Effects of Intubation Location on Risk of Ventilator Associated Events

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Abstract

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Background: Ventilation is a crucial tool in modern medicine that allows for advanced respiratory support in critically ill patients. However, prolonged ventilation has been found to be linked with ventilator-associated conditions (VACs), which in turn are associated with multiple adverse hospital outcomes.

Objectives: To evaluate the association between intubation practices (using intubation locations as a proxy) on the risk of VACs, ventilator-associated conditions (VACs), infection-related ventilator-associated complications (IVACs), and possible VAPs (PVAPs) and the mediating effect of intubation location on the association between VACs and adverse hospital outcomes including prolonged hospital length of stay, prolonged ventilation duration, and hospital mortality.

Methods: We conducted a retrospective cohort study on all patients who underwent mechanical

ventilation for two or more days at Harborview Medical Center (HMC), a 413-bed Trauma 1 Center and teaching hospital in Seattle, Washington. Data was collected between June 2015 and November 2016.

Results: Of the 3,424 patients who were ventilated during our study period, 1,323 had a ventilation duration of 2 or more days and were included in our study. Non-communicable diagnosis was the primary reason for hospitalization (49.06%), and patients tended to be male (70.98%). ICU and in-field intubations were associated with a non-significantly lower hazard of total VACs and PVAPs than emergency room intubations. The hazard of PVAPs was 0.29 (CI: 0.04 – 2.18; P= 0.23) times lower in individuals intubated in the ICU and 0.30 (CI: 0.08 – 1.17; P = 0.08) times lower in individuals intubated in the field than the individuals intubated in the emergency room while holding confounding factors constant. The hazard of IVACs was non-significantly higher in individuals intubated in the ICU (HR: 1.71; CI: 0.383 – 7.59; P = 0.48) and in the field (HR: 1.68; CI: 0.57 – 4.97; P = 0.35) than individuals intubated in the emergency room. Intubation locations did not significantly modify the associations between VAC and any of the outcomes of interest.

Conclusion: Although we did not find a significant associated between intubation location and VAC, non-infectious VACs, IVACs, and PVAPs, the magnitude of the point estimates justifies further research on this topic. We recommend that additional analyses are conducted to examine the directionality of the association between VACs and ventilation duration.

Acknowledgement

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Introduction

Ventilation is a crucial tool in modern medicine that allows for advanced respiratory support in critically ill patients.(1) However, prolonged ventilation has been found to be associated with ventilator-associated pneumonia (VAP), acute respiratory distress syndrome (ARDS), sepsis, pulmonary embolism, pulmonary edema, and barotrauma.(1–3) These ventilator-associated events (VAEs), in turn, have been found to be associated with numerous adverse hospital outcomes including higher hospital costs, prolonged hospital length of stay (LOS), prolonged ventilation duration, and hospital mortality.(2,4–9) Historically, the National Healthcare Safety Network's (NHSN) surveillance of these events was limited to VAPs, but the subjective nature of a VAP diagnosis makes it ill-suited for inter-hospital comparisons.(10)

The VAP diagnostic criterion is comprised of two required and one optional component: lung x-ray (required), presentation of symptoms (required), and positive laboratory tests (optional).(10) Both required components are considered subjective and allow for inaccurate identification of VAPs.(7,10–13) In 2011, Klompas et al. proposed an alternative, less subjective measure defined by minimum changes in ventilator settings following stable or improved respiratory ability.(14) Adopted by the NHSN in 2013, this new and expanded VAE surveillance criterion defines a hierarchical VAE schematic of infectious and non-infectious VAEs. The schematic is as follows: ventilator-associated conditions (VACs), infection-related ventilator-associated complications (IVACs), and possible VAPs (PVAPs).(10) This schematic is depicted in Figure 1 and the clinical criteria are provided in Figure 2.

Following the expanded VAE definition, research has focused on the ability of the new diagnostic criterion to identify VAPs (or how sensitive the criterion is to VAPs) and to provide insight into the etiology and risk factors for the identified VAEs.(15–19) Research on the sensitivity of the VAE diagnostic criterion has shown that VACs, especially the PVAPs, overlap poorly with traditionally (image based) identified VAPs.(15–18,20–22) However, VACs are associated with the same adverse hospital outcomes as traditionally identified VAPs.(3,6,16,20) For this reason, VAC incidence reduction through improved bundle practices has been a focus of recent research.(4,21,23–25) Ventilator bundle practices are a combination of hospital procedures performed upon actively ventilated patients with the goal of improved hospital outcomes.(14)

Ventilator bundle practices within hospitals have been shown to reduce but not eliminate the risk of VACs.(4,21,23–25) Due to the remaining VAC risk, current and future research needs to focus on the identification of additional VAC risk factors. *With this focus*, *we hypothesize that intubation practices make up a portion of the VAC risk that remains following appropriate bundle practices*. *We further hypothesize that intubation practices vary by intubation location (in ICU ward, in emergency room, in-field) and that intubation locations present an appropriate starting point for intubation practice risk analysis.*

The impact of intubation location has been examined in VAPs. Multiple VAP studies found that intubation location was significantly associated with incidence of VAPs, though the findings remain mixed.(26–28) In their 2006 article, Eckert et al. found that trauma patients intubated in the field or emergency department had significantly higher odds of VAPs compared to individuals intubated in an ICU, with corresponding odds ratios of 2.3 (1.1-4.9) and 3.6 (2.5-5.2) respectively.(26) In a similar study, but without the restriction to trauma patients, Decelle et al. found that patients with out-of-hospital intubations were significantly more likely to experience a VAP than individuals intubated within the emergency department.(27) Contrary to these findings, Evans et al. found no association between pre-hospital and emergency department intubation or duration of pre-hospital intubation and VAPs.(28,29) Differences in the literature may be due, in part, to differences in the patient populations within each study,

discrepancies in adjustment factors, disagreement in VAP diagnoses, and differential healthcare professional trainings. Despite these inconsistencies, the size of the odds ratios found in studies examining the effect of intubation locations on the risk of VAPs provide justification for similar research in VACs.

