Intubation is Safe in Respiratory Failure Associated with Septic Shock: An Observational Study

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Research

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Abstract

Background

Acute respiratory failure associated with sepsis contributes to higher in-hospital mortality. Intubation and invasive mechanical ventilation is a common rescue procedure. However, the 2016 International Guidelines for Management of Sepsis and Septic Shock does not provide any recommendation on indication nor timing of intubation. Timely intubation may improve outcome. The decision to intubate those patients is often hampered by the fear of further hemodynamic deterioration following intubation.

Methods

This study aimed at evaluating the impact of timely intubation on outcome in sepsis associated respiratory failure. We conducted an ancillary analysis of a prospective registry of adult ICU patients with septic shock admitted to the medical ICU in a tertiary medical center, between April 30th, 2014 and December 31st, 2017. All cases of sepsis with lactate >4 mmol/L, mean arterial pressure <65 mmHg, or vasopressor use after 30 mL/kg fluid boluses and suspected or confirmed infection. Patients who remained hospitalized at 24 hours following sepsis onset were separated into intubated and non-intubated groups. The primary outcome was hospital mortality. Univariate and multivariable analyses were used, adjusted for admission characteristics and stabilization of shock within 6 hours. In a secondary analysis, time-dependent propensity score matching was used to match intubated and non-intubated patients.

Results

We identified 345 (33%) patients intubated within 24 hours and 707 (67%) not intubated. Intubated patients were younger, transferred more often from an outside facility, had higher severity of illness scores, more lung infection, achieved blood pressure goals more often but less often lactate normalization within 6 hours. The crude in-hospital mortality was higher, 89 (26%) vs. 82 (12%), $p < 0.001$, as were ICU mortality, and ICU and hospital length of stay. After adjustment, intubation showed no effect on hospital mortality but fewer hospital-free days through day 28. After 1:1 propensity score matching, there was no difference in hospital mortality, but fewer hospital-free days in the intubated group.

Conclusions

Intubation within 24 hours of sepsis onset was safe and not associated with hospital mortality, but was associated with less 28-day hospital-free days. Intubation should not be discouraged in appropriate patients with septic shock.

Introduction

Septic shock remains common and is associated with high mortality (1–3). Early recognition and management of septic shock with appropriate antibiotics, fluids, vasopressors, and source control is the

cornerstone of treatment aimed at reducing morbidity and mortality (4, 5). Sepsis-related acute respiratory failure is frequent, occurs early, requires non-invasive or invasive ventilator support, and may contribute to higher in-hospital mortality (6, 7). Intubation and invasive mechanical ventilation is a common rescue procedure in the management of septic patients with acute respiratory failure. Although the 2016 International Guidelines for Management of Sepsis and Septic Shock recommends a low tidal volume strategy once mechanically ventilated, it does not provide any recommendation on the indication nor the timing of intubation (8).

The decision to intubate a critically ill septic patient is influenced by many factors and does not rely solely on the severity or trajectory of the respiratory failure (9). Timely intubation may improve outcomes. Late intubation in patients with acute respiratory distress and inappropriate reliance on non-invasive ventilation has been associated with increased mortality (10, 11). In a large cohort of critically ill patients requiring invasive mechanical ventilation, intubation that was delayed by more than 2 days after admission was associated with higher in-hospital mortality (12). Delaying intubation in patients with severe community-acquired pneumonia symptoms were also associated with worse outcomes in those who ultimately required invasive mechanical ventilation (13).

Intubation is usually limited to the most critically ill patient, as it may worsen cardio-pulmonary status after intubation, and premature intubation may expose patients to unnecessary risks (14, 15). The decision to intubate a patient with sepsis-related respiratory failure superimposed on circulatory failure is often hampered by the fear of further hemodynamic deterioration. Unfortunately, there are no clear guidelines for intubation in these clinical scenarios (16).

Thus, we aimed at studying critically ill patients with septic shock to evaluate the impact of intubation and invasive mechanical ventilation on outcomes. We hypothesized that delaying intubation would be associated with worse in-hospital mortality and reduced hospital-free days in patients with septic shock.

