campus, Phoenix, Arizona, USA

Correspondence to
Dr Jordan A Weinberg; jordanweinberg@creighotn.edu

Received 15 February 2023
Accepted 8 March 2023

To cite: Weinberg JA. *Trauma Surg Acute Care Open* 2023;**8**:e001110.

SUMMARY

Ventilator-associated pneumonia is a well-acknowledged complication after hospitalization for injury or surgical emergency. The contribution to the literature on this topic by Dr Timothy Fabian and the Memphis group at the Elvis Presley Trauma Center resulted in the contemporary recognition that the diagnosis and management of pneumonia is an essential component of surgical critical care. During three decades, the Memphis group, under Dr Fabian's leadership, performed numerous clinical studies that led to the publication of over 40 articles concerning the epidemiology, diagnosis, and treatment of pneumonia after injury. The purpose of this review is to survey the consecutive studies from Memphis specifically that led to the development of a clinical pathway that has stood the test of time. Examination of the research output during this period provides a case study in how bedside clinical research can inform clinical practice and is a model for applied science in the intensive care unit.

Ventilator-associated pneumonia (VAP) is a well-acknowledged complication after hospitalization for injury or surgical emergency. Thirty years ago, that was not the case. At the Southern Surgical Association annual meeting in 1997, in his discussion of one of the first major pneumonia studies conducted at the Elvis Presley Trauma Center in Memphis, Tennessee, Dr Hiram Polk lamented that 'pneumonia is a far more common cause of death in a surgical patient than pulmonary embolism and, yet, the surgical community has not taken any interest in this.'[1] The subsequent output of literature on this topic by Dr Timothy Fabian and the Memphis group contributed to the contemporary recognition that the diagnosis and management of pneumonia is an essential component of surgical critical care. During three decades, surgeons and intensive care unit (ICU) pharmacists at the Elvis Presley Trauma Center, under Dr Fabian's leadership, performed numerous clinical studies that led to the publication of over 40 articles concerning the epidemiology, diagnosis, and treatment of pneumonia after injury (table 1). As stated by former Memphis trauma and surgical critical care fellow Dr Robert Maxwell at the Southern Surgical Association annual meeting in 2014, 'the data produced by the group in Memphis … are responsible in large part for establishing a standard of care for the diagnosis of VAP in the surgical and trauma ICUs.'[2] The purpose of this review is to survey the consecutive studies from Memphis specifically that led to the development of a clinical pathway that has stood the test of time. The applied clinical science during this period is a case study in how bedside clinical research can inform clinical practice.

DIAGNOSIS

Nearing the close of the 20th century, nosocomial pneumonia, now more often referred to as VAP, was a clinical diagnosis suspected by the onset of a new or changing pulmonary infiltrate on X-ray, fever, leukocytosis, and purulent tracheobronchial secretions. Although the development of this clinical picture in a patient previously free of pulmonary disease indicates bacterial pneumonia with a high likeliness, many existing conditions in a mechanically ventilated patient present a similar clinical picture, including chemical pneumonitis, acute respiratory distress syndrome, systemic inflammatory response syndrome (SIRS), pulmonary contusion, atelectasis, pulmonary edema, and pleural effusion. In addition, intubated patients often have proximal airway colonization by potentially pathogenic organisms and often have purulent secretions because of either tracheobronchitis or oropharyngeal secretions that escape the barrier of the endotracheal tube cuff. As a result, patients were often assumed to have pneumonia and treated for such with empiric antibiotics. Investigations performed in the 1980s began to illuminate this deficiency in diagnostic accuracy.[3–5] Taken together, these studies suggested that no combination of clinical variables was accurate in the prediction of nosocomial pneumonia and the misdiagnosis of nosocomial pneumonia was a common occurrence.

Stimulated by their medical colleagues at the University of Tennessee Health Sciences Center who were among the early proponents of fiberoptic bronchoscopy diagnosis of pneumonia,[6] Dr Fabian and his surgical colleagues embarked on the first of many studies that would subsequently confirm and refine the efficacy of a lower-respiratory culture-driven approach to the diagnosis of pneumonia in trauma patients.[7] In 107 trauma patients with clinical suspicion of pneumonia, respiratory cultures were obtained in triplicate—the first by routine sputum collection, the second by fiberoptic bronchoscopy-guided protected specimen brushing, and the third by fiberoptic bronchoscopy-guided bronchoalveolar lavage (BAL). They observed that the incidence of pneumonia according to culture positivity was 73% by sputum culture, 34% by protected brush specimen, and 25% by BAL.

Table 1 Selected studies concerning pneumonia performed at the Elvis Presley Trauma Center