In order to explore our hypothesis that intubation location is associated with the incidence of VACs, we evaluated two primary and two secondary aims.

- Aim 1 - Primary Aim: The first aim of this study was to identify whether differences in intubation practices (using intubation locations as a proxy measure) were associated with VAC incidence.
- Aim 2 - Primary Aim: The second aim of this study was to identify whether differences in intubation practices (using intubation locations as a proxy measure) were associated with VACs incidence by VAC type: non-infectious VAC, IVAC, and PVAP.
- Aim 3 – Secondary Aim: The third aim of this study was to exam if VAC events were associated with the following adverse hospital outcomes: hospital mortality, hospital length of stay, and ventilation duration (measured as time until extubation alive).
- Aim 4 – Secondary Aim: The fourth aim of this study was to exam if intubation location modifies the association between VACs and adverse health outcomes analyzed in aim 3.

This study adds to the literature on VACs by examining upstream risk factors unexamined as of this point. Further, this initial research will provide the basis for a series of studies investigating the impact of intubation practices on VACs and VAC-associated adverse hospital outcomes.

Methods

Study Population and Data Collection

We conducted a retrospective cohort study on all patients who underwent mechanical ventilation for two or more days at Harborview Medical Center (HMC), a 413-bed Trauma 1 Center and teaching hospital in Seattle, Washington.(30) Medical records from ventilated patients aged 18 to 98 and treated between June 2015 and November 2016 were screened for inclusion. All ventilations of two or more days were included within the study regardless of a patient's resent ventilator history. Patients were able to contribute more than one ventilation period during the study period. The study population excluded: individuals <18 and $\geq$ 99 years of age; patients with unknown ventilation duration; burned, asphyxiated, and drowned patients; and patients with surgical airways and transfers from other hospitals.

Exposure and Outcome Definitions

VACs, the primary outcome for this study, were defined in accordance with the CDC's 2017 guidelines.(10) To meet these diagnoses, ventilated patients had to experience two or more consecutive days with improved or stable respiratory function (stable or decreasing daily minimum positive-end expiratory pressure (PEEP) or Fi02) followed by a marked decrease in function (increase in daily minimum PEEP of $\geq$ 3 cm or a $\geq$ 0.2 increase in daily minimum Fio2).(10) Each diagnosis was performed by an HMC physician and recorded in the medical records for reporting and analytic purposes.

For our second aim, examining the association between intubation location and specific types of VACs, we took the definition of infectious VACs (IVACs) and potential VAPs (PVAPs) from the CDC's 2017 guidelines.(10) By definition, PVAPs are first diagnosed as an IVAC, but for

reporting purposes, IVACs exclude PVAPs. Non-infectious VACs were defined as all diagnosed VACs that were subsequently not identified as infectious in nature (non-infectious VACs = VACs – IVACs).(10)

The adverse hospital outcomes of interest were in-hospital mortality, hospital length of stay (LOS), and ventilation duration (time until live extubation). Mortality was defined as any in-hospital death following 2 days of ventilation. We calculated LOS by subtracting the date of discharge from the date of intubation. In accordance with the CDC's definition of the two day VAC requirement, the ventilation duration was calculated as the number of calendar days a person was on a ventilator, regardless whether the day was partial or complete.(10)

The exposure of interest, intubation location, was collected and classified with reference to three locations: HMC emergency department, HMC ICU ward, and in-field (out-of-hospital). In-hospital intubations (both ICU ward and emergency department) locations were collected directly from HMC intubation records. In-field intubations were identified based on a combination of intubation, extubation, and HMC admission records. Patients with an extubation record but no prior intubation record, and for whom the HMC admission records did not indicate transfer from another hospital, were classified as having been intubated in the field.

Confounder Selection

Potential confounders were identified *a priori* using a directed analytic graph (DAG) constructed in DAGitty.(31) Due to the relatively new nature of VACs, limited research has been conducted on VAC risk factors and many of the direct edges of the DAG were justified using VAP research. From the DAG (Figure 3), the minimum set of potential confounders for adjustment was: age, sex, illness type (communicable, non-communicable, and injury), severity (illness severity), and comorbidities. The DAG also demonstrated that bundle practice was a precision variable, but it was assumed that bundle practices were consistent within each patient ventilated within HMC during the study period.

We adjusted for comorbidities using the Charlson Comorbidity Index (CCI). The CCI is a ranked numerical representation of one-year mortality probability based on a person's disease status for 19 conditions including diabetes, congenital heart failure, and metastases.(32) Illness severity was adjusted for using an HMC generated severity index. The index is a continuous variable 1-4 where 1 is the lowest and 4 is the highest. Illness type was taken from the discharge diagnosis ICD9/10 codes and aggregated into communicable, non-communicable, and injury.

