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Approval Sheet

Improving outcomes one breath at a time:
The relationship between lung protective ventilation and risk of developing acute respiratory distress syndrome in patients with sepsis

By

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ABSTRACT COVER PAGE

Improving outcomes one breath at a time:
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An abstract of
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Master of Science in Clinical Research
2019

ABSTRACT

Improving outcomes one breath at a time:
The relationship between lung protective ventilation and risk of developing acute respiratory distress syndrome in patients with sepsis

By: Casey A. Cable

Introduction: Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection, with a mortality of 15%. One contributor to this high mortality is the development of acute respiratory distress syndrome (ARDS), an acute diffuse, inflammatory lung process that manifests as severe hypoxemic respiratory failure. While the use of lung protective ventilation (LPV), a strategy of using low tidal volume and plateau pressure during invasive mechanical ventilation (IMV), significantly reduces mortality in patients who already meet criteria for ARDS and is the standard of care, the utility of LPV in other critically ill patient populations without ARDS is unclear. We hypothesize that in patients with sepsis requiring IMV, the use of early LPV reduces the risk of developing ARDS.

Methods: This is a retrospective cohort study of adult patients with sepsis admitted to two academic hospitals requiring IMV from January 1, 2015, to December 31, 2015. We extracted data on demographics, anthropometrics, physical measurements, severity of illness, sepsis variables, ventilator parameters, and hospital course. LPV was defined as a set ventilator tidal volume <6.5 mL/kg of predicted body weight and plateau pressure ≤ 30 cmH_2O during the first day of IMV.

Results: We identified 533 patients with sepsis requiring IMV. A total of 187 (35%) patients received LPV on the first day of IMV, were more often male, had a higher mean height, had a higher mean body mass index (BMI) and more often had community acquired sepsis. A total of 133 (18%) patients developed ARDS, and had a higher weight, lower BMI, and higher SOFA score. In multivariable analysis adjusted for age, sex, height, BMI, and SOFA, receipt of LPV on the first day of IMV was not associated with a decreased risk of developing ARDS (risk ratio 0.97, 95% confidence interval 0.65 – 1.46, p=0.89).

Conclusions: In this retrospective cohort of adult patients with sepsis requiring IMV, there was no significant association between receipt of LPV on the first day of IMV risk of developing ARDS.

COVER PAGE

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INTRODUCTION

Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection (1). Nearly 1.7 million adults are hospitalized with sepsis in the United States annually, with a mortality of 15% (2). One contributor to this high mortality is the development of acute respiratory distress syndrome (ARDS). With a mortality of 40%, ARDS is characterized by the rapid onset of diffuse, inflammatory pulmonary edema that manifests as severe hypoxic respiratory failure. While ARDS can result from a variety of etiologies, including direct pulmonary injuries such as blunt trauma and indirect injuries such as pancreatitis, sepsis is the most common (3).

Approximately 20% of patients with sepsis develop ARDS and this portends a considerably higher mortality rate (3, 4). The Department of Health and Human Services has made sepsis a national priority, considering it a national health security issue (5). Identifying strategies to reduce the risk of ARDS in patients with the most common risk factor of sepsis could reduce mortality and save thousands of lives per year.

Lung protective ventilation (LPV) is a strategy that utilizes low tidal volumes and inspiratory plateau pressures during invasive mechanical ventilation (IMV). In studies of patients with ARDS, a strategy of using LPV has been consistently shown to be beneficial, decreasing hospital mortality by 22% (6). The use of low tidal volumes is associated with decreased inflammatory markers in the first few days of IMV (7). Conversely, the use of large tidal volumes during IMV has been shown to result in sustained cytokine release and increased inflammatory markers (8-11).

A two-hit model of inflammation has been proposed for the development of ARDS (12, 13). Sepsis is a pro-inflammatory state, predisposing patients with sepsis to

developing ARDS. The second hit of inflammation can be a result of a variety of causes, including the method that mechanical ventilation is delivered. Reducing systemic inflammation through utilization of LPV may decrease the risk of developing ARDS in septic patients.

We conducted a retrospective cohort study of patients with sepsis requiring IMV to assess the use of early LPV and the risk of developing ARDS. Patients admitted to 2 hospitals in an academic healthcare system have a well-defined cohort of patients diagnosed with sepsis (per the CDC Adult Sepsis Surveillance Definition, Appendix A) (14). We utilized this cohort with first hospital admission from January 1, 2015, to December 31, 2015, with the goal of estimating the impact of receipt of LPV on the first day of IMV and the development of ARDS.

BACKGROUND

Sepsis is a clinical syndrome defined most recently by the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) as a life-threatening organ dysfunction due to a dysregulated host response to infection (1). There is currently no diagnostic test for sepsis, the diagnosis is based on evidence of infection and presence of associated organ dysfunction. Consequently, reliably capturing sepsis across large populations and entire healthcare systems is challenging. Electronic health record (EHR) systems allow for the possibility of capturing sepsis on a large scale. The CDC Prevention Epicenter Program utilized clinical criteria as per the Sepsis-3 definition applied to EHR data and validated a CDC sepsis clinical surveillance definition (Appendix A)(14). The definition consists of a presumed serious infection based on drawn blood cultures with specific antibiotic criteria, and organ dysfunction based on discrete clinical values.

ARDS is a type of life-threatening acute respiratory failure characterized by diffuse, inflammatory, pulmonary fluid edema. ARDS can result from either direct pulmonary injury such as blunt trauma or indirect injury such as sepsis or pancreatitis (3, 15). The pathophysiology of ARDS centers around the pulmonary or extrapulmonary insult releasing inflammatory mediators that result in damage of the lung microcirculation leading diffuse pulmonary fluid accumulation (16). This results in impaired oxygen gas exchange and manifests as severe hypoxemia. The Berlin Definition of ARDS, established in 2012, provides a universal definition of ARDS, including specific criteria for the timing of onset, chest imaging findings, origin of edema, and degree of hypoxemia (17).

There is a spectrum of acute respiratory failure, which may require IMV and may include the diagnosis of ARDS. Acute respiratory failure occurs when a patient has difficulty breathing and either low oxygen or elevated carbon dioxide blood levels. Not all patients with acute respiratory failure require IMV. The need for IMV is determined on an individual patient basis by a medical provider(s). ARDS can be a cause of acute respiratory failure, which frequently requires IMV. Conversely, patients with acute respiratory failure that require IMV can also subsequently develop ARDS. This study aims to capture patients with acute respiratory failure that required IMV that was not initially caused from ARDS.

