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Improvements in Pulmonary and General Critical Care Reduces Mortality following Ventilator-Associated Pneumonia

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Abstract

Background—Ventilator-associated pneumonia (VAP) is the most common hospital-acquired infection in the intensive care unit with substantial subsequent mortality. The mortality following VAP declined in the 1980s and 1990s. Experts suggest little progress has been made in outcomes from VAP since several novel interventions have failed. We nonetheless hypothesized that mortality following VAP has continued to decrease due to advances in pulmonary critical care.

Methods—We identified all adult patients with CDC-defined, ICU-acquired VAP between January 1st, 1997 and December 31st, 2008 from a prospectively-collected database.

Results—A total of 793 cases of VAP occurred in the study period. Cases were divided into four time periods (1997-1999, 2000-2002, 2003-2005, 2006-2008) to compare outcomes over time. APACHE II scores were stable, while mortality was significantly lower in period 4 when compared to periods 1 and 2 ($p = 0.004$ and 0.009 , respectively). A logistic regression model predicting death (c-statistic = 0.871) revealed age (OR 1.03, 95% CI 1.02-1.05), APACHE II score (1.09, 1.05-1.14), white blood cell count (1.03, 1.00-1.06), transplant recipient (3.45, 1.40-8.53), transfusions (3.25, 1.37-7.68), and pulmonary disease (3.01, 1.67-5.45) were independent predictors of death, as was the presence of trauma (0.10, 0.06-0.18), chronic steroid therapy (0.39, 0.17-0.91), and patient length of stay (0.99, 0.98-0.99) with odds ratios less than 1.0. Additionally, those patients treated in period 1 (2.23, 1.16-4.29) or period 2 (2.13, 1.12-4.06) had twice the risk of death following an episode of VAP when compared to those treated in the most recent time period.

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Author Contributions:

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Hranjec: data collection, data analysis, data interpretation, critical revision, final approval

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Conclusions—We have shown mortality following an episode of VAP continues to decrease over time and attribute this to advancements in pulmonary and general critical care rather than any specific interventions.

Keywords

Critical care; ventilator-associated pneumonia; organisms; antibiotics; mortality

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most common hospital-acquired infection in the intensive care unit (ICU) among patients receiving mechanical ventilation. (1, 2) It occurs in roughly 10-30% of all intubated patients and nearly all cases of healthcare-associated pneumonia occur in the setting of mechanical ventilation. (3-5) Ventilator-associated pneumonia has been associated with significantly extended days of mechanical ventilation, prolonged ICU and hospital length of stay, and excess costs of roughly \$40,000 when compared to mechanically ventilated patients without VAP. (3, 5)

In 2002, of the estimated 1.7 million total healthcare-associated infections, 250,000 were classified as pneumonia, and 101,000 occurred in the ICU. (6, 7) At that time, an estimated 36,000 deaths were associated with healthcare-associated pneumonia. (6, 8) The reported mortality following VAP ranges from 24 to 50% and is markedly higher in certain subpopulations or when caused by more aggressive organisms.

This high mortality following an episode of VAP declined during the 1980s and 1990s. Chastre and Fagon reviewed 12 studies of VAP in the ICU during these time periods and reported a mean mortality of 55.3% (range 30-76) in the 1980s, declining to a mean mortality of 38.0% (range 24-57) in the 1990s, revealing significant reduction in mortality following VAP. (4) We speculated this trend may have continued in the subsequent decade.

Regrettably, experts suggest little progress has been made in overall outcomes from sepsis, including VAP, since several novel interventions such as anti-TNF antibodies and other immunomodulators have failed to be consistently beneficial. We nonetheless hypothesized that mortality following an episode of VAP has decreased over the last decade due to general advances in pulmonary critical care and not to any specific identifiable single intervention.

MATERIALS and METHODS

This study was approved by the Institutional Review Board for Health Sciences Research (IRB-HSR) at the University of Virginia (IRB-HSR # 16122). Due to the retrospective and observational nature of the analysis the need for individual informed consent was waived.