Methods

STROBE reporting guidelines for observational studies were followed (17).

Patients

All consecutive patients with septic shock by sepsis 2-0 criteria (18), admitted to the 24-bed Medical Intensive Care Unit (ICU) of a tertiary medical center, were prospectively collected for an ongoing quality improvement project previously described (19). Briefly, patients with septic shock were initially identified by screening criteria using an automated surveillance algorithm (sepsis "sniffer") (20). Quality coach nurses subsequently checked the chart of these patients to confirm the diagnosis before the data were manually entered in the database. Team monitors performed periodic checks to guarantee the validity of the data. Patients were included in the registry if they met the following criteria: (1) Age equal or greater than 18 years; (2) sepsis diagnosed upon ICU admission, defined by the presence of a clinically suspected or diagnosed infection in association with systemic inflammatory response criteria (18); (3) If

multiple ICU admissions occurred, only the first admission was recorded. The exclusion criteria were do-not-resuscitate/do-not-intubate within the first 48 hours following ICU admission and patients or legal authorized representative who declined research authorization.

From the registry, for a period spanning between April 30th, 2014 and December 31st, 2017, we reviewed the electronic medical record of those adult patients admitted to the ICU with septic shock defined by lactate level >4 mmol/L, mean arterial pressure <65 mmHg or vasopressor use after 30 mL/kg of predicted body weight (PBW) fluid boluses and a clinically diagnosed or suspected source of infection. During that period and while a sepsis management bundle was imbedded into the computerized physician order entry of the electronic medical record, the ICU team followed a procedural checklist for intubation with automatic back up from anesthesia and the ventilator management followed a ventilator bundle including low tidal volume strategy (6 ml/kg of PBW, range 4 to 8 ml/kg), while maintaining a plateau pressure at 30 cm H₂O or below, most often by volume control mode and less often pressure control mode, combined (unless contra-indicated) with elevation of the head of the bed at 30 to 45 degrees, deep vein thrombosis prophylaxis, peptic ulcer prophylaxis and topical chlorhexidine.

Data collection

The main data were extracted from ICU Data Mart, a Microsoft Structured Query language database, where all the static data, including the State death registry, are updated quarterly (21). The extracted data included: Age, gender, admission source, Acute Physiology Score (APS), Acute Physiology and Chronic Health Evaluation-III (APACHE-III), Sequential Organ Failure Assessment (SOFA) score, lactate level, basic metabolic panel, source and type of infection. Patients who remained hospitalized at 24 hours following sepsis onset were divided into two groups according to the need of intubation and invasive mechanical ventilation within 24 hours. The main outcome was hospital mortality. Secondary outcomes included ICU mortality, ICU- and 28-day hospital-free days.

Statistical analysis

Two analyses were performed to assess the association between intubation and outcomes. In the first analysis, we identified patients alive at 24 hours after sepsis onset and identified intubation during that 24 hour period. Continuous variables are summarized as median (interquartile range) and compared between patients intubated and patients not intubated using rank-sum tests. Categorical variables are summarized as frequencies and percentages and compared using Chi-squared tests. ICU and hospital length of stay are summarized only for patients who were discharged alive from the ICU and hospital respectively. The association between intubation and hospital mortality was assessed using unadjusted and adjusted logistic regression models. ICU mortality was analyzed similarly. The association between intubation and hospital-free days defined within 28 days was analyzed using unadjusted and adjusted linear regression models. Hospital-free days were defined as 28 minus length of stay but with subjects who died having 0 hospital-free days. This approach is preferred to analysis of length of stay so that mortality is defined as the worst outcome response. ICU-free days were analyzed similarly. Adjustment

variables included age, sex, ICU admission source, APACHE III and SOFA score on ICU day 1, resolution of hypotension (3 or more consecutive measurements of mean arterial pressure >65 mmHg) within 6 hours, resolution (decrease by 50% or normalization) of lactic acidosis within 6 hours, and use of non-invasive ventilation within 24 hours after sepsis onset.

