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Ultra short course antibiotics for patients with suspected ventilator-associated pneumonia but minimal and stable ventilator settings

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Running Title: Ultra short course therapy for VAP

Brief Summary:

Amongst 1,290 patients with suspected ventilator-associated pneumonia but minimal and stable ventilator settings, outcomes were similar for patients treated with 1-3 versus >3 days of antibiotics. Assessing serial ventilator settings may help clinicians identify suitable candidates for early antibiotic discontinuation.

ABSTRACT:

Purpose: Many patients started on antibiotics for possible ventilator-associated pneumonia (VAP) do not have pneumonia. Patients with minimal and stable ventilator settings may be suitable candidates for early antibiotic discontinuation. We compared outcomes amongst patients with suspected VAP but minimal and stable ventilator settings treated with 1-3 versus >3 days of antibiotics.

Methods: We identified consecutive adult patients started on antibiotics for possible VAP with daily minimum PEEPs ≤5cm H2O and FiO2s ≤40% for at least 3 days within a large tertiary care hospital between 2006-2014. We compared time to extubation alive versus ventilator death and time to hospital discharge alive versus hospital death using competing risks models amongst patients prescribed 1-3 days versus >3 days of antibiotics. All models were adjusted for patients' demographics, comorbidities, severity of illness, clinical signs of infection, and pathogens.

Results: There were 1,290 eligible patients, 259 treated for 1-3 days and 1,031 treated for >3 days. The two groups had similar demographics, comorbidities, and clinical signs. There were no significant differences between groups in time to extubation alive (HR 1.16 for short versus long course treatment, 95% CI 0.98-1.36), ventilator death (0.82, 95% CI 0.55-1.22), time to hospital discharge alive (HR 1.07, 95% CI 0.91-1.26), or hospital death (HR 0.99, 95% CI 0.75-1.31).

Conclusions: Very short antibiotic courses (1-3 days) were associated with outcomes similar to longer courses (>3 days) in patients with suspected VAP but minimal and stable ventilator settings. Assessing serial ventilator settings may help clinicians identify candidates for early antibiotic discontinuation.

Key Words: ventilator-associated pneumonia, antibiotic stewardship, antibiotic de-escalation, mechanical ventilation, quality improvement

Introduction

Antibiotics administered for suspected respiratory infections account for 50-70% of antibiotic prescribing in ICUs.[1-4] A substantial fraction of these antibiotic courses may be unnecessary. The predilection to over-prescribe antibiotics for patients with possible ventilator-associated pneumonia (VAP) is not due to poor clinical skills per se, but rather the tension between practice guidelines that encourage early and aggressive prescribing arrayed against the difficulty accurately diagnosing VAP. The clinical signs used to diagnose VAP, including fever, leukocytosis, increased secretions, and radiographic infiltrates, are common and non-specific in ventilated patients. Case series comparing clinical diagnoses of VAP with autopsy or expert adjudication suggest that 40-70% of patients diagnosed with VAP do not have VAP.[5-7]

The challenge is to find simple, pragmatic strategies to help clinicians identify suitable candidates for early discontinuation of antibiotics. It is unrealistic to expect clinicians to withhold antibiotics when they first suspect VAP given the difficulty making a certain diagnosis and ample data associating delayed treatment with increased mortality.[8-16] Focusing on early discontinuation instead, once clinicians have had a chance to observe patients' clinical trajectories, may be more promising.

One potential strategy may be to evaluate patients' serial ventilator settings. Clinically significant pneumonias usually impair gas exchange and often require higher levels of ventilator support.[17-21] Conversely, patients with suspected VAP but minimal and stable

ventilator settings may be candidates for stopping antibiotics early. These patients may not have pneumonia at all or they may have comparatively mild pneumonias that can be adequately treated with very short courses.

Given the potential value of serial ventilator setting surveillance to inform antibiotic stewardship efforts, we compared outcomes amongst patients started on empiric antibiotics for suspected VAP but minimal and stable ventilator settings who were treated with antibiotics for ≤3 days versus >3 days.

Methods

We retrospectively identified all patients age ≥18 initiated on mechanical ventilation in Brigham and Women's Hospital between January 1, 2006 and December 31, 2014. Patients were identified using a prospectively populated database of patients on mechanical ventilation maintained by the hospital's respiratory therapy department. We then identified all patients started on antibiotics for possible VAP who had minimal and stable ventilator settings for at least 3 days. We defined minimal and stable ventilator settings as daily minimum positive end-expiratory pressure (PEEP) of ≤5 cm H2O and daily minimum fraction of inspired oxygen (FiO2) of ≤40% on the day antibiotics were started and the following two calendar days. We obtained data on patients' microbiology, drug exposures, and clinical characteristics by merging the database of ventilated patients with the hospital's microbiology database, electronic medical administration record, and clinical data repository. The Partners' Institutional Research Board approved the study for waiver of informed consent.

