Association Between Neuromuscular Blocking Agents and Outcomes of Emergency Tracheal Intubation: A Secondary Analysis of Randomized Trials

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Study objective: To examine the association between the neuromuscular blocking agent received (succinylcholine versus rocuronium) and the incidences of successful intubation on the first attempt and severe complications during tracheal intubation of critically ill adults in an emergency department (ED) or ICU.

Methods: We performed a secondary analysis of data from 2 multicenter randomized trials in critically ill adults undergoing tracheal intubation in an ED or ICU. Using a generalized linear mixed-effects model with prespecified baseline covariates, we examined the association between the neuromuscular blocking agent received (succinylcholine versus rocuronium) and the incidences of successful intubation on the first attempt (primary outcome) and severe complications during tracheal intubation (secondary outcome).

Results: Among the 2,440 patients in the trial data sets, 2,339 (95.9%) were included in the current analysis; 475 patients (20.3%) received succinylcholine and 1,864 patients (79.7%) received rocuronium. Successful intubation on the first attempt occurred in 375 patients (78.9%) who received succinylcholine and 1,510 patients (81.0%) who received rocuronium (an adjusted odds ratio of 0.87; 95% CI 0.65 to 1.15). Severe complications occurred in 67 patients (14.1%) who received succinylcholine and 456 patients (24.5%) who received rocuronium (adjusted odds ratio, 0.88; 95% CI 0.62 to 1.26).

Conclusion: Among critically ill adults undergoing tracheal intubation, the incidences of successful intubation on the first attempt and severe complications were not significantly different between patients who received succinylcholine and patients who received rocuronium. [Ann Emerg Med. 2024;■:1-8.]

Please see page XX for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2024.08.509

INTRODUCTION

Background

Millions of critically ill adults undergo tracheal intubation in an emergency department (ED) or ICU each year in the United States.[1] Approximately 10% to 20% of intubations are not successful on the first attempt.[2] Up to 40% of tracheal intubations in the ED or ICU are complicated by severe complications, including hypoxemia, hypotension, or cardiac arrest.[2,3]

Use of a neuromuscular blocking agent is intended to facilitate successful intubation on the first attempt.[4] The 2 most commonly used neuromuscular blocking agents in the ED or ICU are succinylcholine, a depolarizing neuromuscular blocking agent, and rocuronium, a nondepolarizing neuromuscular blocking agent.[5,6] Limited data exist comparing the effect of succinylcholine and rocuronium for tracheal intubation in the ED and ICU.[7,8] Despite the lack of rigorous evidence to inform which

Editor's Capsule Summary

What is already known on this topic

Rocuronium and succinylcholine are the 2 dominant paralytic agents used in emergency intubation.

What question this study addressed

How does intubation success compare between succinylcholine and rocuronium?

What this study adds to our knowledge

In this secondary analysis of 2,339 participants in 2 clinical trials in the emergency department and ICU, succinylcholine and rocuronium were deployed differently and had similar observed first-pass success (79% versus 81%) and severe complications (14% versus 25%).

How this is relevant to clinical practice

Despite large patient numbers limited by study design features, no clear advantage existed between either of these paralytics during emergency intubations.

neuromuscular blocking agent results in the best outcomes for patients, over the last decade, rocuronium has supplanted succinylcholine as the most commonly used neuromuscular blocking agent in some ED and ICU settings.[9]

Importance

Depolarizing neuromuscular blocking agents and nondepolarizing neuromuscular blocking agents differ in their pharmacokinetics. Depolarizing agents cause persistent stimulation of muscle fibers, which results in a rapid onset of paralysis.[10] However, depolarization also contributes to rare but life-threatening side effects such as hyperkalemia, rhabdomyolysis, and malignant hyperthermia.[10] In contrast, nondepolarizing agents have a longer onset of action (60 to 140 seconds),[10] which might contribute to a decreased incidence of successful intubation on the first attempt. Despite the administration of both agents to millions of critically ill adults undergoing tracheal intubation in clinical care each year, the evidence supporting which neuromuscular blocking agent should be used is limited and conflicting.