Study	Conclusions
Fabian TC, Boucher BA, Croce MA, Kuhl DA, Janning SW, Coffey BC, Kudsk KA. Pneumonia and stress ulceration in severely injured patients. A prospective evaluation of the effects of stress ulcer prophylaxis. Arch Surg. 1993 Feb;128(2):185–91; discussion 191-2.	Sucralfate and cimetidine were found to both be effective for stress ulcer prophylaxis and that there is no association of cimetidine with nosocomial pneumonia.
Croce MA, Fabian TC, Stewart RM, Pritchard FE, Minard G, Trenthem L, Kudsk KA. Empiric monotherapy vs combination therapy of nosocomial pneumonia in trauma patients. J Trauma. 1993 Aug;35(2):303–9; discussion 309-11.	Monotherapy had a higher cure rate than combination therapy for empiric therapy of pneumonia trauma patients. Combination therapy failed because of superinfection (primarily MRSA).
Croce MA, Fabian TC, Shaw B, Stewart RM, Pritchard FE, Minard G, Kudsk KA, Baselski vs Analysis of charges associated with diagnosis of nosocomial pneumonia: can routine bronchoscopy be justified? J Trauma. 1994 Nov;37(5):721-7.	The charges associated with bronchoscopy were high but offset by antibiotic savings. Side effects of unnecessary antibiotic therapy could be avoided. Further study needed to determine the efficacy of PSB or BAL in trauma patients.
Croce MA, Fabian TC, Schurr MJ, Boscarino R, Pritchard FE, Minard G, Patton JH Jr, Kudsk KA. Using bronchoalveolar lavage to distinguish nosocomial pneumonia from systemic inflammatory response syndrome: a prospective analysis. J Trauma. 1995 Dec;39(6):1134-9; discussion 1139-40.	SIRS, which can mimic pneumonia, is common in trauma patients. These entities can be distinguished by bronchoscopy with BAL. Basing antibiotic therapy solely on quantitative BAL cultures is efficacious in trauma patients.
McKindley DS, Boucher BA, Hess MM, Croce MA, Fabian TC. Pharmacokinetics of aztreonam and imipenem in critically ill patients with pneumonia. Pharmacotherapy. 1996 Sep-Oct;16(5):924-31.	Larger volumes of distribution were observed for both aztreonam and imipenem in trauma patients than in volunteers, suggesting that standard initial dosages of the antibiotics may result in lower concentrations in these critically ill patients. Both antibiotics penetrated into the sputum of most patients; however, the degree of penetration was highly variable in relation to serum concentrations.
Croce MA, Fabian TC, Waddle-Smith L, Melton SM, Minard G, Kudsk KA, Pritchard FE. Utility of Gram's stain and efficacy of quantitative cultures for posttraumatic pneumonia: a prospective study. Ann Surg. 1998 May;227(5):743–51; discussion 751-5.	Bronchoscopy with BAL is an effective method to diagnose pneumonia and avoids prolonged, unnecessary antibiotic therapy. Empiric therapy should be adjusted to the duration of the ICU stay because the causative bacteria flora changes over time. Gram stain of BAL effluent correlates poorly with quantitative cultures and is not reliable for dictating empiric therapy.
Hanes SD, Wood GC, Herring V, Croce MA, Fabian TC, Pritchard E, Boucher BA. Intermittent and continuous ceftazidime infusion for critically ill trauma patients. Am J Surg. 2000 Jun;179(6):436-40.	Ceftazidime pharmacokinetics are significantly altered in critically ill trauma patients. Both intermittent and continuous ceftazidime regimens were equally effective for the treatment of nosocomial pneumonia caused by less virulent bacteria.
Croce MA, Fabian TC, Waddle-Smith L, Maxwell RA. Identification of early predictors for post-traumatic pneumonia. Am Surg. 2001 Feb;67(2):105-10.	Logistic regression analysis identified age; Glasgow Coma Scale score; Injury Severity Score; transfusion requirements during resuscitation; spinal cord injury; chest injury severity; and emergent femur fixation, craniotomy, and laparotomy as being independent predictors of pneumonia.
Wood GC, Hanes SD, Croce MA, Fabian TC, Boucher BA. Comparison of ampicillin-sulbactam and imipenem-cilastatin for the treatment of acinetobacter ventilator-associated pneumonia. Clin Infect Dis. 2002 Jun 1;34(11):1425-30.	Treatment efficacy was similar in the ampicillin–sulbactam and imipenem–cilastatin groups (93% vs 83%, respectively; p>0.05). No statistically significant differences between groups were noted with regard to associated mortality, duration of mechanical ventilation, or length of stay in the ICU or hospital. However, adjunctive aminoglycoside therapy was used more often in the ampicillin–sulbactam group. Patients generally received ampicillin–sulbactam because of imipenem resistance.
Hanes SD, Demirkan K, Tolley E, Boucher BA, Croce MA, Wood GC, Fabian TC. Risk factors for late-onset nosocomial pneumonia caused by Stenotrophomonas maltophilia in critically ill trauma patients. Clin Infect Dis. 2002 Aug 1;35(3):228-35.	By multivariate analysis, *Stenotrophomonas maltophilia* pneumonia was found to be associated with cefepime exposure and tracheostomy in patients with a single pneumonia episode and with higher Injury Severity Score and pulmonary contusion in patients with multiple pneumonia episodes. *S. maltophilia* pneumonia was associated with increased patient morbidity; only inadequate empiric antibiotic therapy was associated with a higher mortality rate. In critically ill trauma patients with late-onset VAP and these risk factors, empiric antibiotic therapy should include agents active against *S. maltophilia*.
Wood GC, Boucher BA, Croce MA, Hanes SD, Herring VL, Fabian TC. Aerosolized ceftazidime for prevention of ventilator-associated pneumonia and drug effects on the proinflammatory response in critically ill trauma patients. Pharmacotherapy. 2002 Aug;22(8):972-82.	Aerosolized ceftazidime decreased the frequency of VAP in critically ill trauma patients, without adversely affecting ICU flora. Aerosolized ceftazidime also may attenuate the proinflammatory response in the lung.
Croce MA, Tolley EA, Fabian TC. A formula for prediction of posttraumatic pneumonia based on early anatomic and physiologic parameters. J Trauma. 2003 Apr;54(4):724-9; discussion 729-30.	It is possible to accurately predict risk for VAP in trauma patients based on data available early after injury. This calculation could be useful for counseling families relative to prognosis and research protocols, and addressing hospitalization issues with third-party payors.
Mueller EW, Wood GC, Kelley MS, Boucher BA, Fabian TC, Croce MA. The predictive value of preliminary bacterial colony counts from bronchoalveolar lavage in critically ill trauma patients. Am Surg. 2003 Sep;69(9):749-55; discussion 755-6.	Isolates with significant preliminary growth should be considered clinically important, and antibiotic therapy should be changed, if necessary, to target such organisms. Isolates with insignificant preliminary growth have a low rate of false negatives; therefore, empiric antibiotic therapy specific for such organisms could be discontinued before obtaining final results.
Wood GC, Hanes SD, Boucher BA, Croce MA, Fabian TC. Tetracyclines for treating multidrug-resistant Acinetobacter baumannii ventilator-associated pneumonia. Intensive Care Med. 2003 Nov;29(11):2072-6.	Doxycycline or minocycline may be effective for treating multidrug-resistant *Acinetobacter baumannii* VAP.
Croce MA, Fabian TC, Mueller EW, Maish GO 3rd, Cox JC, Bee TK, Boucher BA, Wood GC. The appropriate diagnostic threshold for ventilator-associated pneumonia using quantitative cultures. J Trauma. 2004 May;56(5):931–4; discussion 934-6.	The VAP diagnostic threshold for quantitative BAL in trauma patients should be $>10^5$ colonies/mL. One may consider a threshold of $>10^4$ colonies/mL in severely injured patients with *Pseudomonas* or *Acinetobacter* spp.
Mueller EW, Hanes SD, Croce MA, Wood GC, Boucher BA, Fabian TC. Effect from multiple episodes of inadequate empiric antibiotic therapy for ventilator-associated pneumonia on morbidity and mortality among critically ill trauma patients. J Trauma. 2005 Jan;58(1):94-101.	Critically ill trauma patients experiencing multiple episodes of inadequate empiric antibiotic therapy for VAP have increased morbidity and mortality. These findings reinforce the importance of developing and refining a unit-specific pathway for the empiric management of VAP.