For our primary analysis, we identified patients with suspected VAP as those in whom clinicians acquired an endotracheal aspirate or bronchoalveolar lavage culture on or after the third day of mechanical ventilation and initiated one or more new antibiotics within 2 calendar days of the culture order date (excluding the first two days of mechanical ventilation). We defined a new antibiotic as one that had not been administered in the preceding 2 calendar days.

We then compared outcomes amongst patients prescribed 1-3 days of antibiotics versus those prescribed >3 days of antibiotics. In determining the duration of antibiotics, we counted all consecutive antibiotic days wherein one or more of the antibiotics started at the time of the pulmonary culture were continued or a new antibiotic was substituted and continued. We included single days between two doses of levofloxacin and vancomycin, as well as the subsequent day, to account for renal dosing. We also reviewed all patients in the short course group who received vancomycin on antibiotic day 3 and who had renal dysfunction (defined as creatinine ≥2.0 mg/dl). We manually extended their vancomycin course in accordance with their dosing history and daily vancomycin levels. We calculated duration of mechanical ventilation as the time from antibiotic start to extubation, and duration of hospitalization as the time from antibiotic start to hospital discharge. We excluded patients who died within 2 days of stopping antibiotics from the short course arm insofar as we wished to restrict the analysis to patients in whom clinicians elected to stop antibiotics early rather than those in whom early antibiotic discontinuation was forced by early death.

We compared outcomes using Fine-Gray subdistribution hazard models to calculate the competing events of time to extubation alive versus ventilator death and time to hospital discharge alive versus hospital death.[22] We adjusted all analyses for age, race, sex, ICU type, predicted probability of hospital death on the first day of mechanical ventilation[23], time from intubation until pneumonia, maximum temperature on the first day of antibiotics, maximum white blood cell count on the first day of antibiotics, use of vasopressors on the first day of antibiotics, presence of ≥25 neutrophils per low power field on pulmonary specimen Gram stain, positive cultures for *Staphylococcus aureus,* Enterobacter sp., Klebsiella sp., Serratia sp., or non-fermenting Gram negative rods. We further adjusted for patients' comorbidities including chronic lung disease, renal failure, cancer, diabetes, peripheral vascular disease, congestive heart failure, coronary artery disease, liver disease, and alcohol abuse. Finally we adjusted for calendar year of diagnosis to account for possible temporal trends in management strategies and outcomes.

We performed three sensitivity analyses using propensity scores to match patients prescribed 1-3 days of antibiotics to patients prescribed >3 days of antibiotics. The first sensitivity analysis included all patients prescribed 1-3 days of antibiotics and their corresponding matches. The second sensitivity analysis was intended to identify a subset of patients with additional evidence that the clinical team specifically suspected VAP. To do so, we restricted the primary study population to patients assigned a pneumonia diagnosis code (ICD9-CM 481-486 or 997.31) for the first time in their hospitalization on or after ventilator day 3 and within 2 days of their respiratory culture and antibiotic start dates.

The third sensitivity analysis was designed to identify a subset of patients with a greater likelihood of having a true pneumonia. To do so, we restricted the study population to patients with ≥25 neutrophils per low power field on endotracheal aspirate or bronchoalveolar lavage Gram stain and a positive culture for a potentially pathogenic organism (i.e. organisms other than oral flora, Candida sp., Enterococcus sp., and coagulase-negative Staphylococci). We calculated propensity scores by fitting logistic regression models using all the same covariates used in the primary analysis. We identified a match for each patient treated with 1-3 days of antibiotics by identifying the patient treated with >3 days of antibiotics with the closest estimated logit propensity score.[24] To assure close matches, we imposed a caliper of 0.2 times the standard deviation of the logit propensity score for each patient.[25]

Results

There were 30,336 episodes of mechanical ventilation between 2006 and 2014. Of these, 2,549 (8.4%) met the primary study definition for clinically suspected VAP (pulmonary culture on or after ventilator day 3 and a new antibiotic start within two days). Ventilator settings were minimal and stable for at least 3 days starting from the first day of antibiotics in 1,290 of the 2,549 patients with possible VAP (50.6%). Of these, 259 were prescribed 1-3 days of antibiotics and 1,031 were prescribed >3 days of antibiotics. The clinical characteristics of these patients and their possible pneumonias are presented in Tables 1 and 2.