The definition of LPV is comprised of two components, tidal volume and plateau pressure. Plateau pressure is the pressure applied to the small airways and alveoli measured at the end of inspiration during positive pressure ventilation. Tidal volume is the volume a ventilator gives with each breath, this is typically set by a medical provider on the ventilator, commonly reported in mL/kg predicted body weight (PBW, calculated based on sex and height). There are some ventilator modes however, that do not set a tidal volume, and instead utilize other set parameters for each breath. The current accepted definition of LPV is a plateau pressure $\leq$30 cmH_2O and a tidal volume between 4-8 mL/kg PBW. In clinical practice, tidal volume is the more focused on aspect of LPV. Numerous key studies target different tidal volume ventilation strategies (e.g. low vs. high) to compare outcomes. However, there is an important distinction between LPV and only low tidal volume ventilation. While the definition of LPV accepts a tidal volume between 4-8 mL/kg PBW, there are historically lower cut off values, specifically 6.5 mL/kg PBW, consistent with the ARDSNet adherence threshold (18, 19).

ARDS treatment is mainly supportive. The most recent guidelines give a strong recommendation for use of LPV with IMV and prone positioning (20). Other accepted strategies include the use of neuromuscular blockade and conservative fluid management (21, 22). The importance of LPV in ARDS was established by the landmark ARDS Network Trial in 2000 (6). In patients with ARDS, LPV showed a reduction in mortality by 22% (mortality was 31% in the lower tidal volume group compared to 38.9% in the traditional tidal volume group). LPV is now the standard of care in the treatment of ARDS (23).

The median time to onset of ARDS is 2 days after hospital admission, providing a window for possible prevention of ARDS (24). Delayed treatment of septic shock and infection as well as large tidal volumes have been associated with development of ARDS (25, 26). An observational study over an 8 year period showed that hospital practices aiming at reducing the incidence of hospital-acquired ARDS included reducing blood transfusions, use of low tidal volume mechanical ventilation, and improvement in treatment of sepsis and pneumonia (27). A large matched case-control study supported that prevention of certain hospital exposures may limit the development of ARDS; specifically, inadequate antimicrobial therapy, injurious tidal volume, aspiration, and greater volumes of blood product transfusion and fluid administration (13).

The role of LPV in the possible prevention of ARDS centers around reducing or rather not increasing lung inflammation and injury. Mechanical ventilation can cause inflammation and lung injury through a number of different mechanisms. Specifically, large tidal volume ventilation can cause injury to the lungs themselves through excess applied pressure (barotrauma) or overdistension with excess breath volume (volutrauma).

The mechanical stress resulting from mechanical ventilation creates an increased inflammatory process with cytokine release and increases in inflammatory markers (biotrauma) (8-11). This biotrauma not only causes local lung injury but can have systemic effects, impacting other organ systems (28).

Extrapolation of LPV to patients requiring IMV but not having ARDS remains unclear which consequently prompted numerous studies and clinical trials (29, 30). Determann and colleagues published one of the first randomized controlled trials of 150 critically ill patients without ARDS or acute lung injury and randomized to receive low tidal volumes of 6 mL/kg PBW or high tidal volumes of 10 mL/PBW (9). A secondary outcome of development of ARDS showed a statistically significant increase in patients who received high tidal volumes ($p=0.01$). This prompted more investigation into the use of LPV in patients without ARDS.

The IMPROVE trial was a randomized controlled trial of 400 patients undergoing abdominal surgery who had risk factors for pulmonary complications. Patients were randomized to LPV (tidal volume 6-8 mL/kg PBW) or non-LPV (tidal volume 10-12 mL/kg PBW) strategies intraoperatively (31). The primary composite outcome of pulmonary and extra pulmonary complications at 7 days was significantly lower in the LPV group (10.5% in LPV vs. 29% in non-LPV, $P=0.001$). These results were largely driven by an increase of pulmonary complications, supporting the important role of LPV in improving pulmonary outcomes.

A systematic review and individual patient data analysis by Neto and colleagues included 2,184 patients from 7 studies in the ICU without ARDS at onset of mechanical ventilation (32, 33). The primary outcome, occurrence of pulmonary complications

(ARDS or pneumonia), was 23% in the low tidal volume group (≤7 mL/kg PBW), 28% intermediate (7-10 mL/kg PBW), and 31% in the high tidal volume group (≥10 mL/kg PBW); there was only statistical significance between low and high tidal volume groups ($p=0.042$). This suggests a dose-response relationship between tidal volume and development of pulmonary complications. Occurrence of pulmonary complications was associated with a lower number of ICU-free, hospital-free days, and alive at 28 days ($p<0.01$, $p<0.01$, $p<0.01$). While this meta-analysis provides a compelling case for the use of LPV in patients without ARDS, patients with sepsis were either excluded or underrepresented. Of the 4 studies included in the primary analysis, 3 excluded patients with an infection or did not report any sepsis baseline characteristics (34-36). The remaining study reported baseline sepsis incidence, with sepsis patients comprising 17% and 27%, before and after LPV protocol implementation, respectively (37). Of the 3 remaining studies added for the secondary analysis, 3 excluded patients with infections and the final reported sepsis rates of less than 10% (9, 11, 38).

As patients with sepsis are at high risk of developing ARDS during a vulnerable period of time while receiving other critical care services, interventions which lower risk of ARDS, such as the use of protocolized lung protective ventilation are important to study. Our current study aims to broaden understanding of the impact and early timing of LPV in septic patients and the risk of developing ARDS, potentially changing practices and protocols to improve patient outcomes.

METHODS

Overview and Study Design

This was a retrospective cohort study of adult patients with sepsis requiring IMV, with initial hospital admission date between January 1, 2015, and December 31, 2015, using EHR data from two large academic hospitals in Atlanta, Georgia. Approval for this study was obtained from the Emory University's Institutional Review Board.

Specific aim 1: To determine if early receipt of LPV decreases the risk of developing ARDS in patients with sepsis requiring IMV.

Hypothesis 1: LPV (i.e. lowest set tidal volume ≤6.5 mL/kg of predicted body weight (PBW) and lowest recorded plateau pressure ≤30 cmH_2O) on the first calendar day of IMV decreases the risk of developing ARDS for patients with sepsis requiring IMV.

Specific aim 2: To characterize the relationship between tidal volume and risk of developing ARDS in patients with sepsis requiring IMV.

Hypothesis 2: Lower set tidal volumes (in ml/kg PBW) on the first calendar day of IMV decreases the risk of developing ARDS for patients with sepsis requiring IMV.