Data Source

A prospective cohort of all adult general surgery, trauma, and transplantation patients admitted to the University of Virginia Medical Center and treated for any infectious complication was reviewed. All ICU-acquired cases of VAP were identified between January 1st, 1997 and December 31st, 2008 from a single surgical/trauma ICU by three times weekly chart review, direct patient examination, and a review of all daily laboratory, microbiology, and pharmacy reports. All data were prospectively collected until patient death or hospital discharge. (9-11)

Variables recorded for each infectious episode include age, sex, race, body mass index, location at time of infection, primary diagnosis, primary operation, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II score (12), maximum temperature and white blood cell count within 24 hours of treatment initiation, sites of infection, pathogens isolated, antibiotics provided, antibiotic susceptibilities, duration of treatment, length of hospitalization, and crude mortality. Comorbidities collected for each patient include diabetes mellitus, hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular disease, renal insufficiency (creatinine ≥ 2.0 mg/dL) prior to admission, hemodialysis dependence, pulmonary disease, mechanical ventilation (excluding immediate post-operative period), malignancy, hepatic dysfunction, chronic corticosteroid use, and solid organ transplantation.

All cases of VAP were defined in accordance with the CDC definition and diagnostic criteria. (13) Pneumonia was defined as production of purulent sputum, isolation of a predominant organism from a properly collected specimen, a new or changed infiltrate on chest radiograph and a quantitative endotracheal suction specimen with 10^4 colony-forming units/mL. (13) For the pneumonia to be classified as ventilator-associated, the patient must have been intubated and ventilated at the time of, or within 48 hours before, the onset of the pneumonia with no minimum duration for ventilation. (7)

Study Design

All identified cases of VAP were divided into four equal time periods (1997-1999, 2000-2002, 2003-2005, 2006-2008) to compare demographics and outcomes over time. For analysis, each independent episode of VAP was treated as a separate infection, even if occurring in the same patient. We also examined the types of isolated organisms, antibiotic selection, and the appropriateness of initial antibiotics.

Statistical Analysis

Demographics and comorbidities were tabulated and reported for each time period. Statistical analyses were performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC). Chi-square analysis or Fisher's exact test compared categorical variables between groups as appropriate, while continuous variables were compared using Student's *t*-test. Statistical significance was considered with a *p*-value ≤ 0.05 . A multiple logistic regression analysis was performed to determine independent predictors of death including variables selected *a priori*. We selected the following variables for inclusion into the model based on prior studies of predictors of death following VAP: age, sex, white blood count, APACHE II score, trauma or transplant patient, transfusion requirement, dialysis dependence, diabetes mellitus, pulmonary disease, corticosteroid therapy, antibiotic therapy, length of stay, and year of diagnosis and treatment (97-99, 00-02, 03-05, 06-08). From this multivariate model, odds ratios were determined.

RESULTS

During the 12-year study period we identified a total of 793 cases of VAP, including 211, 200, 190, 192 cases in each of the four time periods, respectively. The compiled demographics, comorbidities, and outcomes for each study period are shown in Table 1. Our data reveal a very minor trend of declining VAP events by approximately 3 cases per year. The mean age increased significantly over time (48.6 ± 1.1 vs. 52.8 ± 1.3 , $p = 0.01$), however, the APACHE II score remained relatively constant (20.6 ± 0.4 vs. 20.1 ± 0.4 , $p = 0.38$). These data indicate an aging population with overall comparable ICU admission severity-of-illness.

Other notable demographics that changed over time include a higher proportion of trauma patients (63.0% vs. 72.9%, $p = 0.04$) and those with underlying pulmonary disease (7.1% vs. 15.1%, $p = 0.01$). Additionally, there were fewer transfusions (94.8% vs. 76.6%, $p < 0.0001$) and fewer patients on chronic steroid therapy (15.6% vs. 6.3%, $p = 0.004$) over our study period.