Patients treated with short versus long courses were generally similar in sex, race, unit type, comorbidities, and initial clinical characteristics (Tables 1 and 2). Patients prescribed 1-3 days of antibiotics were older (63.4 vs 60.6 years, P=.02), more likely to be located in the medical ICU (27.0% vs 20.7%, P=.03), to have a history of renal failure (18.5% vs 9.9%, P<.001), and to have a higher predicted risk of hospital death on the first day of mechanical ventilation (mean 30.2% vs 25.5%, P=.002). Conversely, more patients prescribed >3 days of antibiotics had positive cultures for *Staphylococcus aureus* (25.6% vs 15.1%, P=.0003), and/or positive cultures for *Klebsiella* species (7.6% vs 3.1%, P=.01). Patients in the short course group were prescribed a median of 2 days of antibiotics (interquartile range 1-3 days) versus 9 days (interquartile range 6-12 days) for those in the long-course group.

Unadjusted outcomes for the two groups are shown in Table 2. There were no significant differences in mean duration of mechanical ventilation, hospital length-of-stay, or hospital mortality rates. The median numbers of days from antibiotic start to extubation and hospital discharge were longer for patients prescribed >3 days of antibiotics. Outcomes adjusted for possible confounders are shown in Table 3. There were no statistically significant differences between the two groups in hazard ratios for time to extubation alive (HR 1.16 for short course treatment, 95% CI 0.98-1.36), ventilator death (HR 0.82, 95% CI 0.55-1.22), time to hospital discharge alive (HR 1.07, 95% CI 0.91-1.26), or hospital death (HR 0.99, 95% CI 0.75-1.31). In all cases, the point estimates for these outcomes favored patients treated with shorter course of antibiotics (hazard ratios above 1 for time to extubation alive and time to hospital discharge alive, hazard ratios below 1 for ventilator death and hospital death).

The results of all three sensitivity analyses using propensity scores mirrored the primary analysis (Table 3). For the primary propensity analysis using all patients, we were able to identify matched controls for 257 of the 259 patients treated with 1-3 days of antibiotics. Propensity matching successfully eliminated all measured differences between short-course and long-course patients (Tables 1 and 2). There were no significant differences in unadjusted or adjusted outcomes for duration of mechanical ventilation, ventilator death, time to hospital discharge alive, or hospital death between short- versus long-course patients (Table 3). These findings further persisted when restricting the analysis to patients with a new diagnosis code for pneumonia concurrent with their respiratory specimen and antibiotic start dates, and when restricting the analysis to patients with ≥25 neutrophils per low power field and positive cultures for potentially pathogenic organism.

Discussion

Amongst patients treated for possible VAP with minimal ventilator settings sustained for at least 3 days, we were unable to identify any differences in outcomes between patients treated with 1-3 days of antibiotics versus those treated with >3 days of antibiotics. The lack of differences between these two groups persisted when restricting the study population to propensity-matched pairs, to patients with diagnosis codes for VAP, and to patients with ≥25 neutrophils per low power field and positive cultures for potentially pathogenic organisms.

These observations suggest the possibility that patients with suspected VAP but minimal and stable ventilator settings can be adequately managed with very short courses of antibiotics. If these findings are confirmed, assessing ventilator settings may prove to be a simple and objective strategy to identify potential candidates for early antibiotic discontinuation. Clinicians will simply need to track patients' ventilator settings: those with daily minimum PEEPs of ≤5cm H2O and daily minimum FiO2s <40% for at least 3 days from the first day of antibiotics may be suitable candidates for early antibiotic discontinuation.

Screening daily ventilator settings is attractive insofar as it is simple, inexpensive, and does not require specialized laboratory tests. This approach has the potential to become a valuable supplement or complement to existing strategies to identify candidates for early antibiotic discontinuation. Existing strategies include clinical judgment, Clinical Pulmonary Infection Score (CPIS) measurement, and serial procalcitonin assays.