Statistical Methods

Impact of Intubation Location on Risk of VACs (Aims 1 & 2)

Two competing events (ventilator death and hospital transfers) prevented us from observing our outcomes of interest. Due to the competing risks introduced by these events, we fit four Cause-specific hazard models in order to assess the association between intubation location and VACs, non-infectious VACs, IVACs, and PVAPs.(33) Cause-specific models were selected over Fine & Gray Competing risk models because they are thought to be better suited for epidemiological questions in the presence of competing risks than Fine & Gray Competing risk models.(34)

Within each model, an individual's time at risk was defined to begin on the second consecutive calendar day of ventilation. We censored patients on extubation, ventilator mortality, and hospital transfer. Without a desired reference intubation location, significance was tested between each location for each type of VAC event. Potential confounders were adjusted in manners appropriate to their data type. We adjusted for ventilator days, age, illness severity, and comorbidities (CCI) as continuous variables, whereas we adjusted for illness type

using dummy (indicator) variables, and included sex as a binary indicator of being male. Statistical significance was defined as a hazard ratio (HR) with a p-value of 0.05 or less and 95% Huber White sandwich estimator (robust) confidence intervals were generated.(35)

Adverse Hospital Outcome Examination (Aims 3 & 4)

To assess the association between VAC and the adverse hospital outcomes of interest (aim 3), we fit two multivariable Fine & Gray Competing risk models and one Cox proportional hazard model.(36,37) The association between VACs and hospital mortality was examined using a Cox model. The associations between VACs and the duration outcomes were examined using Fine & Gray Competing risk models. Fine & Gray Competing risk models, discussed more in the Discussion Section, were selected because they estimate the exposure's actual effect on the incidence of the outcome after accounting for competing events.(34) Binary event outcomes were created for LOS and ventilation duration and defined as the presence(1) or absence(0) of a live discharge and extubation, respectively. We censored patients on hospital transfer. Hospital deaths served as the competing event in the LOS and ventilation duration models.

VAC events were included in a time-varying manner within the hospital mortality Cox model and as a fixed event in the competing risk models. We adjusted for the minimum set of confounders, as identified in our DAG, for all models. A p value of 0.05 or less was defined as significant and 95% Huber White sandwich estimator (robust) confidence intervals were generated for the hazard ratios. To test if intubation location modified the association between VACs and adverse health outcomes (aim 4), intubation location and an interaction term between intubation location and VAC were added to the three adverse hospital event models described above (aim 3).

Missingness and Statistical Programing

Due to the nature of hospital record input, the missingness mechanism within the data was assumed to be missing completely at random. Initial data merging was performed using Microsoft Excel and all analyses were performed using STATA 14.(38) Competing risk models were run using the STATA command stcrreg. The University of Washington Institutional Review Boards approved all research activities (STUDY00000545 approved February 10, 2017).

Results

A total of 3,424 patients were ventilated during our study period. Of these, 1,323 had a ventilation duration of two or more days and met the additional inclusion criteria (Figure 4). These subjects contributed 8,204 days at risk for VACs. Table 1 provides patient characteristics and VAC event counts by intubation location. Table 2 provides the ventilation terminating events and adverse hospital outcomes by intubation location.

In-field intubations contributed the majority of the ventilated patients (47.8%) with emergency departments contributing the second most (28.0%; Table 1). Missingness was present in the form of censoring and observation-specific missingness. The Charlson Index, Illness severity Index, and LOS all contained observation specific missingness. A total of 40 patients (3%) had observation-specific missing data for at least one variable of interest. Of the 40 individuals with missing observations, 37 had missing Charlson Indexes, four were missing an Illness severity, and one was missing LOS.

Non-communicable diagnosis was the primary reason for hospitalization (49.1%), and the patients most frequently were male (71.0%). Compared to patients intubated in either the HMC emergency department or in-field, those patients intubated in the ICU tended to be older (59.6 SD: 15.0), with generally higher comorbidity scores (2.6 SD: 2.4), longer ventilation periods

(35.3 SD: 35.9) and shorter LOS (7.0 SD: 9.1), and were more likely to be female (32.4%) and in the hospital for an injury (43.6%).

Non-infectious VACs were the most common VAC event and occurred in 3.8% of the at risk population (individuals with $\geq$ 2 days of ventilation). VACs were more common in patients intubated in the emergency room (7.8%) than in an ICU ward (5.3%) or in the field (5.5%). Non-infectious VACs were more common in those patients intubated in the emergency room (4.3%) than in either the ICU intubated population (3.74%) or the in-field intubated patients (3.5%). Infectious VACs were least common in patients intubated in the ICU (1.3%), followed by the emergency room (1.4%) and the field (1.6%). Patients intubated in the emergency room were more likely to experience a PVAP (2.2%) than individuals intubated in the ICU (0.3%) or in the field (0.5%).

Of the 1,323 ventilated patients: 1031 (77.8%) were extubated prior to an event, 122 were transferred while on a ventilator (9.2%), and 170 died while on a ventilator (12.8%; Table 2). Patients intubated in the field were more likely to have their ventilation record terminated by a hospital transfer (14.2%) or death (16.5%) than individuals intubated in the ICU or emergency department. Individuals intubated in the ICU were more likely to die during hospitalization (32.1%) than those intubated in the field (23.7%) or in the emergency department (19.7%). Mean ventilation duration was longer in individuals intubated in the emergency room (Days: 6.1; SD: 9.2) than either the ICU (Days: 5.5; SD: 8.3) or in the field (Days: 4.5; SD: 13.4). The mean LOS following intubation was longest in individuals intubated in the emergency room (Days: 28.0; SD: 30.6).