In the latter part of our study the white blood cell count at the time of VAP diagnosis was significantly lower than at the beginning of the study period (13.8 ± 0.5 vs. 16.3 ± 0.6 , $p = 0.001$), suggesting an earlier diagnosis and initiation of treatment. However, neither days of antibiotic treatment (13.4 ± 0.5 vs. 14.0 ± 0.8 , $p = 0.52$) nor the subsequent total length of stay (33.9 ± 2.1 vs. 39.2 ± 2.7 , $p = 0.12$) were significantly different over the course of our study. With each subsequent time period there were approximately ten fewer deaths following an episode of VAP, resulting in a significantly lower per case mortality in the final time period (2006-2008) when compared to the first (1997-1999), (25.6% vs. 14.1%, $p = 0.004$). This trend remained when analyzing patient-level data (as opposed to infection-level data); mortality was significantly lower in the final period (11.8%) as compared to the early period 26.6% ($p = 0.002$, Table 2).

From the 793 cases of VAP, a total of 1102 individual organisms were isolated. These were comprised of 743 gram-negative bacteria, 289 gram-positive, 33 fungi, and 37 isolates with "mixed flora" in the setting of an aspiration pneumonia. Over our study period the proportion of each type of organism did not change significantly. The frequency and distribution of the specific gram-negative and -positive organisms for each study period are shown. (Tables 3, 4) The mean percentage of appropriate initial antibiotic therapy for episodes of VAP throughout the study period was 70.5%. This percentage did not vary significantly from year to year. While we do not have this data for the first study period (1997-1999), the percentage of appropriate initial therapy was 70.9%, 68.4%, and 73.6% for each of the three subsequent study periods, respectively.

The total courses of antibiotic treatments for each time period can be seen in Figure 1. Over the last decade we have used fewer fluoroquinolones (most commonly ciprofloxacin) and aminoglycosides. We used similar courses of the cephalosporins and carbapenems, and have seen a steadily increasing use of penicillins, likely due to the empiric antibiotic selection of piperacillin/tazobactam. Vancomycin and linezolid were used with increasing frequency.

The logistic regression model predicting death revealed age, APACHE II score, admission for trauma, transplant recipient, transfusions, pulmonary disease, chronic steroid use, and length of stay were all independent predictors of death. (Table 5) Additionally, being diagnosed with and treated for an episode of VAP during the time period of 1997-1999 or 2000-2002 conferred an independent prediction of death when compared to the most recent time period. Sex, white blood cell count, the presence of diabetes mellitus or dialysis dependence, and antibiotic treatment length were not predictive of death following an episode of VAP.

DISCUSSION

The classically high mortality following VAP is of great significance and has drawn the attention and efforts of numerous clinical trials over the years, both for the prevention and treatment of VAP. Many novel interventions have either failed or have not consistently shown benefit in the treatment of critically ill patients in general and more specifically those with sepsis, including from VAP.

Many large, randomized clinical trials have attempted to improve survival in the critically ill, e.g., those utilizing the administration of hydrocortisone (14), growth hormone (15), anti-

TNF antibody (16), inhaled nitric oxide or nitric oxide synthase inhibitor 546C88 (17-20), and by placing patients on intensive insulin protocols. (21, 22) Unfortunately, many of these trials resulted in worse clinical outcomes and higher mortality. Other endeavors specifically directed at ventilation and pulmonary therapies have included high-frequency oscillation (23, 24) and the prone position (25-27), yet these also failed to demonstrate survival advantages. (28)

Despite a host of unsuccessful interventions, we have seen small incremental advancements in pulmonary and general critical care leading to overall improved patient outcomes which we attribute our declining mortality following VAP. A number of clinical trials over the last decade have discovered treatments and various interventions to be beneficial, improving patient outcomes.

Pulmonary Critical Care Improvements

For patients with acute respiratory distress syndrome (ARDS), Meduri and colleagues found prolonged methylprednisolone treatment for unresolving ARDS significantly reduced lung injury scores, improved successful extubation, and decreased both ICU- and hospital-associated mortality. (29) While our ICU does give methylprednisolone in the chronic stages of ARDS, fewer than 3 cases occur per year. It is unlikely that the implementation of prolonged methylprednisolone therapy in unresolving ARDS played a significant factor in our ICU mortality reduction.