Continued

Table 1 Continued

Study	Conclusions
Magnotti LJ, Croce MA, Fabian TC. Is ventilator-associated pneumonia in trauma patients an epiphenomenon or a cause of death? Surg Infect (Larchmt). 2004 Fall;5(3):237-42.	VAP is independently associated with death in less severely injured trauma patients. This demonstrates the need for effective diagnostic techniques so that adequate therapy may be initiated. Prevention of VAP in less severely injured trauma patients should increase survival.
Croce MA, Tolley EA, Claridge JA, Fabian TC. Transfusions result in pulmonary morbidity and death after a moderate degree of injury. J Trauma. 2005 Jul;59(1):19-23; discussion 23-4.	Delayed transfusion is independently associated with VAP, ARDS, and death in trauma patients regardless of injury severity.
Wood GC, Mueller EW, Croce MA, Boucher BA, Fabian TC. Candida sp. isolated from bronchoalveolar lavage: clinical significance in critically ill trauma patients. Intensive Care Med. 2006 Apr;32(4):599-603.	The results of this study suggest that isolation of *Candida* sp from BAL in quantities below the diagnostic threshold for VAP in this population does not require antifungal therapy.
Croce MA, Swanson JM, Magnotti LJ, Claridge JA, Weinberg JA, Wood GC, Boucher BA, Fabian TC. The futility of the clinical pulmonary infection score in trauma patients. J Trauma. 2006 Mar;60(3):523-7; discussion 527-8.	The clinical pulmonary infection score (CPIS) cannot differentiate VAP from SIRS in critically injured patients. Using CPIS to initiate antibiotic therapy in trauma patients could be harmful. Whether CPIS is useful to determine duration of antibiotic therapy is unknown.
Claridge JA, Edwards NM, Swanson J, Fabian TC, Weinberg JA, Wood C, Croce MA. Aerosolized ceftazidime prophylaxis against ventilator-associated pneumonia in high-risk trauma patients: results of a double-blind randomized study. Surg Infect (Larchmt). 2007 Feb;8(1):83-90.	The use of aerosolized ceftazidime did not reduce the rate of VAP in high-risk patients admitted after traumatic injury, but neither did it increase the incidence of other infectious complications. Routine use of prophylactic aerosolized ceftazidime to prevent VAP in trauma patients cannot be recommended.
Mueller EW, Croce MA, Boucher BA, Hanes SD, Wood GC, Swanson JM, Chennault SK, Fabian TC. Repeat bronchoalveolar lavage to guide antibiotic duration for ventilator-associated pneumonia. J Trauma. 2007 Dec;63(6):1329-37; discussion 1337.	Repeat BAL decreased the duration of antibiotic therapy for VAP in trauma patients. More adequately powered investigations are needed to appropriately determine the effects of this strategy on patient outcome.
Magnotti LJ, Schroeppel TJ, Fabian TC, Clement LP, Swanson JM, Fischer PE, Bee TK, Maish GO 3rd, Minard G, Zarzaur BL, Croce MA. Reduction in inadequate empiric antibiotic therapy for ventilator-associated pneumonia: impact of a unit-specific treatment pathway. Am Surg. 2008 Jun;74(6):516-22; discussion 522-3.	Trauma patients with multiple IEAT episodes for VAP have increased morbidity and mortality. Adherence to a unit-specific pathway for the empiric management of VAP reduces multiple IEAT episodes. By limiting IEAT episodes, resource utilization and hospital mortality are significantly decreased.
Swanson JM, Wood GC, Croce MA, Mueller EW, Boucher BA, Fabian TC. Utility of preliminary bronchoalveolar lavage results in suspected ventilator-associated pneumonia. J Trauma. 2008 Dec;65(6):1271-7.	Preliminary BALs were highly predictive for final results. Using insignificant preliminary BALs appears to be a safe strategy for promptly discontinuing empirical antibiotics in trauma patients with suspected VAP.
Magnotti LJ, Schroeppel TJ, Clement LP, Swanson JM, Bee TK, Maish GO 3rd, Minard G, Zarzaur BL, Fischer PE, Fabian TC, Croce MA. Efficacy of monotherapy in the treatment of Pseudomonas ventilator-associated pneumonia in patients with trauma. J Trauma. 2009 Apr;66(4):1052-8; discussion 1058-9.	Monotherapy in the treatment of *Pseudomonas* VAP has an excellent success rate in patients with trauma. Empiric monotherapy therapy should be modified once susceptibility of the microorganism is documented (all isolates were sensitive to cefepime) and antibiotic choice should be based on local patterns of susceptibilities. The routine use of combination therapy for synergy is unnecessary. Combination therapy should be reserved for patients with persistent microbiological evidence of *Pseudomonas* VAP despite adequate therapy.