In the second analysis, we used time-dependent propensity score matching to match intubated patients with other patients who were not intubated. Four discrete time periods were used (0-6 hours, 7-12 hours, 13-18 hours and 19-24 hours after onset) to facilitate data collection and imputation of missing data. For a patient intubated in the t -th interval after onset, we identified all subjects who were alive and not intubated at the end of the t -th interval as potential untreated matches. The propensity to be intubated was estimated using time-dependent Cox proportional hazards models over the 4 time intervals. The probability of intubation at or before the end of each interval was obtained as 1 minus the survival estimate from the Cox model using the Breslow estimator. Variables used in the propensity score calculation included time-independent variables: age, sex, source of admission, pre-ICU hospital length of stay, and year of admission; as well as time-dependent variables: acute physiology score and laboratory values (anion gap, bicarbonate, hematocrit, potassium, creatinine, glucose, sodium, blood urea nitrogen, bilirubin, pH, and lactate). Acute physiology score and laboratory values were obtained as the worst observed value in the 6-hour interval or 6-hour period preceding intubation. Functional form and interactions were assessed in the propensity score model; restricted cubic splines were used where appropriate for non-linear functional forms and a sex by admission source interaction was included.

In each time period, we matched 1:1, with replacement, intubated to non-intubated patients using the time-dependent propensity score. Patients intubated late (for example, between 19-24 hours) could serve as non-intubated matches for patients intubated in the early intervals. Balance characteristics are described before and after matching using absolute standardized differences. Mortality and hospital-free days were analyzed in the matched sample using logistic or linear regression, respectively, with generalized estimating equations robust variance estimates to account for matching with replacement. Multiple imputations using the fully-conditional specification approach were used for missing data assuming the missing at random mechanism. Twenty imputed datasets were created and analyses reflect the combined estimate accounting for variation due to missing data. In the propensity-matched analysis, standardized differences are described for the first imputed dataset.

Data were analyzed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Demographics and clinical data

A total of 1,335 encounters were identified between April 1, 2014 and December 31, 2017 of adult patients admitted with septic shock (Fig. 1). Overall, one-third of patients were intubated at any time. After selection and exclusions, 1,052 unique patients still in the ICU within 24 hours of sepsis onset were

analyzed: 345 (33%) patients were intubated within 24 hours and 707 (67%) were not (Table 1). Those intubated were younger, [median (25th, 75th) percentiles] 66.0 years old (55.4, 74.2) vs. 69.5 (59.4, 80.2), $p < 0.001$, originated more often from an outside facility, 45% vs. 35%, $p = 0.007$, had higher median APACHE III score, 92 (74, 115) vs. 68 (57, 82), $p < 0.001$ and SOFA score, 10 (8, 13) vs. 6 (4, 8), $p < 0.001$, achieved mean arterial pressure goals within 6 hours more often but less often lactate level normalization, and stayed on the ventilator for an average of 2.3 days (1.1, 4.8). A source of infection was suspected in 91% and was microbiologically confirmed in 55% of the cases (Table 1S). The most common sources of infection were lungs (32%), abdomen (22%), urinary tract (18%), and skin and soft tissues (12%) with more pulmonary and less abdominal, urinary tract, and skin and soft tissue infections in intubated than in non-intubated patients. The main causes of infection were Gram-negative bacteria (21%), Gram-positive bacteria (20%), and polymicrobial (11%) with no differences between intubated and non-intubated patients (Table 1S).