Soon after Meduri's publication, the ARDS Network compared traditional mechanical ventilation with low tidal volumes and decreased plateau pressures. This trial was stopped early due to a survival benefit in the group treated with lower tidal volumes as well as having fewer days of mechanical ventilation. (30) A major literature review in 2005 reviewed ventilatory management for acute lung injury and ARDS and confirmed strong evidence for volume- and pressure-limited ventilation strategies for lung protection, preventing barotrauma and over distention. (28)

Another development that led to improved outcomes in pulmonary critical care was the bedside percutaneous dilatational tracheostomy initially introduced in 1985 (31). It subsequently has been shown to have lower morbidity than an open tracheostomy, to improve patient comfort, airway suctioning and management, and to expedite weaning from the ventilator. (32, 33)

A large meta-analysis published in 2006, including 17 randomized controlled trials and over 1200 patients, found equivalent results between the percutaneous and open technique in terms of bleeding, major peri-procedural and long term complications for both groups. However, in subgroup analyses they revealed a lower incidence of death in the percutaneous group. (34) Conversely, additional studies found more frequent minor complications and more difficult cannula changes with the percutaneous technique. (35, 36) Lastly, a small randomized clinical trial found a trend toward more complications, including loss of airway, leading to death in the percutaneous tracheostomy group. (37)

Our institution began performing the percutaneous dilatational tracheostomy in 1997, with approximately 70% of all tracheostomies performed using this technique in the early part of our study period. By the latter part of the study period, the percentage of tracheostomies performed percutaneously had risen to greater than 95% due to ease of the procedure, speed of performance and few complications.

Lastly, daily discontinuation of sedative infusions allowed more frequent patient awakenings, reducing ventilator days and improving survival in the ICU. (38) We noted the

decline in mortality following an episode of VAP over the last decade is due at least in part to these advancements in pulmonary critical care.

Non-Pulmonary Critical Care Improvements

Numerous recent studies have revealed an overall decline in mortality in the ICU, including a decline following infectious complications. (11) This improvement can be in part attributed to several developments in intensive care training and specialist team input from ICU nutrition experts, respiratory therapists, and ICU-specific pharmacists, all of whom work in conjunction with the entire ICU team. Advancement continues to occur in ICU diagnostics, monitoring, supportive care, and technology which has improved organ support systems and patient-equipment interfaces. (11, 39) A precise example of this is the development of the equipment and the patient-ventilator interface for mechanical ventilation, allowing better tolerated ventilation, less sedation and fewer total days on the ventilator. (39)

Numerous additional evidence-based guidelines and interventions have improved overall ICU outcomes and without any single, specific intervention. In 2004 and 2008, the Surviving Sepsis Campaign was introduced to provide criteria for early resuscitation and guidelines for ICU care. (40, 41) During this decade a restrictive strategy of red-cell transfusion in certain populations delivered better outcomes (42), as did a daily “FAST HUG”, (Feeding, Analgesia, Sedation, Thromboembolic prevention, elevated Head of bed, Ulcer prophylaxis, and adequate Glucose control), for the routine assessment of the critical ill patient. (43)

The current daily sedation holiday protocol at our institution is to stop all sedative infusions and cut narcotic infusions in half at 5:00 am for all non-chemically paralyzed patients. If the patient requires re-sedation our ICU starts with boluses and then if an infusion is necessary, the infusion is re-initiated at half the rate of what was previously provided.

No Identifiable Cause for Reduction

We conclude the declining mortality following an episode of VAP in our institution is not due to any specific identifiable intervention. Possible more subtle explanations for the decline included a change in isolated pathogens, resistance patterns, antibiotic profiles, isolation practices, or changes in the patient population. We’ve shown the profile of specific pathogens isolated have not significantly changed over time and, if anything, have trended toward more resistant organisms: we previously demonstrated rising resistance patterns have not been associated with a rise in mortality. (11) This again supports the notion of improved critical care and not some infection related intervention or transformation.