Goals of This Investigation

We compared succinylcholine and rocuronium with regard to the incidences of successful intubation on the first attempt and severe complications during tracheal intubation of critically ill adults in the ED or ICU. We hypothesized that the receipt of succinylcholine would be associated with a higher incidence of successful intubation on the first attempt and with similar rates of severe complications.

METHODS

Study Design and Setting

We performed a post hoc secondary analysis of the data sets from the Direct versus Video Laryngoscope (DEVICE) trial and the Pragmatic Trial Examining Oxygenation Prior to Intubation (PREOXI) trial. These trials were unblinded, parallel 2-group, randomized trials of video versus direct laryngoscopy (DEVICE)[9] and preoxygenation with noninvasive ventilation versus oxygen mask (PREOXI) in critically ill adults undergoing emergency tracheal intubation.[11] This analysis includes patients in these trials who received either succinylcholine or rocuronium. In these trials, the neuromuscular blocking agent was selected by treating clinicians according to their usual practice without influence from the trial protocols. This secondary analysis of a deidentified data set represented nonhuman subjects research (IRB# 160158); secondary review and concurrence of nonhuman subjects research were performed by the Department of Defense Office of Human Research Oversight.

Selection of Participants

The DEVICE and PREOXI trials enrolled adult (aged 18 years and older) patients undergoing tracheal intubation using a laryngoscope in a participating ED or ICU. Complete information on the inclusion and exclusion criteria for each trial can be found in the index trial of Appendix E1 (available at http://www.annemergmed.com).[9,11] This secondary analysis included all patients in the data sets who received succinylcholine or rocuronium. Patients in the trial data sets who received both succinylcholine and rocuronium were excluded.

Measurements and Outcomes

The primary outcome was successful intubation on the first attempt, defined as the placement of an endotracheal tube in the trachea with a single insertion of a laryngoscope blade into the mouth and either a single insertion of an endotracheal tube into the mouth or a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube into the mouth (additional details in Appendix E1).[12] The secondary outcome was the occurrence of severe complications between induction and

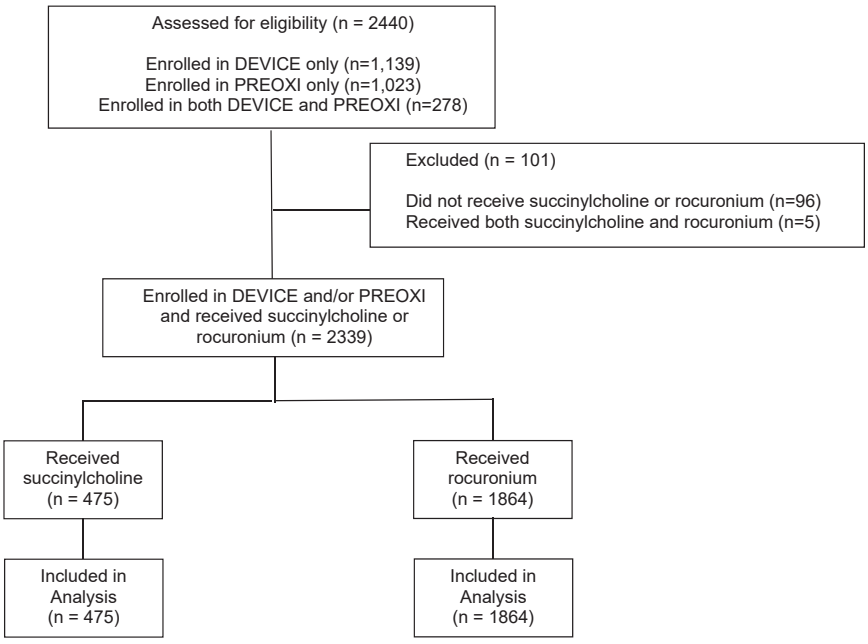

Figure 1. Number of patients screened, excluded, and included in the analysis.