Data extraction and characteristics and of study population

The study was conducted in 16 ICUs within two large academic hospitals from January 1, 2015, and December 31, 2015. Data were extracted from electronic medical records for all patients with sepsis (as per the CDC definition, Appendix A) requiring

IMV to the study ICUs during the 1-year study period (14). The study population was extracted from a previously identified and published patient cohort with sepsis defined by the CDC definition. A data analyst assisted in all extractions from the Clinical Data Warehouse (CDW) of the Emory Healthcare electronic medical record. All patients requiring mechanical ventilation were identified and additional ventilatory parameters were extracted creating the master datafile. Patients with a P_{aO2}/F_{IO2} ratio <300 on two consecutive days were extracted separately for individual chart review for ARDS, chart review results merged into the master datafile. Initial sepsis dates required a separate data extraction and merged into the master datafile.

The cohort excluded patients receiving IMV prior to sepsis diagnosis (or on same calendar day), the total use of IMV for < 1 calendar day, ARDS at the onset of IMV (17), ARDS before receipt of LPV, modes of mechanical ventilation that do not routinely set tidal volume (see Appendix B for complete list), extracorporeal membrane oxygenation (ECMO), unable to determine ARDS per bilateral infiltrates, pregnant, < 18 years of age, or total follow-up available < 1 day. If minimum set tidal volume was missing on the first day of invasive mechanical ventilation or the set tidal volume was <100cc (a clinically infeasible tidal volume), then the patient was excluded.

Definitions and Measured Covariates

Exposure

The exposure of interest was the receipt of LPV on the first calendar day of IMV. In regard to mechanical ventilation, IMV differs from non-invasive mechanical ventilation with the involvement of an apparatus inside the trachea, such an endotracheal

tube or a tracheostomy IMV. Receipt of IMV was determined in the data management process by the recorded mode of mechanical ventilation on each day (Appendix B). For specific aim 1, LPV was defined by defined by lowest set tidal volume ≤6.5 mL/kg PBW and lowest recorded plateau pressure ≤30 cmH_2O, modeled as a dichotomous variable – yes or no receipt of LPV on the first calendar day of IMV. For specific aim 2, lowest set tidal volume on the first day of IMV was treated as a continuous variable in mL/kg PBW. PBW, in kg, was calculated by data management methods from height and sex according to the following formulas (6):

Male (kg): 50 + 0.91 x (height in cm – 152.4)

Female (kg): 45.5 + 0.91 x (height in cm – 152.4)

These equations have not been validated for patients with a height less than 4 feet (121.9 cm) and thus these patients were excluded.

Outcome

The primary outcome of interest was the development of ARDS, within 7 days from the first day of IMV, modeled dichotomously. ARDS was defined as a P_{aO2}/F_{IO2} ratio <300 on two consecutive days and bilateral infiltrates on chest imaging. Digital chest radiographs or computerized tomography (CT) scans were reviewed according to an a priori chest imaging review protocol by one investigator (CAC) who was blinded to the patients' exposure or other clinical data. Radiology reports were only reviewed and taken into consideration in determination of ARDS as an adjudication step. Only the

calendar date was known for each image reviewed, and not the specific day of IMV for the patient (e.g. it was blinded whether it was the first day of IMV or IMV day 6).

Secondary outcomes included hospital length of stay (LOS) among survivors and ventilator free days at day 28. Ventilator free days was defined by the number of days from 1 to 28 the patient was alive and breathing without IMV for at least 2 days, this includes repeated re-intubations and re-extubations until day 28 (39).

Covariates

Baseline characteristics were determined at the first day of IMV. Selected covariates available within the CDW were collected *a priori* based on importance in existing literature, ventilator parameters, as well as association of receiving LPV or development of ARDS. The covariates included demographics and anthropometrics, severity of illness measures, sepsis variables, ventilator parameters, and hospital course information. The Sequential Organ Assessment (SOFA) score is a measure of acute severity of illness, ranging from 0 to 24, with higher numbers indicating more severe illness (40). The Elixhauser Comorbidity Index is a method for measuring patient comorbidity based on ICD-9 and ICD-10 diagnosis codes (41). Community sepsis (versus hospital sepsis) was defined if the date of sepsis was on hospital day 2 or earlier, when the date of admission counts as hospital day 1 (42).

Race was classified as white, black, other, or missing. ICU types were classified as medical, surgical, cardiac/cardiothoracic (CT), neurologic, or other. Post-hospital disposition was classified as home, long term acute care (LTAC) or skilled nursing facility (SNF), hospice (either home or inpatient), or deceased (Appendix B). For the

purpose of inclusion and exclusion criteria, modes of mechanical ventilation were classified as non-IMV, IMV that routinely set tidal volumes, IMV that do not routinely set tidal volumes (Appendix B).

Missing data

Missingness was addressed differently if it was directly required for the exposure and outcome or not. Tidal volume, plateau pressure, height and sex are required to determine the exposure of LPV. Chest imaging is needed to identify the outcome of ARDS (i.e. bilateral infiltrates).

If height was missing on the first day of IMV, then the mean and standard deviation of all daily recorded heights was calculated. The mean documented height was used if the standard deviation was <1cm, else the patient was excluded due to inconsistent data recording. Similarly, if weight was missing on the first day of IMV then the mean and standard deviation of all daily recorded weights was calculated. If the standard deviation was less than 5kg, then this mean was imputed for the weight on the first day of IMV. If the standard deviation was greater than 5kg, then the patient was excluded.

Ventilator-delivered peak pressure was used an exposure in place of plateau pressure if plateau pressure was not recorded. Peak pressure is the same or higher than plateau pressure. If peak pressure was used in lieu of plateau pressure, the threshold for lung protective ventilation was not adjusted ($\leq$ 30 cmH_2O).

Race was missing in approximately 9%. We included patients with missing race with missing as a separate category.

Statistical Analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute: Cary, NC). A two-sided p-value of <0.05 considered statistically significant. Summary statistics include mean and standard deviation (SD) for normally distributed continuous data, median and interquartile range for non-normally distributed continuous data, and proportions for categorical data. Continuous and categorical variables were compared using pooled t tests and chi-squared tests, respectively. Histograms were created for each of the continuous variables and the skewedness and kurtosis evaluated for normality. Secondary analyses were exploratory and formal statistical testing was not performed.