Czosnowski QA, Wood GC, Magnotti LJ, Croce MA, Swanson JM, Boucher BA, Fabian TC. Adjunctive aerosolized antibiotics for treatment of ventilator-associated pneumonia. Pharmacotherapy. 2009 Sep;29(9):1054-60.	Treatment with adjunctive aerosolized antibiotics was associated with a good response rate in critically ill trauma patients with VAP due to non-fermenting gram-negative bacilli (NFGNB). It is noteworthy that episodes of VAP that followed intravenous therapy failure and/or that were due to multidrug-resistant organisms responded well.
Swanson JM, Mueller EW, Croce MA, Wood GC, Boucher BA, Magnotti LJ, Fabian TC. Changes in pulmonary cytokines during antibiotic therapy for ventilator-associated pneumonia. Surg Infect (Larchmt). 2010 Apr;11(2):161-7.	This pilot study indicates pulmonary concentrations of IL-8 and TNF-alpha decrease in microbiologic responders with VAP. Conversely, clinical response parameters were discordant with the microbiologic response. The utility of pulmonary cytokine behavior in evaluating the effectiveness of antibiotic therapy for VAP should be studied further.
Amin PB, Magnotti LJ, Fischer PE, Fabian TC, Croce MA. Prophylactic antibiotic days as a predictor of sensitivity patterns in Acinetobacter pneumonia. Surg Infect (Larchmt). 2011 Feb;12(1):33-8.	The incidence of MDR *Acinetobacter* VAP has increased over time. More severe extremity injuries, as measured by the AIS, may contribute to prolonged antibiotic exposure in those patients with MDR *Acinetobacter* VAP. Multiple logistic regression identified pro-antibiotic days as an independent risk factor for MDR *Acinetobacter* VAP in trauma patients.
Czosnowski QA, Wood GC, Magnotti LJ, Croce MA, Swanson JM, Boucher BA, Fabian TC. Clinical and microbiologic outcomes in trauma patients treated for Stenotrophomonas maltophilia ventilator-associated pneumonia. Pharmacotherapy. 2011 Apr;31(4):338-45.	Critically ill trauma patients with *S. maltophilia* VAP responded well to therapy despite high rates of inadequate empiric antibiotic administration. Trimethoprim–sulfamethoxazole was the most common therapy, but clinical success rates did not differ significantly based on antibiotic selection. This study adds significantly to the available *S. maltophilia* VAP outcomes data.
Magnotti LJ, Croce MA, Zarzaur BL, Swanson JM, Wood GC, Weinberg JA, Fabian TC. Causative pathogen dictates optimal duration of antimicrobial therapy for ventilator-associated pneumonia in trauma patients. J Am Coll Surg. 2011 Apr;212(4):476-84; discussion 484-6.	Repeat BAL provides objective evidence for VAP resolution in the face of potentially confounding clinical factors. Hospital-acquired VAP can be managed effectively by a defined course of therapy with a low recurrence. Duration of antimicrobial therapy for VAP in trauma patients should be dictated by the causative pathogen.
Hamilton LA, Christopher Wood G, Magnotti LJ, Croce MA, Martin JB, Swanson JM, Boucher BA, Fabian TC. Treatment of methicillin-resistant Staphylococcus aureus ventilator-associated pneumonia with high-dose vancomycin or linezolid. J Trauma Acute Care Surg. 2012 Jun;72(6):1478-83.	High-dose vancomycin provided an acceptable cure rate for MRSA VAP in critically ill trauma patients.
Parks NA, Magnotti LJ, Weinberg JA, Zarzaur BL, Schroeppel TJ, Swanson JM, Fabian TC, Croce MA. Use of the clinical pulmonary infection score to guide therapy for ventilator-associated pneumonia risks antibiotic overexposure in patients with trauma. J Trauma Acute Care Surg. 2012 Jul;73(1):52-8; discussion 58-9.	CPIS should not be used to determine VAP resolution in patients with critical injury and trauma. It cannot reliably differentiate VAP from the SIRS in the face of confounding clinical factors. Using CPIS to determine appropriate duration of antimicrobial therapy for patients with trauma is costly and could be harmful by unnecessarily prolonging exposure to antibiotics.