2 minutes after intubation, defined as severe hypoxemia (peripheral oxygen saturation, <80%), severe hypotension (systolic blood pressure, <65 mmHg), new or increased use of vasopressors, cardiac arrest, or death. In both trials, a trained observer who was not involved in the performance of intubation prospectively recorded data. This method of data collection has been previously used and validated.[13]

Primary Analysis

We compared patients who received succinylcholine versus rocuronium with a generalized linear mixed-effects model using a logit link function with the primary outcome as the dependent variable, study site as a random effect, and fixed effects for study group and the following prespecified baseline covariates: age; sex; body mass index; operator experience quantified as the operator's total number of prior intubations; and location of intubation (ED versus ICU). The covariates for the primary outcome were selected from the adjusted analyses in previous trials that investigated successful intubation on the first attempt.[9] The analysis of the secondary outcome used the same model described above, with the following additional prespecified covariates: race and ethnicity, the presence of sepsis or septic shock, the highest fraction of inspired oxygen in the hour prior to initiation of preoxygenation, Acute Physiology and Chronic Health Evaluation II score, vasopressor receipt in the hour prior to enrollment, and hypoxemic respiratory failure as the indication for intubation. These covariates were selected from the adjusted analyses in previous trials that investigated cardiovascular[14] and oxygenation[13] outcomes after intubation of critically ill adults in an effort to control for potential confounders specific to hemodynamic and respiratory parameters during emergency intubation. All continuous variables were modeled assuming a nonlinear relationship with the outcome using restricted cubic splines with between 3 and 5 knots.

We performed 2 sensitivity analyses of the primary outcome. In the first, propensity to receive succinylcholine versus rocuronium was modeled using 74 baseline variables. The resulting propensity score was then added as a covariate to the model used in the primary analysis of the primary outcome. In the second sensitivity analysis of the primary outcome, receipt of the randomized intervention (video versus direct laryngoscopy for the DEVICE trial and preoxygenation with noninvasive ventilation versus oxygen mask for the PREOXI trial) was added as a covariate to the model used in the primary analysis of the primary outcome. Analyses were performed with the use of R software, version 4.1.2 (R Foundation for Statistical Computing).

RESULTS

Characteristics of Patients, Operators, and Intubation Procedure

Of the 2,440 patients in the trial data sets, 1,139 (46.7%) were from the DEVICE trial, 1,023 (41.9%) were from the PREOXI trial, and 278 (11.4%) were enrolled in

Table 1. Characteristics of the patients, operators, and intubation procedure.

Variable	Succinylcholine (N=475)	Rocuronium (N=1864)
Patient baseline characteristics		
Age (y), median (IQR)	51 (34-65)	59 (44-69)
Female sex, no. (%)	153 (32.2)	717 (38.5)
Race or ethnic group, no. (%)*		
Non-Hispanic Black	91 (19.2)	416 (22.3)
Hispanic	87 (18.3)	209 (11.2)
Non-Hispanic White	236 (49.7)	1,063 (57.0)
Other	49 (10.3)	146 (7.8)
Not reported	12 (2.5)	30 (1.6)
BMI, median (IQR)	25.8 (22.7-30.2)	27.0 (22.8-32.3)
Location of intubation procedure, no. (%)		
Emergency department	397 (83.6)	763 (40.9)
ICU	78 (16.4)	1,101 (59.1)
Primary indication for intubation, no. (%)†		
Acute respiratory failure	87 (18.3)	645 (34.6)
Altered mental status	221 (46.5)	573 (30.7)
Emergency procedure	31 (6.5)	187 (10.0)
Cardiac arrest	10 (2.1)	28 (1.5)
Other	127 (26.7)	439 (23.6)
APACHE II, median (IQR)‡	16 (11-20)	17 (12-23)
Anticipated difficulty of intubation, no. (%)§		
Easy	78 (23.2)	366 (36.4)
Moderate	170 (50.6)	442 (44.0)
Difficult	27 (8.0)	84 (8.4)
Vasopressors prior to enrollment, no. (%)	52 (10.9)	447 (24.0)
GCS, median (IQR)	8 (5-13)	12 (7-15)
Baseline oxygen saturation, median (IQR)	100 (97-100)	100 (98-100)
Baseline systolic blood pressure, median (IQR)	131 (112-153)	127 (110-147)
Clinical specialty, no. (%)		
Emergency medicine	400 (84.2)	804 (43.1)
Critical care	63 (13.3)	989 (53.1)
Anesthesiology	8 (1.7)	47 (2.5)
Other	8 (1.7)	35 (1.8)
Level of training, no. (%)		
Resident physician	394 (82.9)	840 (45.1)
Fellow physician	47 (9.9)	829 (44.5)
Attending physician	19 (4.0)	77 (4.1)
Other clinician‖	15 (3.2)	108 (5.8)
Operator's prior intubations, median (IQR)	50 (30-85)	50 (25-100)
Intubation procedure		
Preoxygenation received, no. (%)	475 (100)	1,860 (99.8)
Sedative medication used for induction, no. (%)		
Etomidate	401 (84.4)	1,502 (80.6)
Ketamine	57 (12.0)	276 (14.8)
Propofol	33 (6.9)	85 (4.6)
None	1 (<1)	4 (<1)
≥1 Difficult airway characteristics, no. (%)	238 (50.1)	811 (43.5)