Multivariate model building

We selected several a priori covariates to be included in the model (age, sex, height, BMI). The remaining covariates in the model were chosen using statistical criteria to define a generalized linear model (binomial regression) with a log link function for the dichotomous outcome. A link log function was used rather than logit link, commonly used for logistic regression, because we preferred to estimate risk ratios rather than odds ratios. Multicollinearity between continuous covariates was assessed by the variance inflation factor (if >10). Additional covariates were initially selected for multivariate model inclusion if they were associated with the outcome at a p <0.25 in the bivariate analysis. All of these were included in an initial multivariate model, and covariates were retained in the model if the p <0.20. Then each covariate was assessed individually by the likelihood ratio test (LRT) of the full vs. reduced model, and retained if p <0.20. Additionally, covariates were then removed if they did not affect the exposure

parameter estimate by ≥20%. Interaction terms were individually assessed in a full and reduced model and retained if the LRT p <0.10.

The Model

$$\log P(ARDS=1) = \beta_0 + \beta_1 Exposure + \beta_2 age + \beta_3 sex + \beta_4 height + \beta_5 BMI + \ldots + \beta_i X_i$$

Where:

P = the probability of ARDS = 1 (yes)

Exposure:

Specific aim 1: LPV on first day of IMV, dichotomous 1=yes, 0=no

Specific aim 2: lowest set tidal volume (mL/kg PBW) on first day of IMV, continuous

Covariates:

Age = age of the patient in years

Sex = female vs. male

Height = centimeters, continuous

BMI = body mass index, continuous in kg/m^2, continuous

X = covariates that met inclusion into final model

RESULTS

A total of 1458 patients were admitted with sepsis to the two academic hospitals during 2015 and required IMV (Figure 1). Of these, 749 were excluded, the most frequent exclusions were IMV prior to sepsis (n=234) and modes of mechanical ventilation that do not set tidal volume (n=333). An additional 176 patients were excluded due to inconsistent data, outliers or missingness unable to be adjudicated or corrected. The remaining 533 patients were included in the primary analysis.

The mean age of the entire cohort was 58.9 ±16.5 years with females representing 44% (Table 1). The racial composition of the cohort was 44% white, 45% black, 3% other and 9% missing. The initial source of sepsis was community acquired in 69%. In hospital mortality was 19%, with an additional 18% of patients discharged to hospice. The overall mean lowest tidal volume on the first day of IMV was 7.0 ±1.1 mL/kg PBW.

Of the 533 patients in the cohort, 187 received LPV on the first day of IMV (35%) and 346 did not (65%). Patients who did not receive LPV on the first day of IMV were more likely to be female ($p<0.01$), shorter ($p<0.01$), have lower BMI ($p<0.01$), and have community-acquired sepsis ($p=0.03$). The mean tidal volume on the first day of IMV for patients who received LPV was 6.0 ±0.1 mL/kg PBW versus 7.5 ±1.0 mL/kg PBW for who did not receive LPV ($p<0.01$).

Of the 244 patients that ever received LPV, 187 (77%) received LPV on the first day of IMV, and 36 (15%) on the following day (Figure 2). Twelve patients received LPV between the third and eighth day of IMV.

Of the 533 patients in the cohort, 97 (18%) developed ARDS (Table 2). Patients who developed ARDS had higher mean weight ($p<0.01$), BMI ($p<0.01$), and SOFA score

(p=0.01). In-hospital mortality of patients with ARDS was 31%, with an additional 25% discharged to hospice.

LPV was delivered on the first day of IMV to 34% of the 97 patients who ultimately developed ARDS and to 35% of the 436 patients who did not ultimately develop ARDS (Table 3). The mean overall tidal volume on the first day of IMV was 6.9 ±1.1 mL/kg PBW in patient who developed ARDS, compared to 7.0 ±1.1 mL/kg PBW in patients who did not develop ARDS (p=0.44).Patients that developed ARDS had median 17 (IQR, 0 – 22) ventilator-free days compared to 23 (IQR, 9.5 – 25) for those who did not develop ARDS. The median hospital LOS was 15 days for both patients who developed ARDS (IQR, 10 – 22) and did not develop ARDS (IQR, 8 – 23).

For specific aim 1, receipt of LPV on the first day of IMV was not associated with a decreased risk of developing ARDS (RR 0.97, 95% CI 0.65 – 1.46, p=0.89) using binomial regression adjusting for age, sex, height, BMI, and SOF. For specific aim 2, with binomial regression there was no association detected between lowest set tidal volume on the first day of IMV and risk of developing ARDS. For each increase of 1 mL/kg PBW the risk ratio for development of ARDS was estimated at 1.06 (95% CI 0.90 – 1.25, p=0.48).

DISCUSSION

In this retrospective study of patients with sepsis who received IMV, receipt of LPV on the first day of IMV was not associated with as significant decrease in risk of ARDS. The baseline characteristics of those who received LPV on the first day of IMV are similar to published literature, namely they are more often male and on average are taller (43). In our cohort, 18% of patients with sepsis requiring IMV developed ARDS, which is comparable to existing literature estimates of 19% (3).

The receipt of LPV on the first day of IMV was not associated with a decreased risk of developing ARDS. Lowest set tidal volume on the first day of IMV was also not significantly associated with a decreased risk of developing ARDS.

A closer investigation of tidal volumes may help explain the lack of an observable clinical effect on risk of ARDS development. Since published reports showing a benefit to LPV in patients with ARDS, there has been a change in ventilatory practices in all patients towards lower tidal volumes. While patients were once ventilated with tidal volumes greater than 10 cc/kg PBW, this is no longer routine practice. While the tidal volume cut point for LPV in this study was 6.5 mL/kg PBW, the current accepted range of LPV is 4-8 mL/kg PBW (23). The vast majority of patients in this cohort (n=456, 86%) had tidal volume on the first day of IMV less than 8mL/kg PBW (Figure 3), consistent with guideline recommendations for LPV. The mean tidal volume for patients who received LPV was 6.0 ±0.1 mL/kg PBW versus 7.5 ±1.0 mL/kg PBW who did not receive LPV ($p<0.001$). While the difference in tidal volumes was statistically significant, this difference may not be as clinically relevant as that observed in earlier medical eras where higher tidal volumes were used.