Continued

Table 1 Continued

Study	Conclusions
Swanson JM, Wood GC, Xu L, Tang LE, Meibohm B, Homayouni R, Croce MA, Fabian TC. Developing a gene expression model for predicting ventilator-associated pneumonia in trauma patients: a pilot study. PLoS One. 2012;7(8):e42065.	A logistic regression model was developed that accurately predicted critically injured trauma patients who went on to develop VAP (VAP+) and those who did not (VAP–). Five genes (PIK3R3, ATP2A1, PI3, ADAM8, and HCN4) were common to all top 20 significant genes that were identified from all independent training sets in the cross-validation. Hierarchical clustering using these five genes accurately categorized 95% of patients and PCA visualization demonstrated two discernible groups (VAP+ and VAP–).
Swanson JM, Connor KA, Magnotti LJ, Croce MA, Johnson J, Wood GC, Fabian TC. Resolution of clinical and laboratory abnormalities after diagnosis of ventilator-associated pneumonia in trauma patients. Surg Infect (Larchmt). 2013 Feb;14(1):49-55.	Clinical and laboratory abnormalities in critically injured patients with VAP do not resolve as quickly as suggested in the guidelines. Future studies should evaluate new methods to determine the response to antibiotic therapy in critically injured patients with VAP.
Zarzaur BL, Bell TM, Croce MA, Fabian TC. Geographic variation in susceptibility to ventilator-associated pneumonia after traumatic injury. J Trauma Acute Care Surg. 2013 Aug;75(2):234-40.	Spatial factors that are independent of healthcare quality may potentiate the likelihood of a patient developing VAP and possibly other types of healthcare-acquired infections. Unmodifiable environmental patient characteristics may predispose certain populations to developing infections in the setting of trauma.
Hill DM, Schroeppel TJ, Magnotti LJ, Clement LP, Sharpe JP, Fischer PE, Weinberg JA, Croce MA, Fabian TC. Methicillin-resistant Staphylococcus aureus in early ventilator-associated pneumonia: cause for concern? Surg Infect (Larchmt). 2013 Dec;14(6):520-4.	Although the incidence of early *Staphylococcus aureus* VAP with methicillin resistance increased significantly within the first 7 days of admission, this study showed no difference in mortality and resource utilization between early VAP from MRSA and other causative organisms, despite lack of empiric MRSA coverage.
Sharpe JP, Magnotti LJ, Weinberg JA, Brocker JA, Schroeppel TJ, Zarzaur BL, Fabian TC, Croce MA. Gender disparity in ventilator-associated pneumonia following trauma: identifying risk factors for mortality. J Trauma Acute Care Surg. 2014 Jul;77(1):161-5.	That females develop less VAP but experience increased mortality confirms previous studies. Characteristics of severe VAP are increased in females and may contribute to this observed mortality difference. Multivariable logistic regression identified eNVAP as an independent predictor of mortality in females with severe VAP after trauma.
Sharpe JP, Magnotti LJ, Weinberg JA, Swanson JM, Wood GC, Fabian TC, Croce MA. Impact of pathogen-directed antimicrobial therapy for ventilator-associated pneumonia in trauma patients on charges and recurrence. J Am Coll Surg. 2015 Apr;220(4):489-95.	Hospital-acquired VAP can be managed effectively by a defined course of therapy dictated by the causative pathogen. Adherence to an established algorithm simplified the management of VAP and contributed to a cumulative reduction in patient charges without impacting recurrence.
Sharpe JP, Magnotti LJ, Weinberg JA, Swanson JM, Schroeppel TJ, Clement LP, Wood GC, Fabian TC, Croce MA. Adherence to an established diagnostic threshold for ventilator-associated pneumonia contributes to low false-negative rates in trauma patients. J Trauma Acute Care Surg. 2015 Mar;78(3):468-73; discussion 473-4.	Continued adherence to the diagnostic threshold of equal to or greater than 10^5 for quantitative BAL in trauma patients has maintained a low incidence of FN BALs and reduced patient charges without impacting mortality. The purported benefit of a lower threshold is not supported. In addition, the potential sequelae of increased resistant organisms, antibiotic-related complications, and costs associated with prolonged unnecessary antibiotic exposure are minimized.
Wood GC, Jonap BL, Maish GO 3rd, Magnotti LJ, Swanson JM, Boucher BA, Croce MA, Fabian TC. Treatment of Achromobacter Ventilator-Associated Pneumonia in Critically Ill Trauma Patients. Ann Pharmacother. 2018 Feb;52(2):120-125.	*Achromobacter* is a rare but potentially serious cause of VAP in critically ill patients. In this study, there was an acceptable success rate compared with other causes of NFGNB VAP in this patient population.
Lewis RH, Sharpe JP, Swanson JM, Fabian TC, Croce MA, Magnotti LJ. Reinventing the wheel: Impact of prolonged antibiotic exposure on multidrug-resistant ventilator-associated pneumonia in trauma patients. J Trauma Acute Care Surg. 2018 Aug;85(2):256-262.	Prolonged exposure to unnecessary antibiotics remains one of the strongest predictors for the development of antibiotic resistance. Multivariable logistic regression identified prophylactic antibiotic days and mIEAT an independent risk factors for MDR VAP. Thus, limiting prophylactic antibiotic days is the only potentially modifiable risk factor for the development of MDR VAP in trauma patients.
Evans CR, Sharpe JP, Swanson JM, Wood GC, Fabian TC, Croce MA, Magnotti LJ. Keeping it Simple: Impact of a Restrictive Antibiotic Policy for Ventilator-Associated Pneumonia in Trauma Patients on Incidence and Sensitivities of Causative Pathogens. Surg Infect (Larchmt). 2018 Oct;19(7):672-678.	A comprehensive protocol for the diagnosis and management of VAP, along with antibiotic stewardship, can prevent the development of bacterial resistance to empiric therapy.
Gibson BH, Sharpe JP, Lewis RH, Newell JS, Swanson JM, Wood GC, Fabian TC, Croce MA, Magnotti LJ. Use of Aerosolized Antibiotics in Gram-Negative Ventilator-Associated Pneumonia in Trauma Patients. Am Surg. 2018 Dec 1;84(12):1906-1912.	Multivariable logistic regression identified VAP persistence and relapse as independent predictors for the use of aerosolized antibiotics. Combined with systemic therapy, aerosolized antibiotics broaden the spectrum of therapy. They are valuable adjuncts with minimal risk of antibiotic resistance and/or systemic complications.

AIS, Abbreviated Injury Scale; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CPIS, Clinical Pulmonary Infection Score; eNVAP, Early (within 7 days of admission) nosocomial ventilator associated pneumonia; FN, False negative; ICU, intensive care unit; IEAT, inappropriate empirical antibiotic therapy; IL-8, interleukin 8; MDR, multidrug-resistant; mIEAT, Multiple episodes of inappropriate empirical antiobiotic therapy; MRSA, methicillin-resistant *Staphylococcus aureus*; NFGNB, Non-fermenting gram negative bacillus; PCA, principal component analysis; PSB, protected specimen brush; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor; VAP, ventilator-associated pneumonia.

Importantly, this article included the details of a provocative pilot study to determine if empiric therapy could be stopped safely should the lower respiratory tract cultures be negative. It is important to note that it was common practice at that time to continue antibiotics irrespective of culture results should the clinical picture resemble pneumonia, and cessation of antibiotics would have been perceived as putting the patient at risk. Ten patients were studied and seven did not meet the prespecified lavage criteria for diagnosis of pneumonia of $\geq 10^5$ colony-forming units (cfu)/mL and antibiotics were discontinued. One of these patients subsequently died of their head injury, but the remaining six patients clinically improved without continuation of antibiotic therapy. From this observation, the Memphis group proposed that bronchoscopy with BAL was able to differentiate trauma patients with de facto lower respiratory tract infection from those with SIRS, paving the way for their next study.