Isolation practices have remained relatively stable over time, however, small changes have occurred in both more conservative and more liberal practice directions. For example, we have lessened the isolation practices for MRSA, from droplet precautions (requiring a mask, gown, gloves) to contact precautions (no longer requiring mask). On the other hand, we have improved isolation for highly resistant organisms in the presence of an outbreak, implementing strict cohorting and “superisolation” to prevent transmission. (44) These changes, however, are unlikely to explain the changes in VAP-related mortality we have seen.

Over the last decade we have used fewer courses of fluoroquinolones and aminoglycosides with stable use of the cephalosporins and carbapenems. We see a trend toward increasing courses of penicillins, likely due to the empiric antibiotic selection of piperacillin/tazobactam. As resistant organisms, such as MRSA and VRE, are more frequently isolated we have utilized vancomycin and linezolid with increasing frequency. While not delineated here, the

appropriateness of initial antibiotics has remained stable over time. The majority of organisms that do not receive coverage by our empiric antimicrobial therapy are yeasts and VRE. We did see a significantly lower WBC in the final time period as compared to the first (16.3 ± 0.6 vs. 13.8 ± 0.5 , $p = 0.001$) perhaps indicating an earlier diagnosis and initiation of treatment. It is possible this earlier treatment in the course of the infection may have resulted in fewer deaths following the episode of VAP. Our overall impression however, is that the courses or profiles of antibiotics has not played a major factor in the reduction of mortality following VAP.

Lastly, we have not identified any major shifts in our patient population except in the proportion of trauma patients. A stable APACHE II score demonstrates a consistent severity of illness at the time of VAP diagnosis. We do see a slightly higher proportion of trauma patients in the population, likely reflecting improvements in critical care preventing lengthy mechanical ventilation and subsequent VAP in the non-trauma population, although we do not have data to confirm this. Trauma has a known protective effect on mortality following an episode of VAP, as seen in the multiple logistic regression analysis (OR 0.1, 95% CI 0.06 – 0.18). From our data we cannot definitively conclude that the rise in the proportion of trauma patients in our population fully explains the decline in subsequent mortality as there is a declining trend in the non-trauma population as well (45.5% vs. 37.1%). Nonetheless, in our regression model, era of treatment is still a predictor of outcome even when adjusting for trauma status.

CONCLUSION

We have shown mortality following an episode of VAP continues to decrease over time and attribute this to advancements in pulmonary and general critical care rather than any specific intervention. Whether these findings are true for other forms of severe infections deserves further study.

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REFERENCES

1. Chastre J. Ventilator-associated pneumonia: What is new? *Surgical Infections*. 2006; 7(Suppl 2):S81–S85. [PubMed: 16895514]
2. Bonten MJ. Ventilator-associated pneumonia: Preventing the inevitable. *Clin Infect Dis*. 2011; 52:115–121. [PubMed: 21148529]
3. 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. [PubMed: 15699079]
4. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2002; 165:867–903. [PubMed: 11934711]
5. Rello J, Ollendorf DA, Oster G, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest*. 2002; 122:2115–2121. [PubMed: 12475855]
6. Kleven RM, Edwards JR, Richards CL, et al. Estimating health care-associated infections and deaths in U.S. hospitals in 2002. *Public Health Rep*. 2007; 122:160–166. [PubMed: 17357358]
7. Centers for Disease Control and Prevention. [Accessed February 17, 2012] Ventilator-Associated Pneumonia (VAP) Event. 2001. Available online at: <<http://www.cdc.gov/nhsn/PDFs/pscManual/6pscVAPcurrent.pdf>>
8. McFee RB. Nosocomial or hospital-acquired infections: an overview. *Dis Mon*. 2009; 55:422–438. [PubMed: 19540995]