At the time of completing of our retrospective study, we became aware that there was an ongoing randomized controlled trial whose results were recently published (44). The Protective Ventilation (PReVENT) trial randomized 961 ICU patients without ARDS to low (4-6 mL/kg PBW) or intermediate (8-10 mL/kg PBW) tidal volume ventilation strategies. The authors concluded that a ventilation strategy of low tidal volume was not more effective than a strategy using intermediate tidal volume. There was no difference in the primary outcome of ventilator-free days at day 28, or secondary outcomes including hospital length of stay, mortality rate, or pulmonary complications. While this trial achieved a much larger difference in tidal volumes between arms than our observational study, still no difference in outcomes was observed. It is important to note that approximately 10% of patients had sepsis as a reason for intubation. The development of ARDS was 3.8% vs. 5.0%, low tidal vs. intermediate tidal volume, respectively (unadjusted RR 0.86, 95% CI 0.59 – 1.24, p=0.38). These are lower than the 18% overall ARDS rate we observed, which may reflect the difference in percentage of sepsis patients between cohorts. Median hospital LOS (14 days, IQR, 6-26 low vs. 15, IQR, 8-26 intermediate) and ventilator-free days (21, IQR, 0-26 low vs. 21, IQR, 0-26 intermediate) were comparable to what our study observed. The in-hospital mortality was 31.7% vs. 28.0 (HR 1.06 0.93 – 1.22, p = 35), slightly higher than what we observed.

Of the 244 patients in our study that ever received LPV during their hospitalization, more than 90% received LPV on the first or second day of IMV. Thus, if a patient did not receive LPV on the first two days of IMV, they were unlikely to ever receive LPV. The proportion of patients who eventually received LPV after the first two days of IMV was very low (n=21, 9%), and only 5% within the first week of IMV.

This study has several limitations. First, confounding by indication is a potential in any observational study in which a particular therapy is prescribed (or not prescribed). If the indication that LPV was given on the first day of IMV (e.g. sicker patients) is related to the risk of developing ARDS, then the direction of the bias would likely be in the positive direction and could explain an observed null effect or even if the effect was truly preventive. However, measures of severity of illness (SOFA score and Elixhauser Comorbidity Index) were not different between receipt of LPV or not on the first day of IMV, suggesting that the exposed and unexposed groups were comparable. Additionally, there was a subset of patients who had tidal volumes on the first day of IMV less than 6cc/kg PBW and still developed ARDS. Secondary analysis of this subgroup did not yield any difference in severity of illness, ICU type, or any other covariates.

Second, there are some inherent limitations in a retrospective study. These include that some data were not documented (e.g. plateau pressure) and some important variables were inconsistently documentation (e.g. height). Third, this study comprised two hospitals but within one academic hospital system, thus potentially limiting generalizability. Patients transferred into the hospital on IMV were unable to be identified, and thus the ventilator data on the first day of IMV would be unknown, however, this likely represents a small number of patients. Fourth, ventilator modes that excluded set tidal volumes were excluded, and the set tidal volumes were investigated and not the exhaled tidal volume. In certain ICUs, non-traditional modes of ventilation may be used in 20-30% of patients (45). Fifth, while the use of PaO_2 was used in the determination of ARDS (based on the accepted Berlin Definition), this does require that a patient have an arterial blood gas (ABG). In recent years, the routine use of ABGs has

declined, thus introducing possible selection bias of sicker patients or possibly specific ICUs that still routinely obtain daily ABGs. Furthermore, other factors that are known to affect a subject's PaO_2 and thus the definition of the outcome variable in this study (such as the presence of cardiogenic pulmonary edema) were unable to be determined and therefore were not considered in the determination of ARDS, largely because this information is difficult to gather retrospectively and/or unavailable. However, this study did utilize a previously validated cohort of sepsis patients. Chart reviewing was also performed by a blinded single individual for evaluation of bilateral infiltrates on chest imaging which increases the chance of observer bias.

Future directions include evaluating the ICD-9 and ICD-10 admission diagnosis codes to evaluate if there is an association with receipt of LPV as well as development of ARDS (e.g. pneumonia). While the routine use of ABGs has decreased as discussed above, all patients are monitored with a continuous pulse oximeter (SpO_2). Well published correlation between PaO_2 and SpO_2 would likely allow inclusion of a larger number of patients (46, 47). The question remains why some patients develop ARDS and others do not, despite the use of LPV.

In conclusion, we did not demonstrate a relationship between receiving LPV or the absolute tidal volume received on the first day of IMV and risk of developing ARDS. This study highlights the trend in use of relatively low tidal volumes in patients with sepsis, and supports recent evidence that tidal volumes in critically ill patients do not impact clinical outcomes.

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TABLES / FIGURES

Table 1: Baseline characteristics of patients with sepsis requiring invasive mechanical ventilation according to patients who received or did not receive lung protective ventilation on the first day of invasive mechanical ventilation in 2015 across two academic hospitals

Variable	Total patients (n=533)	LPV on the first day of IMV (n=187)	No LPV on the first day of IMV (n=346)	p-value
Demographics and Anthropometrics				
Age, years, mean ±sd	58.9 ±16.5	60.1 ±17.2	58.3 ±16.2	0.22
Sex, Female, n (%)	234 (44)	60 (32)	179 (49)	<0.01
Race				0.97
White, n (%)	233 (44)	81 (43)	152 (44)	
Black, n (%)	239 (45)	86 (46)	153 (44)	
Other, n (%)	15 (3)	5 (3)	10 (3)	
Missing, n (%)	46 (9)	15 (8)	31 (9)	
Height, cm, mean ±sd	171 ±11	177 ±10	169 ±11	<0.01
Weight, kg, mean ±sd	84.5 ±25.4	83.5 ±25.2	85.0 ±25.5	0.53
PBW, kg, mean ±sd	65.4 ±11.8	70.5 ±10.8	62.7 ±11.4	<0.01
BMI, (kg/m^2) mean ±sd	28.7 ±8.1	26.7 ±7.2	29.8 ±8.4	<0.01
Severity of Illness				
SOFA score, first day of IMV, mean ±sd	8.4 ±3.5	8.4 ±3.5	8.4 ±3.4	0.91
Elixhauser Comorbidity Index*, mean ±sd	5.9 ±2.3	5.8 ±2.4	5.9 ±2.3	0.49
Sepsis Variables				
Community sepsis (vs. hospital sepsis), n (%)	367 (69)	140 (75)	227 (66)	0.03
Time from sepsis onset to IMV, days, median (IQR)	1 (0, 2)	1 (0, 2)	0 (0, 2)	
Invasive Mechanical Ventilation, Day 1				
Lowest set V_t, mL, median (IQR)	450 (400, 500)	430 (370, 470)	460 (400, 500)	
Lowest set V_t, mL/kg PBW, mean ±sd	7.0 ±1.1	6.0 ±0.4	7.5 ±1.0	<0.01
Lowest set V_t, mL/kg PBW, median (IQR)	6.9 (6.2, 7.6)	6.0 (5.8, 6.3)	7.2 (6.9, 8.0)	
Highest set V_t, mL, median (IQR)	480 (410, 500)	450 (400, 500)	500 (450, 500)	
Highest set V_t, mL/kg PBW, median (IQR)	7.0 (6.4, 7.9)	6.2 (6.0, 6.5)	7.5 (7.0, 8.4)	
Hospital Course				
ICU type				<0.01
Medical, n (%)	134 (25)	74 (40)	60 (17)	
Surgical, n (%)	60 (11)	20 (11)	40 (12)	
Cardiac/CT surgery, n (%)	143 (27)	34 (18)	109 (32)	
Neuro, n (%)	126 (24)	29 (11)	97 (28)	
Other, n (%)	70 (13)	30 (16)	40 (12)	
Length of IMV*, days, median (IQR)	5 (3, 9)	4 (3, 8)	5 (3, 11)	
Hospital LOS**, days, median (IQR)	15 (8, 23)	13 (7, 22)	15 (9, 24)	
Discharge disposition				0.01
Home, n (%)	190 (36)	57 (30)	133 (38)	
LTAC / SNF, n (%)	147 (28)	43 (23)	104 (30)	
Hospice, n (%)	96 (18)	45 (24)	51 (15)	
Died, n (%)	100 (19)	42 (22)	58 (17)	