Table 1
characteristics of patients alive at 24 hours after sepsis onset, summarized by intubation requirement

Variable	Non-intubated within 24 hours		Intubated within 24 hours		P Value
	(N = 707)		(N = 345)		
Age (y)	69.5	(59.4, 80.2)	66.0	(55.4, 74.2)	< 0.001
Sex					0.24
Male	383	(54)	200	(58)	
Female	324	(46)	145	(42)	
BMI (kg/m ²), n = 701/339	28.2	(23.6, 34.5)	28.5	(24.5, 35.1)	0.18
ICU admission source					0.007
Emergency Department	328	(46)	134	(39)	
Direct admit (from an outside facility)	249	(35)	156	(45)	
Transfer from the floor	130	(18)	55	(16)	
APACHE III score	68	(57, 82)	92	(74, 115)	< 0.001
SOFA score (day 1)	6	(4, 8)	10	(8, 13)	< 0.001
SOFA score (day 2), n = 589/334	4	(2, 7)	7	(4, 10)	< 0.001
Failed to resolve within 6 hours per MAP	113	(16)	30	(9)	0.001
Failed to resolve within 6 hours per lactate	230	(33)	137	(40)	0.022
Non-invasive ventilation use	108	(15)	62	(18)	0.26
Days on invasive ventilation, n = 153/345	0.8	(0.3, 2.0)	2.3	(1.1, 4.8)	< 0.001
ICU mortality	37	(5)	59	(17)	< 0.001

Continuous variables are summarized as median (Q1, Q3) and compared using rank-sum tests. Categorical variables are summarized as n (%) and compared using Chi-squared tests. ICU and hospital length of stay are summarized only for patients who were discharged alive from the ICU and hospital respectively. When information is missing, the number of observations with complete data is presented. Abbreviations: ICU = Intensive Care Unit; APACHE III = Acute Physiology and Chronic Health Evaluation III; SOFA = Sequential Organ Failure Assessment; BMI = Body Mass Index; MAP = Mean Arterial Pressure

Variable	Non-intubated within 24 hours		Intubated within 24 hours		P Value
	(N = 707)		(N = 345)		
ICU length of stay (d), n = 670/286	2.0	(1.3, 3.1)	3.7	(2.3, 6.9)	< 0.001
Hospital mortality	82	(12)	89	(26)	< 0.001
Hospital length of stay (d), n = 625/256	6.8	(4.5, 11.4)	10.3	(6.6, 20.6)	< 0.001
Continuous variables are summarized as median (Q1, Q3) and compared using rank-sum tests. Categorical variables are summarized as n (%) and compared using Chi-squared tests. ICU and hospital length of stay are summarized only for patients who were discharged alive from the ICU and hospital respectively. When information is missing, the number of observations with complete data is presented. Abbreviations: ICU = Intensive Care Unit; APACHE III = Acute Physiology and Chronic Health Evaluation III; SOFA + Sequential Organ Failure Assessment; BMI = Body Mass Index; MAP = Mean Arterial Pressure					

Table 1

S: Source and type of infection among patients with single episode of sepsis and ICU stay ≥ 6 hours summarized by intubation requirement

<i>Variable</i>	<i>Total</i>		<i>Non-intubated anytime</i>		<i>Intubated anytime</i>		<i>P Value</i>
	<i>(N = 1,096)</i>		<i>(N = 738)</i>		<i>(N = 358)</i>		
Source of infection							< 0.0001
Urinary tract	195	(18)	157	(21)	38	(11)	< 0.0001
Lung	351	(32)	165	(22)	186	(52)	< 0.0001
Abdomen	242	(22)	183	(25)	59	(16)	0.0019
Skin and soft tissue	129	(12)	100	(14)	29	(8)	0.0086
Line and device	26	(2)	25	(3)	1	(< 1)	0.0015
Heart	17	(2)	11	(2)	6	(2)	0.8157
Joint and bone	16	(1)	11	(2)	5	(1)	0.9032
Nose and throat	12	(1)	9	(1)	3	(1)	0.5692
Neutropenia	8	(1)	7	(1)	1	(< 1)	-
Central nervous system	3	< 1)	0	(0)	3	(1)	-
Unknown	97	(9)	70	(9)	27	(8)	0.2881
Type of infection							0.5790
Gram negative bacteria	226	(21)	162	(22)	64	(18)	-
Gram positive bacteria	217	(20)	151	(20)	66	(18)	-
Polymicrobial	118	(11)	80	(11)	38	(11)	-
Viruses	22	(2)	13	(2)	9	(3)	-
Fungi	11	(1)	6	(1)	5	(1)	-
Mycobacteria	2	(< 1)	1	(< 1)	1	(< 1)	-
Parasites	2	(< 1)	1	(< 1)	1	(< 1)	-
Unknown	498	(45)	324	(44)	174	(49)	-
Categorical variables are summarized as n (%) and compared using Chi-squared tests. Only the number of observations with complete data is presented.							