9. Raymond DP, Pelletier SJ, Crabtree TD, et al. Impact of antibiotic-resistant gramnegative bacilli infections on outcome in hospitalized patients. *Crit Care Med.* 2003; 31:1035–1041. [PubMed: 12682469]
10. Metzger R, Swenson BR, Bonatti H, et al. Identification of risk factors for the development of *Clostridium difficile*-associated diarrhea following treatment of polymicrobial surgical infections. *Ann Surg.* 2010; 251:722–727. [PubMed: 20101175]
11. Rosenberger LH, LaPar DJ, Sawyer RB. Infections caused by multidrug resistant organisms are not associated with overall, all-cause mortality in the surgical intensive care unit: the 20,000 foot view. *J Am Coll Surg.* 2012; 214:747–755. [PubMed: 22421258]
12. Knaus WA, Drapier EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985; 13:818–829. [PubMed: 3928249]
13. Garner JS, Jarvis WR, Emori TG, et al. CDC definitions of nosocomial infections. *Am J Infect Control.* 1988; 16:128–140. [PubMed: 2841893]
14. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med.* 2008; 358:111–124. [PubMed: 18184957]
15. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med.* 1999; 341:785–792. [PubMed: 10477776]
16. Abraham E, Anzueto A, Gutierrez G, et al. NORASEPT II Study Group. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. *Lancet.* 1998; 351:929–933. [PubMed: 9734938]
17. Lopez A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med.* 2004; 32:21–30. [PubMed: 14707556]
18. Lundin S, Mang H, Smithies M, et al. The European Study Group of Inhaled Nitric Oxide. Inhalation of nitric oxide in acute lung injury: results of a European multicentre study. *Intensive Care Med.* 1999; 25:911–919. [PubMed: 10501745]
19. Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA.* 2004; 291:1603–1609. [PubMed: 15069048]
20. Sokol J, Jacobs SE, Bohn D. Inhaled nitric oxide for acute hypoxic respiratory failure in children and adults: A meta-analysis. *Anesth Analg.* 2003; 97:989–998. [PubMed: 14500146]
21. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med.* 2008; 358:125–139. [PubMed: 18184958]
22. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009; 360:1283–1297. [PubMed: 19318384]
23. Derdak S, Mehta S, Stewart TE, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. *Am J Respir Crit Care Med.* 2002; 166:801–808. [PubMed: 12231488]
24. Bollen CW, van Well GT, Sherry T, et al. High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]. *Crit Care.* 2005; 9:R430–R439. [PubMed: 16137357]
25. Pelosi P, Brazzi L, Gattinoni L. Prone position in acute respiratory distress syndrome. *Eur Respir J.* 2002; 20:1017–1028. [PubMed: 12412699]
26. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med.* 2001; 345:568–573. [PubMed: 11529210]
27. Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome. *JAMA.* 2009; 302:1977–1984. [PubMed: 19903918]
28. Fan E, Needham DM, Stewart TE. Ventilatory management of acute lung injury and acute respiratory distress syndrome. *JAMA.* 2005; 294:2889–2896. [PubMed: 16352797]
29. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 1998; 280:159–165. [PubMed: 9669790]