BMI = body mass index, LPV = defined by lowest set tidal volume ≤6.5 mL/kg of predicted body weight (PBW) and lowest recorded plateau pressure ≤30 cmH_2O, IQR = interquartile range, SOFA = Sequential Organ Failure Assessment, V_t = tidal volume, CT = cardiothoracic, LOS = length of stay, LTAC = long term acute care, SNF = skilled nursing facility. *Elixhauser Comorbidity Index is based on ICD-9 and ICD-10 diagnosis codes, **among survivors. P-values calculated using a pooled two-sided t-test for continuous variables and chi-squared for categorical variables

Table 2: Demographics and characteristics between patients with sepsis that developed acute respiratory distress syndrome (ARDS) and did not develop ARDS in 2015 across two academic hospitals

Variable	ARDS (n=97)	No ARDS (n=436)	p-value
Demographics and Anthropometrics			
Age, years, mean ±sd	59.5 ±14.6	58.9 ±17.0	0.73
Sex, Female, n (%)	39 (40)	195 (45)	0.42
Race			0.67
White, n (%)	46 (47)	187 (43)	
Black, n (%)	39 (40)	200 (46)	
Other, n (%)	2 (2)	13 (<1%)	
Missing, n (%)	10 (10)	36 (8)	
Height, cm, mean ±sd	173 ±11	171 ±11	0.26
Weight, kg, mean ±sd	94.6 ±30.2	82.2 ±24.0	<0.01
PBW, kg, mean ±sd	66.6 ±11.5	65.1 ±11.8	0.26
BMI, (kg/m^2) mean ±sd	31.7 ±9.5	28.0 ±7.7	<0.01
Severity of Illness			
SOFA score, first day of IMV, mean ±sd	9.2 ±3.7	8.2 ±3.4	0.01
Elixhauser Comorbidity Index*, mean ±sd	6.2 ±2.4	5.8 ±2.3	0.20
Sepsis Variables			
Community sepsis (vs. hospital sepsis), n (%)	65 (67)	302 (69)	0.50
Time from sepsis onset to IMV, days, median (IQR)	0 (0, 2)	1 (0, 2)	
Invasive Mechanical Ventilation, Day 1			
Lowest set V_t, mL, median (IQR)	450 (400, 500)	450 (400, 500)	
Lowest set V_t, mL/kg PBW, mean ±sd	6.9 ±1.1	7.0 ±1.1	0.44
Lowest set V_t, mL/kg PBW, median (IQR)	6.8 (6.0, 7.4)	6.9 (6.2, 7.6)	
Highest set V_t, mL, median (IQR)	500 (450, 500)	470 (400, 500)	
Highest set V_t, mL/kg PBW, median (IQR)	7.1 (6.5, 8.4)	7.0 (6.4, 7.9)	
Hospital Course			
ICU type			0.15
Medical, n (%)	16 (16)	118 (27)	
Surgical, n (%)	14 (14)	46 (11)	
Cardiac/CT surgery, n (%)	24 (25)	119 (27)	
Neuro, n (%)	27 (28)	99 (23)	
Other, n (%)	16 (16)	54 (12)	
Length of IMV*, days, median (IQR)	7 (5, 12)	4 (2, 8)	
Hospital LOS**, days, median (IQR)	15 (10, 22)	15 (8, 23)	
Discharge disposition			<0.01
Home, n (%)	26 (27)	164 (38)	
LTAC / SNF, n (%)	17 (18)	130 (30)	
Hospice, n (%)	24 (25)	72 (17)	
Died, n (%)	30 (31)	70 (16)	

BMI = body mass index, LPV = defined by lowest set tidal volume ≤6.5 mL/kg of predicted body weight (PBW) and lowest recorded plateau pressure ≤30 cmH_2O, IQR = interquartile range, SOFA = Sequential Organ Failure Assessment, V_t = tidal volume, CT = cardiothoracic, LOS = length of stay, LTAC = long term acute care, SNF = skilled nursing facility. *Elixhauser Comorbidity Index is based on ICD-9 and ICD-10 diagnosis codes, **among survivors.

P-values calculated using a pooled two-sided t-test for continuous variables and chi-squared for categorical variables

Table 3: Outcomes between patients with sepsis requiring invasive mechanical ventilation (IMV) who did and did not develop acute respiratory distress syndrome (ARDS)

Variable	ARDS (n=97)	No ARDS (n=436)	p-value
Received LPV on first day of IMV, n (%)	33 (34)	154 (35)	0.81
Lowest set tidal volume on first day of IMV, mL/kg PBW, mean ±sd	6.9 ±1.1	7.0 ±1.1	0.44
Ventilator free days at 28 days, median (IQR)	17 (0, 22)	23 (9.5, 25)	
Hospital LOS*, median (IQR)	15 (10, 22)	15 (8, 23)	

LPV = lung protective ventilation (defined by lowest set tidal volume ≤6.5 mL/kg of predicted body weight (PBW) and lowest recorded plateau pressure ≤30 cmH_2O.), LOS = length of stay, IQR = interquartile range.
P-values calculated using a pooled two-sided t-test
*among survivors

Table 4: Binomial regression estimating the risk ratios for the receipt of LPV on the first day of IMV on the development of acute respiratory distress syndrome (ARDS), adjusting for covariates