Statistical Analysis

Impact of Intubation Location on Risk of VACs (Aims 1 & 2)

Associations between intubation location and VAC events are summarized in Table 3. The table provides hazard ratios comparing ICU and in-field intubations to intubations performed in the emergency room, as well as the ratios comparing ICU intubations to in-field intubations. ICU and in-field intubations were associated with a non-significantly lower hazard of PVAPs than emergency room intubations. The hazard of PVAPs was 0.29 (CI: 0.04 – 2.18; P= 0.23) times lower in individuals intubated in the ICU and 0.30 (CI: 0.08 – 1.17; P = 0.08) times lower in individuals intubated in the field than for individuals intubated in the emergency room (while holding confounding factors constant). The hazard of IVACs was non-significantly higher in individuals intubated in the ICU (Hazard ratio (HR): 1.71; CI: 0.38 – 7.59; P = 0.48) and in the field (HR: 1.68; CI: 0.57 – 4.97; P = 0.35) than for individuals intubated in the emergency room. No significant hazard differences were found between individuals intubated in the field when compared to individuals intubated in the ICU.

Adverse Hospital Outcome Examination (Aims 3 & 4)

From the competing risk analyses, we found that VAC events were significantly associated with ventilation duration and LOS (Table 4). VACs were associated with a lower hazard of live extubation (subdistribution hazard ratio (SHR): 0.259; CI: 0.169 – 0.397; P < 0.001) and live discharge (SHR: 0.478; CI: 0.345 – 0.663; P < 0.001). The lower hazards of live extubation and discharge in the VAC group can be interpreted as the VAC group having a lower instantaneous risk of live extubation and discharge than the non-VAC group. It suggests a longer ventilation duration and LOS within patients who had a VAC event. VACs were not found to be significantly associated with hospital mortality (SHR: 1.105; CI: 0.752 – 1.623; P = 0.612).

Table 5 summarizes the modifying effect of intubation location on the associations between VACs and adverse hospital outcomes. Intubation locations did not significantly modify

the associations between VAC and any of the outcomes of interest.

Discussion

We found no statistically significant association between intubation location and hazard of VACs within our study. However, we argue that the magnitude of the point estimate for multiple associations of interest justifies further research. The point estimate for the PVAP hazard was 71.4% lower in individuals intubated in the ICU than in the emergency department and 70.4% lower in patients intubated in the field than the emergency room. Further, the point estimate of the IVAC hazard was 70.5% higher in individuals intubated in the ICU than in the emergency room. Despite the lack of statistical significance, these point estimates are clinically significant and should not be disregarded.

The disagreement in the directionality of the association between intubation location and VACs with suspected infectious etiologies (IVACs and PVAPs) was surprising. Due to the suspected etiology-based hierarchical nature of the VAC diagnosis, we expected to find more agreement in the intubation locations identified as high-risk between IVACs and PVAPs than between PVAPs and non-infectious VACs. However, the hazard ratios (HR) indicate that the emergency room was the intubation location with the highest adjusted hazard for PVAPs, while it was the location with the lowest adjusted hazard for IVACs. Conversely, the ICU was the intubation location with the lowest adjusted hazard of PVAPs but the location with the greatest hazard for IVACs. The variation in the direction of the point estimates provides justification for the need to examine each VAC diagnosis type individually when evaluating potential risk factors.

In agreement with prior literature, we found VACs to be associated with the following adverse hospital outcomes: longer ventilation duration and longer LOS.(6,8,14) The magnitudes of the effects we estimated were larger than those previously reported using time until event methods. In their 2013 study examining the effects of VACs on adverse hospital outcomes, Hayashi et al. found a ventilation duration HR of 0.7 (0.6-0.8) and LOS HR of 0.8 (0.5 – 1.1).(6) Our ventilator duration SHR of 0.26 (0.2 – 0.4) and LOS SHR of 0.5 (0.3 – 0.7) illustrate a larger association between VAC and adverse hospital outcomes than that seen by Hayashi et al.(6) The disagreement in our estimates may be due to our use of Fine & Gray Competing risk models instead of Cox proportional hazard models, as well as disagreements in the adjusting factors.(6)

We did not find VACs to be significantly associated with hospital mortality, an outcome found to be associated with VACs in previous literature.(2,7,8,14,20,22) Further, we did not find reason to reject the null hypothesis that intubation location modifies the association between VACs and adverse hospital outcomes. This suggests that instantaneous risk of adverse hospital outcomes are similar in patients with VACs regardless of their intubation location.

We chose to use cause-specific hazard ratios for the analysis of intubation location and VACs because the literature suggests it to be a more informative model type for epidemiological studies than the Fine & Gray Competing risk models. Digman et al. showed that in comparison to Fine & Gray Competing risk models, cause-specific Hazard models lead to more accurate estimates in the presence of independent competing events, though they can lead to larger biases away from the null in the presence of dependent competing risks.(33) This bias away from the null was largest when the hazards of both events were lower within one exposure group but differed by the magnitude to which they were lower.(33) Without the true adjusted hazard of either event, we cannot be sure that our estimated cause-specific hazard ratios are not biased away from the null and we caution against their use in policy or action plans.

The use of Competing Risk analysis for the evaluation of risk factors for VACs is not novel. In their 2016 publication on the associations between bundle practice components and risk of VACs, Klompas et al. used Fine & Gray Competing risk models to evaluate the effect of

bundle components on the risk of adverse hospital outcomes.(39) For their analysis, Klompas et al. restricted the sample to individuals who were ventilated for ≥ 3 consecutive days (similarly to how we restricted ours to individuals with a ventilation duration of 2 or more days).(39) Restricting the study participants to individuals with 2 or 3 days of consecutive ventilation limits the population to individuals who were at risk of experiencing a VAC. It thus allows for the generation of ratios that specifically examine the effects of exposures on the risk of outcomes among individuals who were at risk of experiencing the exposure of VAC. However, we advise individuals to be cautious with the interpretation of these results as they do not provide duration event risk comparisons between all ventilated individuals. Instead they provide duration event risk comparisons between ventilated patients who experienced risk of VAC.