Clinical judgment requires clinicians to weigh patients' clinical signs and clinical trajectories to identify those in whom pneumonia is either unlikely or in whom pneumonia has been adequately treated. This strategy has been shown to decrease antibiotic utilization, is theoretically robust, and closest to the ideal of the physician as a rational decision maker.[26] In practice, however, clinicians are often uncertain about the diagnosis of VAP and many defer to guidelines' headline recommendations to treat VAP for 7-8 days regardless of their particular patient's trajectory.[17, 27] At Johns Hopkins Hospital for example, a multidisciplinary adjudication committee reviewed the evolution of clinical

signs, chest radiographs, and microbiological specimens of all patients diagnosed with VAP in 6 ICUs over a one year period.[5] The adjudication panel determined that by treatment day 3 it was apparent that 158/231 (74%) of patients diagnosed with VAP most likely did not have VAP. Frontline clinicians nonetheless continued antibiotics in 120/158 (76%) of these patients, on average for a total of 9.9 days per patient. Providing clinicians with simple, objective, quantitative clinical signs (i.e. daily minimum PEEP and FiO2) that they can use to identify appropriate candidates for antibiotic discontinuation may enhance their comfort and willingness to stop antibiotics.

The CPIS has been proposed as a tool to help clinicians' systematize their assessment of VAP and its clinical trajectory. The CPIS assigns patients 0-2 points for each of six clinical signs: temperature, white blood cell count, radiographic findings, pulmonary secretions, PaO2:FiO2 ratio, and Gram stain or culture results. Patients with a score of >5 or >6 (depending on the study) are deemed to have VAP.[28, 29] The score was originally designed as a diagnostic aide but at least one randomized controlled trial has demonstrated that it may help with antibiotic de-escalation. Singh and colleagues randomized 81 patients with suspected VAP but low CPIS to three days of ciprofloxacin monotherapy versus routine care. Patients randomized to short course ciprofloxacin were prescribed significantly fewer days of antibiotics but had similar outcomes to patients in the usual care arm.[30] The CPIS score is not ideal for informing antibiotic de-escalation, however, insofar as it correlates poorly with histologically proven pneumonia, it is complicated and subjective to calculate, and it is not in widespread use in routine critical care practice.

Daily ventilator setting surveillance by contrast only requires two data points (PEEP and FiO2) and measurement is objective.

Procalcitonin surveillance is a third strategy to inform antibiotic discontinuation. Clinical trials have evaluated daily procalcitonin monitoring paired with advice to clinicians to stop antibiotics if the relative level of procalcitonin drops by more than 80% from baseline and / or if the absolute level of procalcitonin falls below a specified threshold. Bouadma and colleagues, for example, randomized 630 critically ill patients with suspected bacterial infections to daily procalcitonin monitoring versus usual care.[31] Patients assigned to daily procalcitonin monitoring were prescribed significantly fewer days of antibiotics compared to usual care (absolute difference 2.7 days, 95% CI 1.4-4.1) without any apparent evidence of harm. These findings held true in the subset of patients with suspected VAP, were mirrored by a second trial of procalcitonin monitoring restricted solely to patients with VAP, and further affirmed in a patient-level meta-analysis that pooled these two trials together.[31-33] Procalcitonin monitoring is attractive insofar as it provides clinicians with a tangible measure they can use to justify stopping antibiotics. This strategy is not ideal, however, because procalcitonin assays are not available in all hospitals, they can sometimes take hours to days to return, they incur costs, and they can be difficult to interpret as there are different versions of the assay and different cut-offs for stopping antibiotics.[31-34] Daily ventilator setting surveillance by contrast is universally available, equally quantitative and concrete, does not incur delay, and does not incur costs.

Our findings need to be interpreted within the context of the limitations of the study. This was a retrospective observational study and hence our findings may be confounded by unmeasured differences between the short course and long course populations. In particular, clinicians may have selected patients for shorter courses because they were less ill, because their pneumonias were less severe, or because they were less confident about the diagnosis. We tried to adjust for these factors by incorporating variables for patients' comorbidities, severity of illness, temperature, white blood cell count, vasopressor requirement, pulmonary specimen characteristics, and culture results. In addition, we performed multiple sensitivity analyses using propensity scores to improve matching between cohorts, to restrict the population to patients with unambiguous diagnoses of VAP, and to restrict the population to patients with purulent pulmonary secretions growing potentially pathogenic organisms. The propensity-matched analyses eliminated observable differences between short-course and long-course patients. Nonetheless, residual differences in unmeasured patient traits may have persisted. Additional limitations of our study include the single center setting, our imputation that antibiotics were prescribed for pneumonia and not for another indication, and the difficulty calculating duration of antibiotics in patients prescribed overlapping courses of antibiotics for the same or different indications. Antibiotics started ≥3 days prior to VAP onset and continued for >3 days beyond VAP onset were not counted in our study as new antibiotics but they may have mitigated potential differences between the short and long treatment groups.