30. The Acute Respiratory Distress Syndrome (ARDS) Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000; 342:1301–1308. [PubMed: 10793162]
31. Ciaglia P, Firsching R, Syniec C. Elective percutaneous dilatational tracheostomy: a new simple bedside procedure-preliminary report. *Chest*. 1985; 87:715. [PubMed: 3996056]
32. Cobean R, Beals M, Moss C, Bredenberg CE. Percutaneous dilatational tracheostomy. A safe, cost-effective bedside procedure. *Arch Surg*. 1996; 131:265–269. [PubMed: 8611091]
33. Hill BB, Zweng TN, Maley RH, et al. Percutaneous dilatational tracheostomy: report of 356 cases. *J Trauma*. 1996; 41:238–243. [PubMed: 8760530]
34. Delaney A, Bagshaw SM, Nalos M. Percutaneous dilatational tracheostomy versus surgical tracheostomy in critically ill patients: a systematic review and meta-analysis. *Crit Care*. 2006; 10(2):R55. [PubMed: 16606435]
35. Gysin C, Dulguerov P, Guyot JP, et al. Percutaneous versus surgical tracheostomy: a double-blind randomized trial. *Ann Surg*. 1999; 230:708. [PubMed: 10561096]
36. Oliver ER, Gist A, Gillespie MB. Percutaneous versus surgical tracheostomy: an updated meta-analysis. *Laryngoscope*. 2007; 117:1570–1575. [PubMed: 17667139]
37. Porter JM, Ivatury RR. Preferred route of tracheostomy – percutaneous versus open at the bedside: a randomized, prospective study in the surgical intensive care unit. *Am Surg*. 1999; 65:142–146. [PubMed: 9926749]
38. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000; 342:1471–1477. [PubMed: 10816184]
39. Vincent JL, Singer M. Critical care: Advances and future perspectives. *Lancet*. 2010; 376:1354–1361. [PubMed: 20934211]
40. Dellinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004; 32:858–873. [PubMed: 15090974]
41. Dellinger RP, Levy MM, Carlet JM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008; 36:296–327. [PubMed: 18158437]
42. Hebert PC, Wells G, Blajchman MA, et al. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med*. 1999; 340:409–417. [PubMed: 9971864]
43. Vincent JL. Give your patient a fast hug (at least) once a day. *Crit Care Med*. 2005; 33:1225–1229. [PubMed: 15942334]
44. Rosenberger LH, Hranjec T, Politano A, et al. Effective cohorting and “superisolation” in a single intensive care unit in response to an outbreak of diverse multi-drug-resistant organisms. *Surgical Infections*. 2011; 12:345–350. [PubMed: 21936667]

* Penicillin, ampicillin, amoxicillin, nafcillin/oxacillin, dicloxacillin, piperacillin, mezlocillin, amoxicillin/clavulanate, ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam
 † Cephalexin, cefazolin, cefaclor, cefuroxime, cefoxitin, cefotetan, cefotaxime, ceftriaxone, ceftazidime, cefepime, cefadroxil, cefpodoxime
 ‡ Imipenem, meropenem, ertapenem
 § Ciprofloxacin, ofloxacin, moxifloxacin, trovafloxacin, levofloxacin, gatifloxacin
 ¶ Gentamicin, tobramycin, amikacin, streptomycin

Figure 1.
 Number of discrete courses of antibiotic treatment

Table 1

Demographics, comorbidities, and outcomes of VAP cases by time period

Demographic/Outcome	1997-1999	2000-2002	2003-2005	2006-2008	<i>P</i> [‡]
VAP cases	211	200	190	192	-
Age, years [*]	48.6 ± 1.1	52.5 ± 1.3	50.8 ± 1.3	52.8 ± 1.3	0.01
Male sex [‡]	151 (71.6)	140 (70.0)	142 (74.7)	146 (76.0)	0.36
White blood count (k/ μ L)	16.3 ± 0.6	15.6 ± 0.5	13.3 ± 0.5	13.8 ± 0.5	0.001
Temperature, maximum	38.6 ± 0.1	38.6 ± 0.1	38.4 ± 0.1	38.5 ± 0.1	0.48
APACHE II score	20.6 ± 0.4	19.7 ± 0.3	19.2 ± 0.4	20.1 ± 0.4	0.38
Trauma	133 (63.0)	131 (65.6)	127 (66.8)	140 (72.9)	0.04
Transfused	200 (94.8)	186 (93.0)	165 (86.8)	147 (76.6)	< 0.0001
Transplant recipient	21 (10.0)	15 (7.5)	15 (7.9)	7 (3.6)	0.02
Dialysis dependence	48 (22.7)	29 (14.5)	28 (14.7)	23 (12.0)	0.01
Diabetes mellitus (I or II)	28 (13.3)	23 (11.5)	30 (15.8)	31 (16.1)	0.48
Pulmonary disease	15 (7.1)	27 (13.5)	30 (15.8)	29 (15.1)	0.01
Chronic steroid therapy	33 (15.6)	26 (13.0)	37 (19.5)	12 (6.3)	0.004
Antibiotic therapy, days	13.4 ± 0.5	14.5 ± 0.6	13.9 ± 0.6	14.0 ± 0.8	0.52
Length of stay, days	33.9 ± 2.1	32.3 ± 2.0	44.0 ± 3.5	39.2 ± 2.7	0.12
Died, (crude mortality)	54, (25.6%)	49, (24.5%)	39, (20.5%)	27, (14.1%)	0.004