Variable	Risk Ratio	95% CI	p-value
Receipt of LPV on first day of IMV	0.97	0.65, 1.46	0.89
Age, (per year)	1.00	0.99, 1.02	0.42
Male sex (female reference)	0.91	0.57, 1.45	0.70
Height, (per cm)	1.01	0.99, 1.03	0.40
BMI, (per km/m^2)	1.04	1.02, 1.06	<0.01
SOFA, (per point)	1.07	1.02, 1.13	0.01

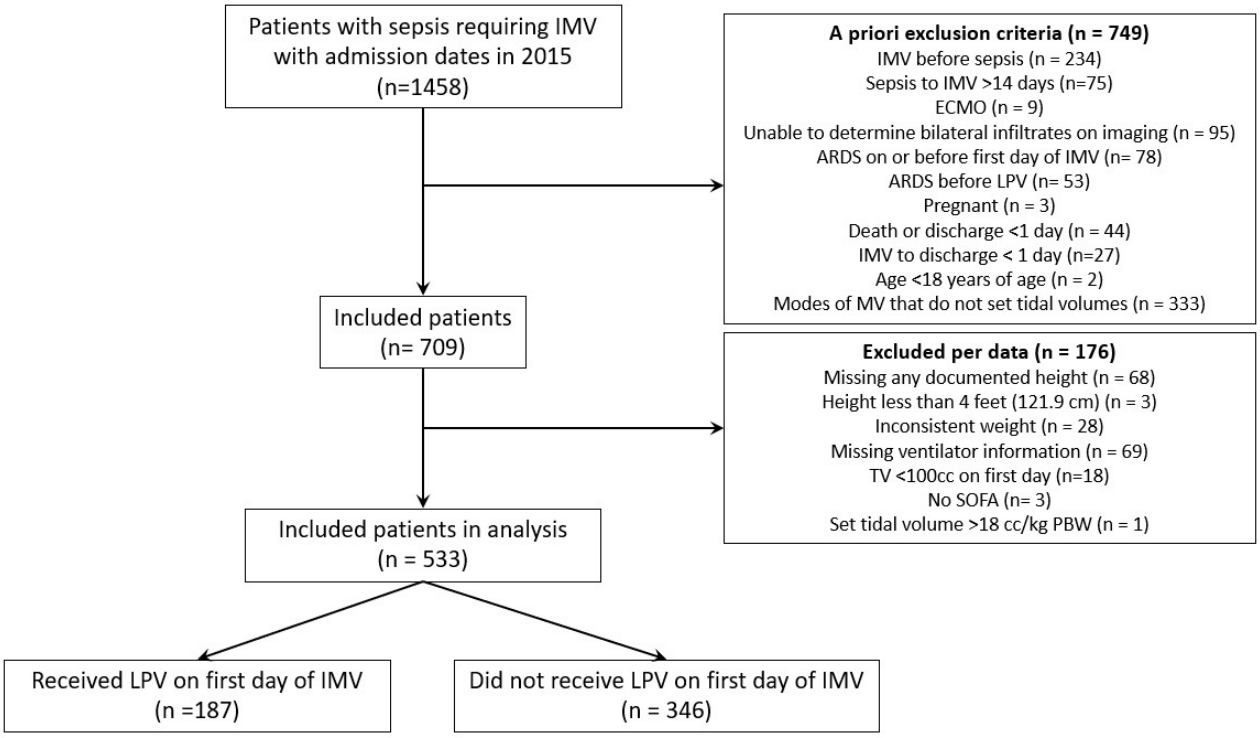
LPV = lung protective ventilation (defined by lowest set tidal volume ≤6.5 mL/kg of predicted body weight (PBW) and lowest recorded plateau pressure ≤30 cmH_2O), IMV = invasive mechanical ventilation, BMI = body mass index, SOFA = Sequential Organ Failure Assessment, CI = confidence interval.

Table 5: Binomial regression estimating the risk ratio for the effect of lowest tidal volume on the first day of IMV on the development of acute respiratory distress syndrome (ARDS), adjusting for covariates

Variable	Risk Ratio	95% CI	p-value
Lowest set tidal volume (mL/kg PBW) on the first day of IMV	1.06	0.90, 1.25	0.48
Age, (per year)	1.03	1.00, 1.06	0.05
Male sex (female reference)	0.96	0.62, 1.5	0.83
Height, (per cm)	1.01	0.99, 1.04	0.23
BMI, (per km/m^2)	1.04	1.02, 1.06	<0.01
SOFA, (per point)	1.23	1.04, 1.46	0.02
Age*SOFA	0.99	0.99, 1.0	0.08

LPV = lung protective ventilation (defined by lowest set tidal volume ≤6.5 mL/kg of predicted body weight (PBW) and lowest recorded plateau pressure ≤30 cmH_2O), IMV = invasive mechanical ventilation, SOFA = Sequential Organ Failure Assessment, CI = confidence interval.

Figure 1: Patient flow diagram.



IMV = invasive mechanical ventilation, LOS = length of stay, ECMO = extracorporeal membrane oxygenation, ARDS = acute respiratory distress syndrome, SOFA = sequential organ failure assessment, LPV = lung protective ventilation.

Figure 2: Histogram of days until receipt of lung protective ventilation (LPV) for patients who ever received LPV