In sum, patients treated for suspected VAP who have minimal and stable ventilator settings for at least 3 days appear to have similar outcomes when treated with antibiotics for ≤3 days or >3 days. These observations merit further evaluation in a randomized controlled trial. If these observations are confirmed, then serial ventilator settings surveillance could be a valuable tool to help clinicians identify suitable candidates for early antibiotic discontinuation.

Conflicts of Interest: The authors have no conflicts to declare.

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Table 1. Patient characteristics

	All Patients Prescribed 1-3 Days of Antibiotics N=259	All Patients Prescribed >3 Days of Antibiotics N=1,031	P value	Propensity-Matched Patients Prescribed 1-3 Days of Antibiotics N=257	Propensity-Matched Patients Prescribed >3 Days of Antibiotics N=257	P value
Mean Age (SD)	63.4 (15.8)	60.6 (16.7)	.02	63.4 (14.7)	65.0 (14.7)	.94
Count of Males (%)	155 (59.9%)	645 (62.6%)	.42	153 (59.5%)	155 (60.3%)	.86
Race-Ethnicity						
White	190 (73.4%)	768 (74.5%)	.71	189 (73.5%)	193 (75.1%)	.69
Black	26 (10.0%)	109 (10.6%)	.80	26 (10.1%)	22 (8.6%)	.54
Hispanic	16 (6.2%)	42 (4.1%)	.14	15 (5.8%)	17 (6.6%)	.72
Asian	5 (1.9%)	19 (1.8%)	1.00	5 (2.0%)	5 (2.0%)	1.00
Other	22 (8.5%)	93 (9.0%)	.79	22 (8.6%)	20 (7.8%)	.75
Unit type						
General Medical	70 (27.0%)	213 (20.7%)	.03	69 (26.9%)	78 (30.4%)	.38
General Surgery	53 (20.5%)	248 (24.1%)	.22	53 (20.6%)	48 (18.7%)	.58
Cardiac Medical	32 (12.4%)	142 (13.8%)	.55	32 (12.5%)	26 (10.1%)	.40
Cardiac Surgery	32 (12.4%)	96 (9.3%)	.14	31 (12.1%)	40 (15.6%)	.25
Neuroscience	55 (21.2%)	255 (24.7%)	.24	55 (21.4%)	49 (19.1%)	.51
Thoracic Surgery	17 (6.6%)	78 (7.5%)	.62	17 (6.6%)	16 (6.2%)	.86
Comorbidities						
Chronic lung disease	25 (9.7%)	105 (10.2%)	.80	25 (9.7%)	25 (9.7%)	1.00
Congestive heart failure	54 (20.9%)	178 (17.3%)	.18	52 (20.2%)	57 (22.2%)	.59
Coronary artery disease	81 (31.3%)	259 (25.1%)	.05	80 (31.1%)	77 (30.0%)	.77
Renal failure	48 (18.5%)	102 (9.9%)	<.001	46 (17.9%)	45 (17.5%)	.91
Liver disease	10 (3.9%)	26 (2.5%)	.24	10 (3.9%)	10 (3.9%)	1.00
Diabetes	61 (23.6%)	197 (19.1%)	.11	60 (23.4%)	58 (22.6%)	.83
Alcohol abuse	13 (5.0%)	72 (7.0%)	.25	13 (5.1%)	17 (6.6%)	.45
Cancer	26 (10.0%)	123 (11.9%)	.39	26 (10.1%)	28 (10.9%)	.77
Probability of hospital death on first day of mechanical ventilation (mean, SD)	30.2 (23.8)	25.5 (20.8)	.002	30.1 (23.8)	29.5 (23.1)	.78