Discussion

In this ancillary analysis of a prospectively collected cohort of septic shock patients in a single tertiary center, patients intubated within 24 hours were younger, and were transferred more often from outside facilities. They presented with higher severity of illness scores, had more lung infections, and more persistent shock. They had also higher ICU and hospital mortality and longer ICU and hospital length of stays. When the analysis was limited to those patients who were alive 24 hours following sepsis onset, and after adjusting for multiple confounders, intubation had no association with hospital mortality but was associated with a small decrease in hospital-free days. When the analysis was stratified and matched by time sequence of 6 hours within the first 24 hours, including those not alive 24 hours following sepsis onset, intubation still had no association with hospital mortality but still had a small association with hospital-free days at 28 days, reflecting a longer hospital length of stay for patients who were intubated and ventilated. These findings suggest that, in patients with septic shock, intubation and invasive mechanical ventilation is not by itself overall a risk factor for increased mortality and should render the clinician more confident in initiating intubation in septic shock patients when deemed appropriate. This result should help the clinician overcome the hesitation of intubation for fear of worse outcomes, especially with hemodynamic compromise, since delaying intubation (rather than timely initiation) may worsen outcomes.

Sepsis is a major risk factor for the development of acute respiratory distress syndrome especially in the presence of shock (22). Other factors that contribute to the development of respiratory failure include younger age, higher APACHE II score, a pulmonary source of infection, acute pancreatitis, and acute abdomen. Delayed antibiotics, delayed goal-directed resuscitation, excessive fluid administration and transfusion, lack of source control, and comorbidities (alcohol, recent chemotherapy) are also contributory (23). The presence of organ dysfunction defines septic shock and is associated with greater risk of mortality (24). In sepsis, acute respiratory failure remains associated with worse outcome (7, 25). Early identification and intervention of patients at risk of acute respiratory failure is possible (26). In sepsis-related respiratory failure, early liberal and late conservative fluid strategy is associated with better outcomes (27). Timely intubation may also reduce hospital mortality (12), and prevent acute respiratory failure by limiting contributing factors such as high tidal volumes during spontaneous or non-invasive ventilation (28, 29) and patient self-inflicted lung injury (30). In our study, while septic patients who were intubated and ventilated within 24 hours after sepsis onset were more critically ill and had higher hospital mortality, intubation itself did not contribute to worse outcomes. Importantly, when adjusted for severity of illness, mechanical ventilation did not result in higher mortality. This could raise the possibility that early intubation may actually have a protective effect.

Although some studies suggest that the timing of intubation matters, the data available for patients with sepsis are still limited. Delay in intubation may be associated with worse outcomes (13, 31). The place of intubation in septic shock may also impact outcome: ICUs with the highest frequency of early intubation (greater than 90% of intubation within 12 hours) had a higher mortality rate in comparison to ICUs with middle frequency (between 80 and 90% of early intubation) whereas ICUs with the lowest frequency (less than 80% of patients with early intubation) had a tendency to be associated with increased mortality as well (32). This finding suggested that some intubations may have been too premature (highest frequency

group) or too late (lowest frequency group) and that the timing of intubation itself may impact outcomes. In our study, we did not find the timing of intubation within the first 24 hours to be a contributing factor of mortality, maybe related to a systematic and structured approach of intubation in our institution. The 2016-updated Surviving Sepsis Campaign guidelines for the management of septic shock only indirectly addresses the role of early intubation by suggesting that noninvasive ventilation should only be used in a minority of sepsis-induced acute respiratory failure patients in whom the benefits outweigh the risks (8). In our study, the use of non-invasive ventilation was low and similar to what was recently observed in WEAN SAFE, a large observational study (11); moreover the decision to intubate and the timing of intubation were left at the discretion of the care team which did not seem to affect outcome for those who remained alive 24 hours after sepsis onset.