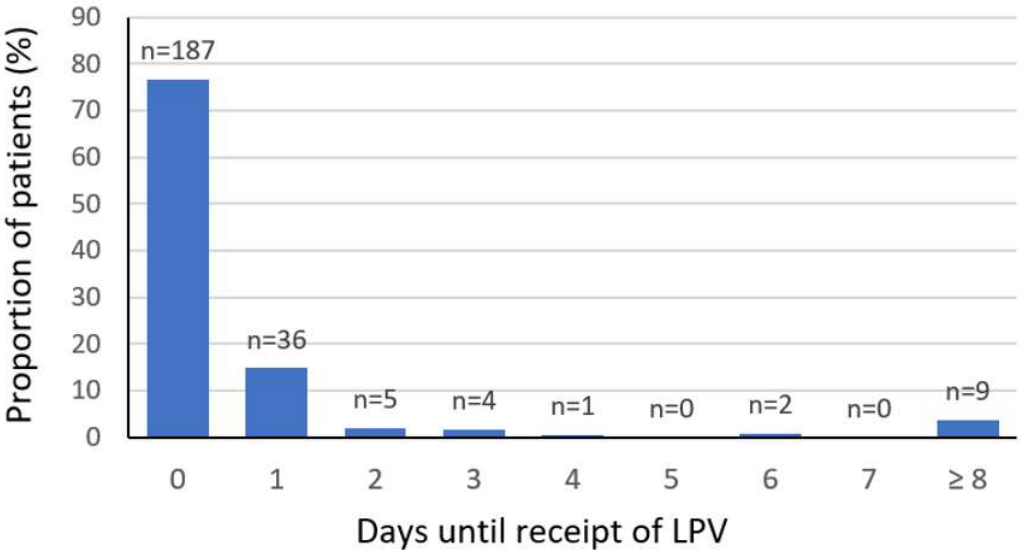
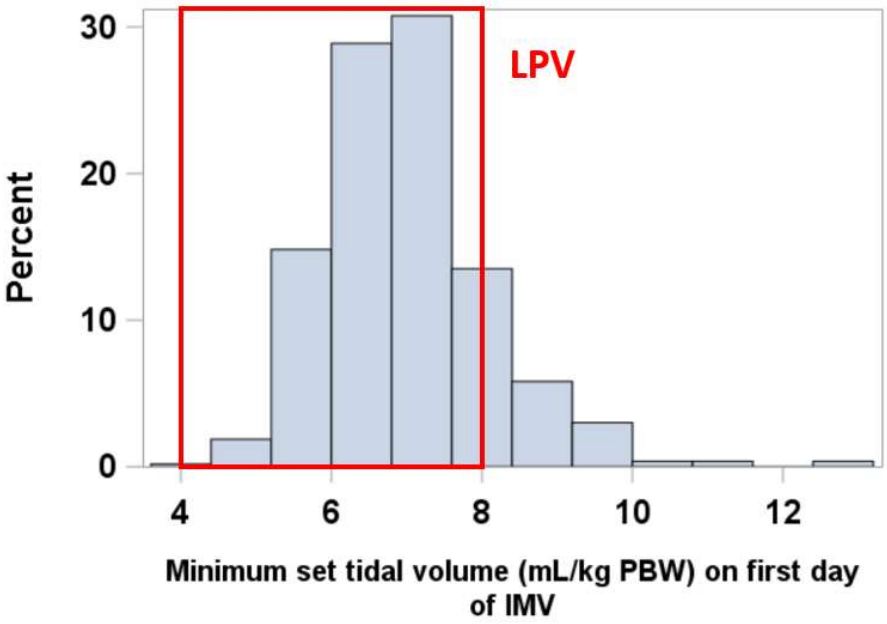


Figure 3: Histogram of the entire cohort of minimum set tidal volume on the first day of invasive mechanical ventilation.



LPV = lung protective ventilation, PBW = predicted body weight, IMV = invasive mechanical ventilation

Appendix A. CDC Adult Sepsis Surveillance Definition (2)

1. Presumed serious infection:
    a. Blood culture obtained (regardless of result),
        AND
    b. ≥4 Quality antibiotic days (QAD) – starting with ±2 days of blood culture day[a]

    AND

2. Acute organ dysfunction (any 1 of the following criteria within ±2 days of blood culture day):
    a. Vasopressor initiation (norepinephrine, dopamine, epinephrine, phenylephrine, or vasopressin)[b]
    b. Initiation of mechanical ventilation[b]
    c. Doubling in serum creatinine level or decrease ≥50% of estimated glomerular filtration rate relative to baseline (excluding patients with ICD-9-CM code for end-stage kidney disease [585.6])
    d. Total bilirubin level ≥2.0 mg/dL and doubling from baseline
    e. Platelet count <100 cells/μL and ≥50% decline from baseline (baseline must be ≥100 cells/μL)[c]
    f. Serum lactate ≥2.0 mmol/L[d]

[a] QADs start with the first "new" antibiotic (not given in the prior 2 calendar days) within the ±2-day period surrounding the day of the blood culture draw. Subsequent QADs can be different antibiotics as long as the first dose of each is "new." Days between administration of the same antibiotic count as QADs as long as the gap is not more than 1 day. At least 1 of the first 4 QADs must include an intravenous antibiotic. If death or discharge to another acute care hospital or hospice occurs prior to 4 days, QADs are required each day until 1 day or less prior to death or discharge.

[b] Vasopressors and mechanical ventilation are considered to be "initiated" during the ±2-day period surrounding the day of the blood culture draw if there were no vasopressors or mechanical ventilation administered on the prior calendar day.

[c] For presumed infection present on admission (blood culture day or first QAD occurring on hospital day 1 or 2), baseline laboratory values are defined as the best values during hospitalization. For hospital-onset infection (blood culture day and first QAD occurring on hospital day ≥3), baseline laboratory values are defined as the best values during the ±2-day period surrounding the day of the blood culture draw.

[d] Serum lactate criterion was excluded from the primary 2009-2014 trends analysis because of risk of ascertainment bias from increasing rates of lactate testing over time.

Appendix B. Select Categorical Covariate Classifications

Table 1B: Disposition groups from EMR coded disposition

Disposition	Coded DISP from EMR
Home	HOME HEALTH SERVICE HOME SELF CARE LEFT AMA
LTAC/SNF	SHORT TERM HOSPITAL SKILLED NURSING FAC OTHER REHAB FACILITY LONG TERM CARE HOSP DISCH/XFR TO OTHER TO A FEDERAL HOSP TO PSYCH HOSP STILL A PATIENT
Hospice (home or inpatient)	HOSPICE-HOME HOSPICE-MED FACILITY
Died	EXPIRED

Table 2B: Ventilator mode groups from EMR coded vent mode

Ventilator Mode	Coded vent mode from EMR
Non-invasive mechanical ventilation	AC Pressure, CPAP CPAP CPAP+PS CPAP, NIPPV NIPPV NIPPV, Other: BiPaP Other: bmv Other: stand by Other: stand-by
Invasive mechanical ventilation that do not routinely set tidal volume	AC Pressure AC/CMV Volume, AC Pressure AC/CMV Volume, Bi-Level/DuoPAP/APRV AC/CMV Volume, HFOV ASV ASV, AC/CMV Volume, CPAP+PS Bi-level/DuoPAP/APRV CPAP+PS, HFOV HFOV Other: APRV T. low - 0.6 P High - 28 P low - 5 T High 3.5 PAV+ SIMV Pressure
Invasive mechanical ventilation that routinely set tidal volume	AC/CMV Volume AC/CMV Volume, CPAP+PS AC/CMV Volume, Other: AC/CMV Volume, Other: emergency APV CMV APV SIMV SIMV Volume SIMV Volume, Other: with TC