Table 2. Clinical characteristics and outcomes of possible pneumonias

	All Patients Prescribed 1-3 Days of Antibiotics N=259	All Patients Prescribed >3 Days of Antibiotics N=1,031	P value	Propensity-Matched Patients Prescribed 1-3 Days of Antibiotics N=257	Propensity-Matched Patients Prescribed >3 Days of Antibiotics N=257	P value
Clinical characteristics on the day antibiotics started						
Days since start of mechanical ventilation (mean, SD)	8.1 (8.4)	7.3 (6.1)	.08	8.1 (8.4)	7.6 (6.3)	.45
Maximum temperature (mean, SD)	99.9 (1.4)	100.1 (1.4)	.15	99.9 (1.4)	99.9 (1.4)	.78
Maximum white blood cell count (mean, SD)	14.0 (9.0)	13.2 (6.8)	.13	14.0 (8.9)	14.7 (8.4)	.36
≥25 neutrophils per low power field on Gram stain of respiratory secretions (count, %)	121 (46.7%)	545 (52.9%)	.08	121 (47.1%)	127 (49.4%)	.60
Vasopressors required (count, %)	25 (9.7%)	132 (12.8%)	.17	25 (9.7%)	25 (9.7%)	1.00
Organisms isolated from pulmonary specimens						
Staphylococcus aureus	39 (15.1%)	264 (25.6%)	.0003	39 (15.2%)	34 (13.2%)	.53
Pseudomonas aeruginosa	21 (8.1%)	95 (9.2%)	.58	21 (8.2%)	23 (9.0%)	.75
Klebsiella sp.	8 (3.1%)	78 (7.6%)	.01	8 (3.1%)	8 (3.1%)	1.00
Enterobacter sp.	8 (3.1%)	56 (5.4%)	.12	8 (3.1%)	10 (3.9%)	.63
Serratia sp.	8 (3.1%)	39 (3.8%)	.59	8 (3.1%)	3 (1.2%)	.13
Haemophilus sp.	4 (1.5%)	40 (3.9%)	.06	4 (1.6%)	5 (2.0%)	1.00
Escherichia coli	8 (3.1%)	36 (3.5%)	.75	8 (3.1%)	9 (3.5%)	.81
Acinetobacter species	6 (2.3%)	27 (2.6%)	.78	6 (2.3%)	7 (2.7%)	.78
Oral flora	158 (61.0%)	592 (57.4%)	.30	156 (60.7%)	160 (62.3%)	.72
Outcomes						
Duration of antibiotics (SD)						
Mean (SD)	2.0 (0.8)	10.0 (5.9)	<.0001	2.0 (0.8)	9.6 (5.8)	<.0001
Median (IQR)	2 (1-3)	9 (6-12)	<.0001	2 (1-3)	8 (5-12)	<.0001
Days from antibiotic start to extubation						
Mean (SD)	9.0 (15.6)	9.3 (11.0)	.77	9.0 (15.6)	9.2 (10.1)	.83
Median (IQR)	4 (2-10)	6 (3-11)	.004	4 (2-10)	6 (3-11)	.01
Days from antibiotic start to hospital discharge						
Mean (SD)	17.1 (17.3)	17.7 (14.5)	.52	17.1 (17.4)	16.5 (11.7)	.63
Median (IQR)	13 (8-22)	14 (9-22)	.03	13 (8-22)	13 (9-20)	.45
Hospital death (%)	75 (29.0%)	258 (25.0%)	.20	73 (28.4%)	78 (30.4%)	.63

Table 3. Competing risk analyses of outcomes amongst patients prescribed 1-3 days of antibiotics versus >3 days of antibiotics

	N	Time to Extubation Alive		Ventilator Death		Time to Hospital Discharge Alive		Hospital Death	
		HR (95% CI)*	P	HR (95% CI)**	P	HR (95% CI)*	P	HR (95% CI)**	P
All patients	1,290	1.16 (0.98-1.36)	.08	0.82 (0.55-1.22)	.32	1.07 (0.91-1.26)	.43	0.99 (0.75-1.31)	.96
Propensity matched population	514	1.15 (0.97-1.38)	.12	0.89 (0.57-1.38)	.60	1.08 (0.88-1.32)	.45	0.92 (0.67-1.27)	.62
Patients with VAP diagnosis codes (propensity matched population)	104	1.27 (0.86-1.88)	.24	0.69 (0.26-1.79)	.44	0.94 (0.59-1.51)	.80	1.24 (0.66-2.34)	.51
Patients with ≥25 neutrophils per low power field and positive cultures for potentially pathogenic organisms (propensity matched population)	100	1.00 (0.67-1.49)	.98	0.85 (0.29-2.50)	.77	1.33 (0.85-2.07)	.21	0.60 (0.27-1.31)	.20

Abbreviations: VAP – ventilator-associated pneumonia, HR – hazard ratio

* Hazard ratios >1 indicate a greater probability of extubation per day and hence less time to extubation alive and hospital discharge.

** Hazard ratios <1 indicate a lower probability of death per day and hence greater overall probability of survival