This study has several strengths. It encompasses a large number of prospectively and consecutively collected septic shock patients with predetermined standard institutional protocols for intubation and mechanical ventilation as well as sepsis management. Although a difference in outcome was noticeable by univariate analysis, both multivariable analysis and propensity score matching using a stratified sampling strategy demonstrated no effect of intubation on the outcome of interest, i.e. hospital mortality. This study has some limitations. First, it is a single center study. Second, no data are provided regarding the induction drug(s) used for anesthesia, immediate complications after intubation, ventilator setting, and compliance with the sepsis bundle. Third, in one of the two analyses, we limited the cohort to patients who were still hospitalized 24 hours after sepsis onset. Fourth, whether patients were immunocompromised or not was not specified. Fifth, this was a secondary data analysis and there is always the possibility of unmeasured confounding factors (33). However, to limit the risk of confounding, we performed two sets of analysis, regression modeling and propensity scoring, both showing that even if patients who required intubation were more severe and had a worse outcome, intubation itself and its timing did not influence hospital mortality.

Conclusions

Intubation and invasive mechanical ventilation within 24 hours of septic shock was safe and not associated with hospital mortality but was associated with reduced 28-day hospital-free days which corresponded to longer hospital stays. These results should render the clinician more confident in initiating intubation in appropriate patients with septic shock.

Abbreviations

APACHE-III

Acute Physiology and Chronic Health Evaluation-III score

APS

Acute Physiology Score

BUN

Blood Urea Nitrogen

ICU
Intensive Care Unit
MAP
Mean Arterial Pressure
PBW
Predicted Body Weight
SOFA
Sequential Organ Failure Assessment score

Declarations

- **Ethics approval and consent to participate**

This study was approved by the Institutional Review Board (#14-008754) of Mayo Clinic, Rochester, Minnesota which approved a waiver of consent, and excluded patients who specifically declined to have their electronic medical record reviewed for research purpose.

- **Consent for publication**

Not applicable

- **Availability of data and materials**

The datasets generated and/or analysed during the current study are not publicly available due Institution Data Sharing Agreement Policy but are available from the corresponding author on reasonable request.

- **Competing interests**

The authors declare that they have no competing interests

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- **Authors' contributions**

TY and YS contributed equally to this work and are joint first authors. TY participated in the conception and design of the study, and in the acquisition and interpretation of data, helped to draft and revise the manuscript. YS participated in the conception and design of the study, and in the acquisition and interpretation of data, helped to draft and revise the manuscript. JGP participated in the design of the study, and in the acquisition and interpretation of data, helped to draft and revise the manuscript. PJS participated in the conception and design of the study, performed the statistical analysis, participated in the interpretation of data, helped to draft and revise the manuscript. ACH participated in the design of the

study, performed the statistical analysis, participated in the interpretation of data, helped to draft and revise the manuscript. VH participated in design of the study, and in the interpretation of data, helped to draft and revise the manuscript. YD participated in the conception and design of the study, participated in the interpretation of data, helped to draft and revise the manuscript. PRB conceived of the study, and participated in its design and coordination, in the interpretation of data, helped to draft and revise the manuscript. All authors have read and approved the final manuscript.

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Not applicable

- **Authors' information**

PRB is a Consultant in Pulmonary Critical Care and Associate Professor at Mayo Clinic, Rochester, USA. His research interests include factors influencing the timing of intubation in respiratory failure and sepsis.

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Figures

Figure 1

Flowchart: A= univariate and multivariable analysis; B= propensity matching

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Flowchart: A= univariate and multivariable analysis; B= propensity matching

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