This study suffers from a number of limitations. As discussed above, the current methods for competing risk analysis are limited and may have allowed the introduction of bias into our analyses. Further, the associations between VAC events and ventilation duration may be bidirectional. It has been found that prolonged ventilation is associated with VAP events and that VAPs are associated with prolonged ventilation.(23, 40–42) While the causal direction shifts within these statements, the directional component of ventilation time has not been explored in the context of ventilator associated events. VACs/VAPs cannot be included within ventilation duration models in a time-varying manner as they are in mortality models. This is because, in a model with time-varying VAC/VAP events, the time prior to the event would be contributed to the control group (non-VAC/VAP) while the actual control group would maintain its total ventilation time. However, in the absence of a time-varying VAC/VAP variable, we are unable to determine that a VAC/VAP event leads to more ventilation time or that increased ventilation time increases the risk of VACs/VAPs. Because of the issue with causal direction, we encourage future research to explore this topic using longitudinal data analysis techniques. For clarity, this concept is outlined in Figure 5 and the time is dichotomized by pre and post VAC event in the DAG (Figure 2).

Additional limitations with this study include our assuming that ventilated patients in HMC over the study period were subject to the same bundling practices, our use of complete case analysis, and the limited sample size. Bundle practice components have been shown to be associated with the risk of VACs.(4,21,23–25) By assuming that all study participants were subject to the same bundle practices, we may have failed to adjust for known confounders and, by doing so, reduced our ability to make reliable causal inferences based on our analysis. Compete case analysis was employed because of the opportunity for missingness to be introduced randomly by providers and other health professions. However, missingness within our study may not have been completely random, and the use of complete case analysis may have introduced bias into our analysis.(43) Our study's limited sample size may have led to our study being underpowered. With a lack of power, the risk of type II error increases and the ability to correctly reject the null hypothesis diminishes. This limitation is of large concern due to the number of clinically significant point estimates that lacked statistical significance.

Conclusion

We failed to find a significant association between intubation location and VAC, non-infectious VACs, IVACs, and PVAPs. IVACs were non-significantly less common in patients intubated in the emergency department than individuals intubated in either the ICU (HR: 1.7 (0.4 – 7.6)) or in the field (HR: 1.7 (0.6 – 5.0)). PVAPs were non-significantly more common in patients intubated in the emergency department than the ICU (HR: 0.3 (0.04 – 2.2)) or in the field (HR: 0.3 (0.08 – 1.2)). We further found that while VACs were associated with increased length of hospital stay and ventilation duration, intubation location did not modify this

association.

Despite the lack of significance, we argue that the magnitude of the point estimates justifies further research on this topic. Additionally, we recommend that analyses be conducted to examine the directionality of the association between VACs and ventilation duration.

Tables and Figures

Figure 1: Hierarchical VAC Breakdown

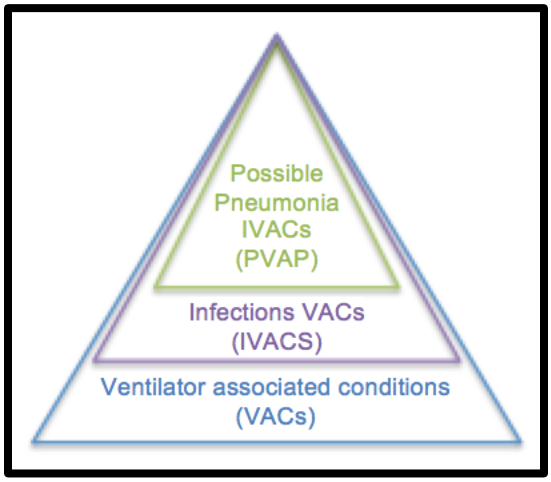

Figure 2: Diagnostic Criteria (10)

Worsening (increasing) FiO_2 or PEEP value following two or more days of stable or decreasing values (bettering)
- FiO_2 increase of 0.20+ OR over lowest value during baseline period
- PEEP increase of 3 cmH_2O+ over lowest value during baseline period

** Daily minimums must be maintained for at least one hour*

= **Ventilator-Associated Conditions (VAC)**

+

Infection-related Ventilator-Associated Complication (IVAC) =

Temperature of greater than 38 or less than 36 degree C or white blood cell count of >= 12,000 cell/mm3 or <=4,000 cells/mm3)
AND
New antimicrobial agent(s) is started and is continued for 4+ days
Infection onset most occur 2 days before or after of worsening oxygenation and following at least two days of ventilation

+

One of the following:
Criteria 1: Positive culture of one of the following specimens, without requirement for purulent respiratory secretions:
- Endotracheal aspirate, ≥ 105 CFU/ml or corresponding semi-quantitative result
- Bronchoalveolar lavage, ≥ 104 CFU/ml or corresponding semi-quantitative result
- Lung tissue, ≥ 104 CFU/g or corresponding semi-quantitative result
- Protected specimen brush, ≥ 103 CFU/ml or corresponding semi-quantitative result

Criteria 2: Purulent respiratory secretions + organism identified from one of the following specimens:
- Sputum, endotracheal aspirate, bronchoalveolar lavage, lung tissue, protected specimen brush

Criterion 3: One of the following positive tests:
- Organism identified from pleural fluid
- Lung histopathology, defined as: 1) abscess formation or foci of consolidation with intense neutrophil accumulation in bronchioles and alveoli; 2) evidence of lung parenchyma invasion by fungi
- Diagnostic test for Legionella species
- Diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus

Infection onset most occur 2 days before or after of worsening oxygenation and following at least two days of ventilation

= **Possible Ventilated-Associated Pneumonia (PVAP)**

Figure 3: DAG (31)

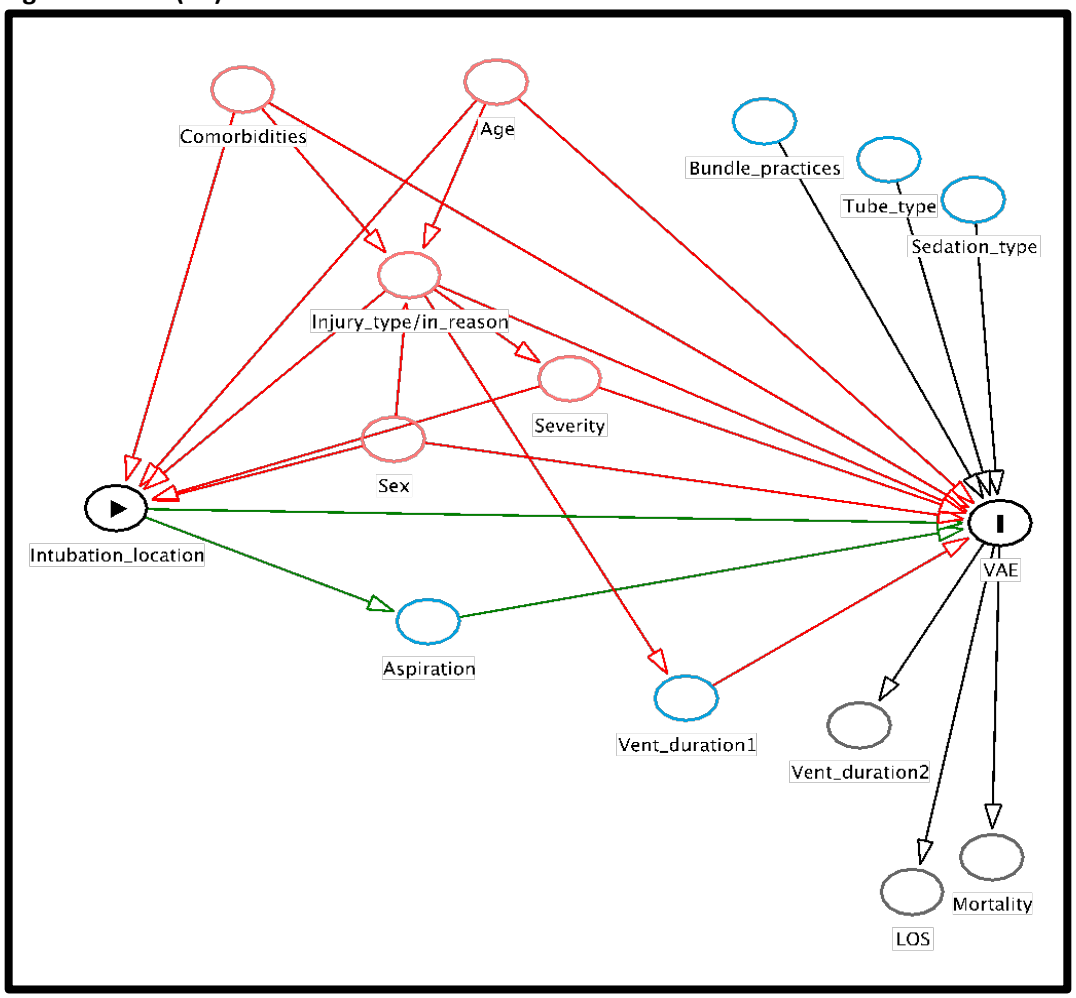

Figure 4: Participant Flow Chart

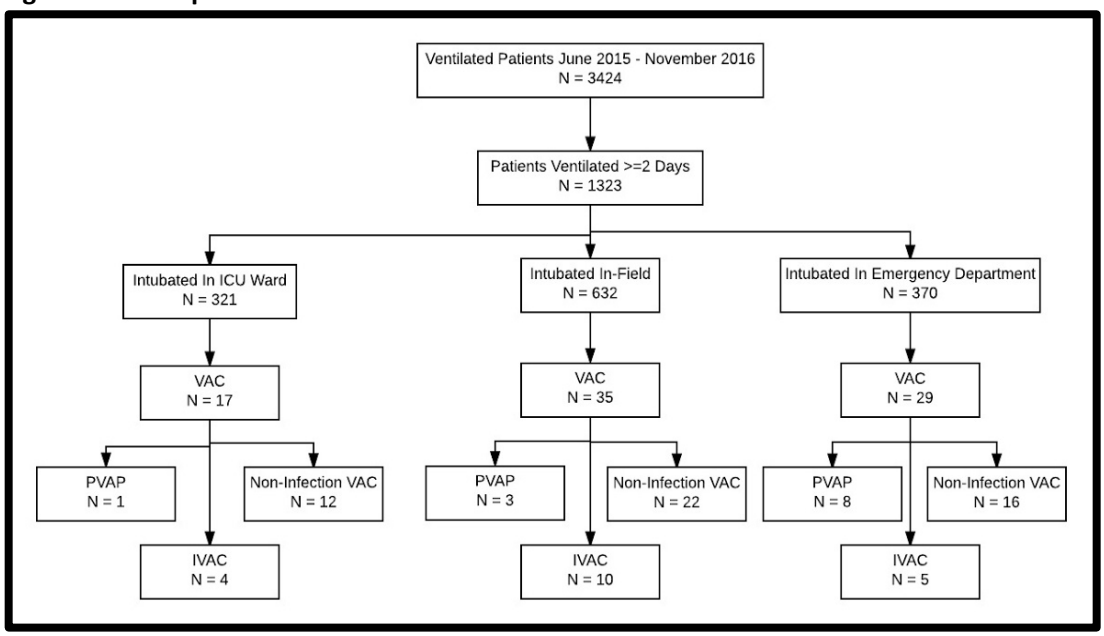

Figure 5: Directionality of the Ventilation Duration Increase Associated with VACs