The proof-of-concept study was completed in 1994 and presented at the Eastern Association of Trauma Annual Meeting in 1995.[8] This study sought to answer two questions with respect to suspected pneumonia in mechanically ventilated trauma patients: (1) can quantitative BAL culture differentiate pneumonia from SIRS, and (2) can antibiotic therapy be based solely

on quantitative BAL cultures? In this prospective study, patients with clinically suspected VAP (based on the presence of abnormal body temperature, leukocytosis, grossly purulent sputum, and new or changing infiltrate on chest X-ray) underwent fiberoptic bronchoscopy with BAL, and only those with significant bacterial colony counts ($\geq 10^5$ cfu/mL) were treated with a full course of therapeutic antibiotics. Forty-three patients underwent bronchoscopy 55 times, and 20 were identified to have pneumonia according to quantitative culture result (the remaining 23 were designated as having SIRS). For the patients with SIRS, antibiotics were stopped after culture result (average 3.3 days). Sixty-five percent of these patients clinically improved after antibiotic cessation. The remaining 35% continued to demonstrate clinical suspicion of pneumonia and underwent repeat bronchoscopy with BAL. Among these eight patients, three were identified to have developed pneumonia per quantitative culture result on repeat bronchoscopy; the remaining five ultimately had clinical improvement without continuation of antibiotics. From this study, it was concluded that bronchoscopy with quantitative culture from BAL could in fact distinguish pneumonia from SIRS and dictate the appropriateness of the continuation of antibiotic therapy. This approach to the diagnosis of pneumonia then became standard practice in the Memphis Trauma ICU.

A follow-up prospective study involving 232 patients during a 2-year period was presented at the annual meeting of the Southern Surgical Association in 1997 and served to establish a false negative rate of 7% when using a cut-off point of $\geq 10^5$ cfu/mL to establish the diagnosis of pneumonia.[1] In this study, empiric antibiotic therapy was instituted on all patients after BAL. A third-generation antipseudomonal cephalosporin, a quinolone, or a carbapenem was administered at the discretion of attending physician, and vancomycin was added if the gram stain demonstrated gram-positive organisms. This study revealed two important findings. Organisms identified by quantitative culture $\geq 10^5$ cfu/mL were compared with the gram stain, and it was observed that the gram stain of the BAL effluent correlated poorly with the ultimate culture result and would therefore not be useful in guiding specific antibiotic empiric therapy. However, the investigators identified that duration of hospital stay could guide empiric therapy with respect to antibiotic choice. In the first week of ICU stay, BAL primarily identified *Haemophilus influenzae* and gram-positive organisms, whereas *Acinetobacter* and *Pseudomonas* were more common after the first week (figure 1).

The third study from Memphis related to the diagnosis of pneumonia among ventilated trauma patients was presented at the annual meeting of the American Association for the Surgery of Trauma (AAST) in 2003.[9] The purpose of that study was to determine the optimal diagnostic threshold for pneumonia with respect to quantitative cultures. Based on their own mortality data, the Memphis group had chosen a threshold of 10^5 cfu/mL to distinguish pneumonia from SIRS. As derived from their first study, the mortality rate of all patients with 10^5 cfu/mL was significantly higher than patients with less than 10^5 cfu/mL (29% vs. 14%, $p<0.04$). Nonetheless, there was not a consensus at the time as to what diagnostic threshold was optimal and, in fact, a lower diagnostic threshold was generally recommended in the medical ICU setting. In this study of 526 patients who underwent 1372 bronchoscopies with BAL, the sensitivities, specificities, positive and negative predictive values were determined with respect to the diagnostic thresholds of 10^5 cfu/mL and 10^4 cfu/mL. As demonstrated in table, test performance was better at 10^5 cfu/mL with improved specificity and positive predictive value without any large reduction in either sensitivity or negative predictive value. This study solidified the diagnostic threshold of 10^5 cfu/mL for trauma patients and remains the diagnostic threshold in the Memphis trauma ICU today. In accordance with the theme of continuous performance improvement, the diagnostic threshold was re-evaluated a decade later, presented at the annual meeting of the AAST in 2014.[10] This study comprised 1679 patients who underwent 3202 bronchoscopies with BAL, during a 9-year period. Using 10^5 cfu/mL as a diagnostic threshold, a low false negative rate continued to be achieved (2.3%), the false negative rate among those with 10^4 cfu/mL remained low (7.5%) as well. The current clinical pathway for initial diagnosis is demonstrated in figure 2.

TREATMENT

Continuous querying of their own data led the Memphis group to refine the treatment of pneumonia as well as the diagnosis. At a time when most patients were treated for 14–21 days for

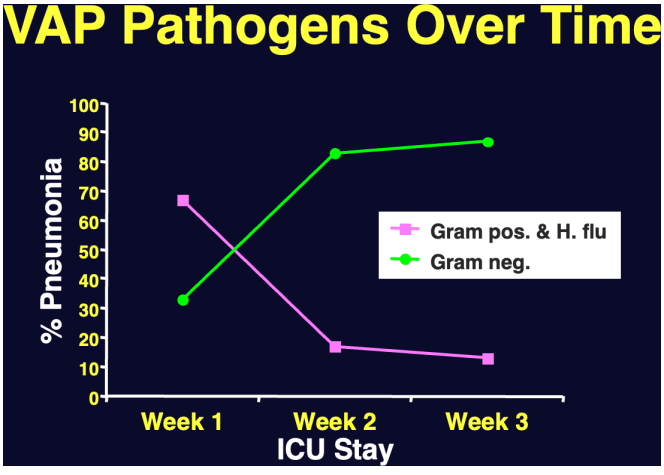

Figure 1 Change in incidence of VAP pathogens over time (week of ICU length of stay). Courtesy of Dr Martin Croce. ICU, intensive care unit; VAP, ventilator-associated pneumonia.