^{*} Continuous variables reported as mean ± standard error[‡] Categorical variables reported as N, (%)[‡] Comparison between recent study group (2006-2008) vs. early study group (1997-1999)

Table 2

Patients, deaths, and mortality by time period

Time Period	1997-1999	2000-2002	2003-2005	2006-2008	P [‡]
Patients	143	142	126	144	-
Deaths	38	28	15	17	-
Mortality	26.6%	19.7%	11.9%	11.8%	0.002
Mortality, trauma	16.8%	11.7%	3.2%	5.5%	0.011
Mortality, non-trauma	45.5%	46.2%	45.2%	37.1%	0.51

[‡]Comparison between recent study group (2006-2008) vs. early study group (1997-1999)

Table 3

Frequency and distribution of gram-negative organisms

Organism Isolated	1997-1999	2000-2002	2003-2005	2006-2008	Total Cases
<i>Pseudomonas aeruginosa</i>	40	34	46	50	170
<i>Enterobacter cloacae</i>	16	25	21	14	76
<i>Acinetobacter species</i>	24	25	18	6	73
<i>Stenotrophomonas maltophilia</i>	18	16	16	10	60
<i>Klebsiella pneumoniae</i>	14	19	13	13	59
<i>Haemophilus influenzae</i>	7	18	13	13	51
<i>Serratia species</i>	13	15	11	9	48
<i>Escherichia coli</i>	9	6	11	15	41
<i>Enterobacter aerogenes</i>	14	7	6	10	37
<i>Klebsiella oxytoca</i>	4	4	4	14	26

Table 4

Frequency and distribution of gram-positive organisms

Organism Isolated	1997-1999	2000-2002	2003-2005	2006-2008	Total Cases
<i>Staphylococcus aureus</i>	24	24	17	32	97
Methicillin-resistant <i>S. aureus</i>	29	32	7	19	87
<i>Streptococcus</i> species	6	5	6	6	23
<i>Streptococcus pneumoniae</i>	9	1	7	5	22
Methicillin-resistant <i>S. epidermidis</i>	3	4	4	1	12
Vancomycin-resistant <i>E. faecium</i>	2	0	2	5	9
<i>Staphylococcus epidermidis</i>	2	3	2	0	7

Table 5

Logistic regression analysis of risk factors associated with death

Predictor	Wald Chi-square	Odds Ratio	95% CI
Trauma	72.23	0.10	0.06 – 0.18 *
APACHE II score (per point)	18.93	1.09	1.05 – 1.14 *
Length of stay (per day)	16.63	0.99	0.98 – 0.99 *
Age (per year)	15.54	1.03	1.02 – 1.05 *
Pulmonary disease	13.44	3.01	1.67 – 5.45 *
Transplant recipient	7.21	3.45	1.40 – 8.53 *
Transfused	7.18	3.25	1.37 – 7.68 *
Chronic steroid therapy	4.71	0.39	0.17 – 0.91 *
White blood count (k/ μ L)	3.53	1.03	1.00 – 1.06 *
Group 97-99 vs. 06-08	2.07	2.23	1.16 – 4.29 *
Group 00-02 vs. 06-08	1.47	2.13	1.12 – 4.06 *
Antibiotic therapy (per day)	1.31	0.98	0.96 – 1.01
Dialysis dependence	0.53	0.80	0.43 – 1.47
Diabetes mellitus	0.11	0.91	0.51 – 1.61
Sex (male)	0.06	0.94	0.58 – 1.54
Group 03-05 vs. 06-08	0.04	1.78	0.90 – 3.50

c statistic = 0.871

R-squared = 0.282

* Significant independent predictors of death