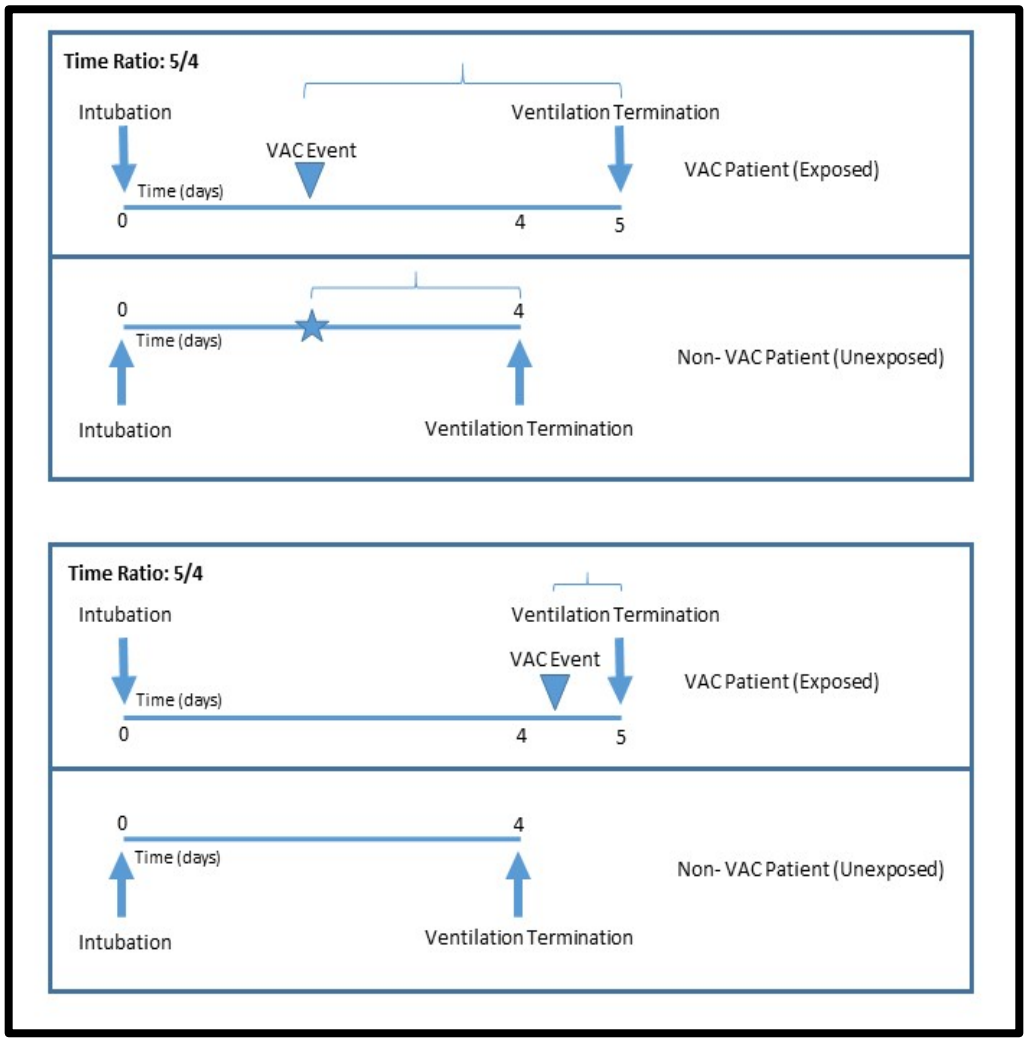

Table 1: Patient Characteristics by Intubation Location

Characteristic	Missing	Emergency Department (n = 370)		ICU Ward (n= 321)		In-Field (n = 632)		Total (n = 1323)	
Age, Mean +- SD	0	55.4	16.9	59.6	15	48.4	17.6	53.1	17.5
18 to 40 years old	-	70	18.9%	37	11.5%	210	33.2%	317	24.0%
40 to 60 years old	-	147	39.7%	103	32.1%	246	38.9%	496	37.5%
60 to 80 years old	-	129	34.9%	159	49.5%	156	24.7%	444	33.6%
80 years or older	-	24	6.5%	22	6.9%	21	3.3%	67	5.1%
Gender	0	370	100.0%	321	100.0%	632	100.0%	1323	100.0 %
Male	-	262	70.8%	217	67.6%	460	72.8%	939	71.0%
Female	-	108	29.2%	104	32.4%	172	27.2%	384	29.0%
Medical Category	0	370	-	321	-	632	-	1323	100.0 %
Communicable	-	71	19.2%	70	21.8%	74	11.7%	215	16.3%
Non-communicable	-	181	48.9%	111	34.6%	357	56.5%	649	49.1%
Injury	-	118	31.9%	140	43.6%	201	31.8%	459	34.7%
Charlson Index, Mean +-SD	37	1.984	2.1	2.604	2.366	1.5	1.814	1.9	2.1
Illness Severity Index, Mean +-SD	4	3.824	0.5	3.938	0.242	3.6	0.757	3.8	0.604
1	-	4	1.1%	0	0.0%	27	4.3%	31	2.3%
2	-	1	0.3%	0	0.0%	25	4.0%	26	2.0%
3	-	51	13.8%	20	6.2%	107	17.0%	178	13.5%
4	-	314	84.9%	301	93.8%	469	74.7%	1084	81.9%
Ventilator-Associated Conditions	0	29	7.8%	17	5.3%	35	5.5%	81	6.1%
Non-Infectious VAC	-	16	4.3%	12	3.7%	22	3.5%	50	3.8%
IVAC	-	5	1.4%	4	1.3%	10	1.6%	19	1.4%
PVAP	-	8	2.2%	1	0.3%	3	0.5%	12	0.9%