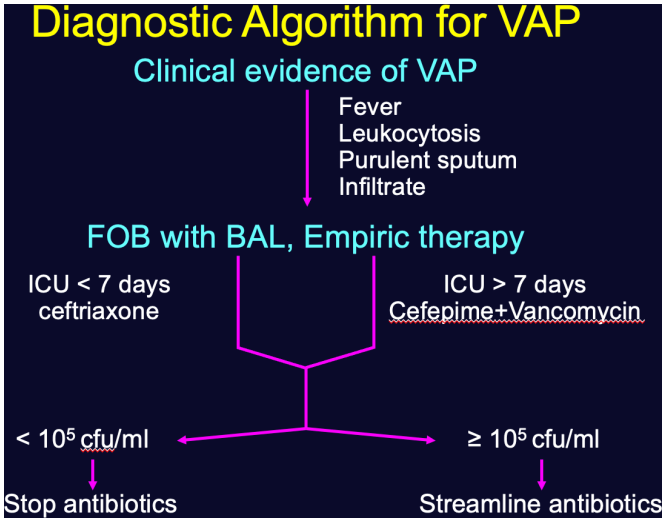

Figure 2 Diagnostic algorithm for the determination of VAP at the Elvis Presley Trauma Center. Courtesy of Dr Louis Magnotti. BAL, bronchoalveolar lavage; cfu, colony-forming units; FOB, fiberoptic bronchoscopy; ICU, intensive care unit; VAP, ventilator-associated pneumonia.

hospital-acquired pneumonia, the Memphis group recognized that, in trauma patients, clinical resolution of pneumonia may be as difficult to determine as onset of pneumonia, given the often-present confounders of pulmonary contusion, atelectasis, ongoing SIRS from multiple injuries and or multiple operations to manage multiple injuries. Guidelines from the American Thoracic Society suggested that patients with VAP should respond clinically by day 3 of appropriate antibiotic treatment.[11] The Memphis group demonstrated in a retrospective study of 126 trauma patients with VAP that neither temperature nor white cell count or the ratio of partial pressure arterial blood oxygenation to the fractional inspired oxygen changed significantly during the course of a 16-day follow-up suggesting that clinical and laboratory abnormalities in injured patients with pneumonia do not in fact resolve promptly.[12]

Dr Fabian and colleagues proposed a microbiological-based approach to treatment duration, first described in a study presented at the Critical Care Congress of the Society of Critical Care Medicine in 2004.[13] The purpose of this pilot study was to determine if the duration of antibiotic therapy could be safely abbreviated in critically ill trauma patients who demonstrate a significant reduction in pulmonary bacterial growth on repeat quantitative BAL culture on day 4 of therapy. Significant reduction was defined as less than 10^4 cfu/mL quantitative culture growth. Ninety-six percent of early VAP isolates (ie, 7 days or less from admission) responded (ie, significant reduction) on repeat BAL compared with 71% of late-occurring VAP isolates (ie, beyond 7 days). It was therefore concluded that patients with early VAP (eg, less than 7 days and methicillin-sensitive *Staphylococcus aureus*, *Haemophilus*, or *Streptococcus* spp) could be treated for 7 days without need for repeat BAL. This prompted a clinical practice of treating early VAP for 7 days and late-occurring VAP according to repeat BAL as performed on day 4 and every 3 days thereafter as dictated by bacterial quantitative cultures.

This clinical practice was further refined as a result of a performance analysis presented in 2010 at the annual meeting of the Southern Surgical Association.[14] The purpose of this study was to determine the appropriate duration of antimicrobial therapy for VAP in trauma patients secondary to hospital-acquired pathogens (ie, late pneumonia) based solely on the causative pathogen by using quantitative cultures on repeat BAL. The results of this study demonstrated that by using a bacteriologic response threshold on repeat quantitative BAL culture, the optimal duration of antimicrobial therapy for VAP in trauma patients secondary to hospital-acquired pathogens could be determined accurately. To achieve microbiologic resolution in patients with either methicillin-resistant *S. aureus* VAP or *Pseudomonas* sp VAP, the majority of patients (62% with methicillin-resistant *S. aureus* VAP and 81% with *Pseudomonas* sp VAP) required 14 days of appropriate antimicrobial therapy. Although up to one-third of patients with methicillin-resistant *S. aureus* VAP responded to shorter-course therapy (7 or 10 days), this abbreviated treatment would have resulted in an unacceptable number of undertreated patients. In contrast, nearly 60% of patients with *Acinetobacter* (60%), *Stenotrophomonas* (58%), or *Enterobacter* spp (62%) VAP achieved microbiologic resolution after 10 days of appropriate antimicrobial therapy. However, an additional 30% of these patients required prolonged therapy (for a total of 14 days). By performing repeat BAL on day 7 of appropriate therapy, both patients who have achieved microbiologic resolution (by day 10) and those requiring additional therapy could be identified. This study led to a change in practice whereby early community-acquired pneumonia would receive antibiotic treatment for 7 days and hospital-acquired pneumonia would receive antibiotic treatment according to microbiologic resolution with repeat bronchoscopy performed on day 7. This clinical pathway (figure 3) remains the current management algorithm in Memphis and has been demonstrated to be durably efficacious without contributing to antimicrobial resistance.[15]

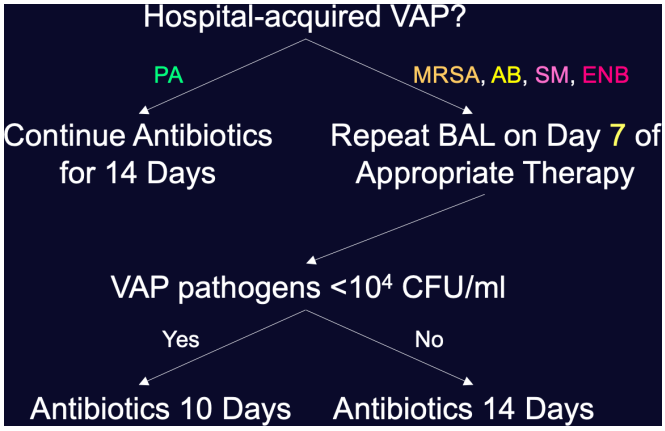

Figure 3 Management pathway for the treatment of hospital-acquired VAP at the Elvis Presley Trauma Center. Courtesy of Dr Louis Magnotti. AB, *Acinetobacter*; CFU, colony-forming units; ENB, *Enterobacter;* MRSA, *methicillin-resistant Staphylococcus aureus;* PA, *Pseudomonas;* SM, *Stenotrophomonas;* VAP, ventilator-associated pneumonia.