Table 2: Terminal events by Intubation Location

	Emergency Department (n = 370)		ICU Ward (n= 321)		In-Field (n = 632)		Total (n = 1323)	
Ventilation Terminating Events								
Extubation	322	87.0%	271	84.4%	438	69.3%	1031	77.8%
Death*	32	8.7%	34	10.6%	104	16.5%	170	12.8%
Hospital Transfer*	16	4.3%	16	5.0%	90	14.2%	122	9.2%
Adverse Hospital Outcomes								
Hospital Death	73	19.7%	103	32.1%	150	23.7%	326	24.6%
Length of Hospital Stay, Mean +- SD	27.96	30.61	26.16	33.45	21.62	32.72	24.49	32.43
Less than 20 Days	184	49.7%	177	55.1%	415	65.7%	776	58.6%
20 to 40 days	107	28.9%	98	30.5%	136	21.5%	341	25.7%
40 to 60 days	45	12.2%	21	6.5%	42	6.7%	108	8.2%
60 to 80 days	17	4.6%	12	3.7%	17	2.7%	46	3.5%
80 to 100 days	8	2.2%	6	1.9%	7	1.1%	21	1.6%
100 or more days	9	2.4%	7	2.2%	16	2.5%	32	2.4%
Ventilation Duration in Days, Mean +- SD	8.91	10.40	7.01	9.11	8.26	18.60	8.14	14.69
2 days	87	23.5%	89	27.7%	217	34.3%	393	29.7%
3 days	45	12.2%	59	18.4%	97	15.4%	201	15.2%
4 days	30	8.1%	32	10.0%	61	9.7%	123	9.3%
5 to 10 days	101	27.3%	73	22.7%	118	18.7%	292	22.1%
10 to 20 days	73	19.7%	52	16.2%	90	14.2%	215	16.3%
20 to 40 days	24	6.5%	10	3.1%	37	5.9%	71	5.4%
40 to 80 days	9	2.4%	5	1.6%	8	1.3%	22	1.7%
80 or more days	1	0.3%	1	0.3%	5	0.8%	7	0.5%

* Events occurred prior to Extubation

Table 3: Adjusted Hazard Ratios for the association between Intubation Location and Ventilator-Associated Conditions

	HR	Lower	Upper	Pvalue
VAC				
Emergency Department	-	-	-	-
ICU	0.9	0.5	1.7	0.8
In-Field	1.0	0.6	1.6	0.9
In-Field**	1.0	0.6	1.9	0.9
Non-Infectious VAC				
Emergency Department	-	-	-	-
ICU	1.0	0.5	2.1	1.0
In-Field	1.1	0.6	2.2	0.7
In-Field**	1.1	0.5	2.3	0.7
IVAC				
Emergency Department	-	-	-	-
ICU	1.7	0.4	7.6	0.5
In-Field	1.7	0.6	5.0	0.3
In-Field**	1.0	0.3	3.6	1.0
PVAP				
Emergency Department	-	-	-	-
ICU	0.3	0.0	2.2	0.2
In-Field	0.3	0.1	1.2	0.1
In-Field**	1.0	0.1	7.9	1.0

** Compared against ICU intubated Patients

Table 4: Association between VAC events and Adverse Hospital Outcomes

	SHR	Lower	Upper	P Value
Hospital Mortality*	1.1	0.8	1.6	0.6
Ventilation Duration**	0.3	0.2	0.4	0.0
Length of Stay**	0.5	0.3	0.7	0.0

* Hazard Ratio from Cox Proportional Hazard Model

** Subdistribution Hazard Ratio from Fine & Gary Competing risk model

Table 5: Examination of the Modification of VACs association on Adverse Hospital outcomes by Intubation Location

	SHR	Lower	Upper	P Value
Hospital Mortality*				
VAC x Emergency Department	-	-	-	-
VAC x ICU	0.6	0.3	1.5	0.3
VAC x In-Field	0.5	0.2	1.2	0.1
VAC x In-Field***	0.8	0.3	2.0	0.6
Ventilation Duration**				
VAC x Emergency Department	-	-	-	-
VAC x ICU	0.7	0.2	2.7	0.6
VAC x In-Field	1.3	0.5	3.3	0.6
VAC x In-Field***	1.8	0.5	6.5	0.4
Length of Stay**				
VAC x Emergency Department	-	-	-	-
VAC x ICU	1.1	0.4	3.3	0.8
VAC x In-Field	1.5	0.7	3.2	0.3
VAC x In-Field***	1.3	0.5	3.5	0.6

* Hazard Ratio from Cox Proportional Hazard Model

** Subdistribution Hazard Ratio from Fine & Gary Competing Risk Model

*** Compared against ICU intubated Patients

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