CONCLUSION

The Memphis contribution to the diagnosis and management of pneumonia within the domain of surgical critical care is

Figure 4 The author (left) with Dr Timothy Fabian (center) and Dr Louis Magnotti (right) at the annual meeting of the American Association for the Surgery of Trauma in 2019.

commendable. As can be understood from this review, it also is demonstrative as to how an iterative quality improvement process can both inform and influence the practice at a single institution and contribute to the body of clinical research so that other centers may learn from, implement, and further refine clinical pathways for the betterment of patient care. We often think of 'bench to bedside' when considering translational research. Without minimizing the importance of bench research, I hope to have illuminated the high yield of performing bedside research and applying it directly to bedside care. Dr Fabian applied this approach to clinical research across many domains; in fact, there is scarcely a topic related to trauma patient care that he and his Elvis Presley Trauma Center colleagues have not had influence. As a past trauma/critical care fellow and faculty member in Memphis, I am grateful to have had the privilege of Dr Fabian's mentorship and the opportunity to participate in the clinical research that has shaped the contemporary care of the trauma patient (figure 4).

Twitter Jordan A Weinberg @traumajaw

Contributors JAW wrote the article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

ORCID iD

Jordan A Weinberg http://orcid.org/0000-0001-5045-3524

REFERENCES

1 Croce MA, Fabian TC, Waddle-Smith L, Melton SM, Minard G, Kudsk KA, Pritchard FE. Utility of gram's stain and efficacy of quantitative cultures for posttraumatic pneumonia: a prospective study. *Ann Surg* 1998;227:743–51;
2 Sharpe JP, Magnotti LJ, Weinberg JA, Swanson JM, Wood GC, Fabian TC, Croce MA. Impact of pathogen-directed antimicrobial therapy for ventilator-associated pneumonia in trauma patients on charges and recurrence. *J Am Coll Surg* 2015;220:489–95.
3 Andrews CP, Coalson JJ, Smith JD, Johanson WG. Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. *Chest* 1981;80:254–8.
4 Chastre J, Viau F, Brun P, Pierre J, Dauge MC, Bouchama A, Akesbi A, Gibert C. Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. *Am Rev Respir Dis* 1984;130:924–9.
5 Fagon JY, Chastre J, Hance AJ, Guiguet M, Trouillet JL, Domart Y, Pierre J, Gibert C. Detection of nosocomial lung infection in ventilated patients. Use of a protected specimen brush and quantitative culture techniques in 147 patients. *Am Rev Respir Dis* 1988;138:110–6.
6 Meduri GU. Ventilator-Associated pneumonia in patients with respiratory failure. A diagnostic approach. *Chest* 1990;97:1208–19.
7 Croce MA, Fabian TC, Shaw B, Stewart RM, Pritchard FE, Minard G, Kudsk KA, Baselski VS. Analysis of charges associated with diagnosis of nosocomial pneumonia: can routine bronchoscopy be justified? *J Trauma* 1994;37:721–7.
8 Croce MA, Fabian TC, Schurr MJ, Boscarino R, Pritchard FE, Minard G, Patton JH Jr, Kudsk KA. Using bronchoalveolar lavage to distinguish nosocomial pneumonia from systemic inflammatory response syndrome: a prospective analysis. *J Trauma* 1995;39:1134–9;
9 Croce MA, Fabian TC, Mueller EW, Maish GO 3rd, Cox JC, Bee TK, Boucher BA, Wood GC. The appropriate diagnostic threshold for ventilator-associated pneumonia using quantitative cultures. *J Trauma* 2004;56:931–4;
10 Sharpe JP, Magnotti LJ, Weinberg JA, Swanson JM, Schroeppel TJ, Clement LP, Wood GC, Fabian TC, Croce MA. Adherence to an established diagnostic threshold for ventilator-associated pneumonia contributes to low false-negative rates in trauma patients. *J Trauma Acute Care Surg* 2015;78:468–73;
11 American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388–416.
12 Swanson JM, Connor KA, Magnotti LJ, Croce MA, Johnson J, Wood GC, Fabian TC. Resolution of clinical and laboratory abnormalities after diagnosis of ventilator-associated pneumonia in trauma patients. *Surg Infect (Larchmt)* 2013;14:49–55.
13 Mueller EW, Croce MA, Boucher BA, Hanes SD, Wood GC, Swanson JM, Chennault SK, Fabian TC. Repeat bronchoalveolar lavage to guide antibiotic duration for ventilator-associated pneumonia. *J Trauma* 2007;63:1329–37;
14 Magnotti LJ, Croce MA, Zarzaur BL, Swanson JM, Wood GC, Weinberg JA, Fabian TC. Causative pathogen dictates optimal duration of antimicrobial therapy for ventilator-associated pneumonia in trauma patients. *J Am Coll Surg* 2011;212:476–84;
15 Evans CR, Sharpe JP, Swanson JM, Wood GC, Fabian TC, Croce MA, Magnotti LJ. Keeping it simple: impact of a restrictive antibiotic policy for ventilator-associated pneumonia in trauma patients on incidence and sensitivities of causative pathogens. *Surg Infect (Larchmt)* 2018;19:672–8.