Table 1. Continued.

Variable	Succinylcholine (N=475)	Rocuronium (N=1864)
Device used on first laryngoscope insertion, no. (%)		
Bougie	196 (41.3)	588 (31.6)
Endotracheal tube with a stylet	261 (54.9)	1,197 (64.2)
Neither[¶]	18 (3.8)	78 (4.2)

APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; GCS, Glasgow Coma Score; IQR, interquartile range.
*Race and ethnic group were reported by patients or their surrogates as part of clinical care and obtained from the electronic health record and grouped into fixed categories.
†Data on primary indication for intubation were abstracted from the electronic health record.
‡Scores on the APACHE II range from 0 to 71; higher scores indicate greater severity of illness.
§Anticipated difficulty of intubation was recorded by the operator as a subjective assessment before randomization.
‖Other clinician comprises certified registered nurse anesthetists, nurse practitioners, physician assistants, or other listed training levels.
¶Cases in which neither a stylet nor a bougie was used on the first laryngoscopy attempt are cases in which the laryngoscope blade was removed from the mouth without any attempt to intubate the trachea.

both the DEVICE and PREOXI trials. Patients who did not receive a neuromuscular blocking agent (n=96) or received both succinylcholine and rocuronium (n=5) were excluded (Figure 1). Of the 2,339 patients in the analysis, 1,065 (45.5%) were from the DEVICE trial, 998 (42.7%) were from the PREOXI trial, and 276 (11.8%) were enrolled in both the DEVICE and the PREOXI trial. Patients' median age was 58 years, 49.6% were intubated in the ED, and the most common indications for intubation were altered mental status (33.9%) and acute respiratory failure (31.3%). The baseline characteristics of the 475 patients (20.3%) who received succinylcholine and the 1,864 patients (79.6%) who received rocuronium are displayed in Table 1.

Main Results

In the primary analysis, successful intubation on the first attempt occurred in 375 patients (78.9%) in the succinylcholine group and 1,510 patients (81.0%) in the rocuronium group [adjusted odds ratio (OR), 0.87; 95% CI 0.65 to 1.15] [Figure 2 and Table E1 (available at http://www.annemergmed.com)]. Severe complications occurred in 67 patients (14.1%) in the succinylcholine group and 456 patients (24.5%) in the rocuronium group, a difference that was not significant (adjusted OR, 0.88; 95% CI 0.62 to 1.26) (Table 2). Cardiac arrest during intubation occurred in no patients who received succinylcholine and 13 patients (0.7%) who received rocuronium. The sensitivity analysis of the primary outcome including propensity score adjustment resulted in an adjusted OR of 0.88 (95% CI 0.65 to 1.19). The sensitivity analysis of the primary outcome with the addition of the variables for randomized trial group assignment (laryngoscope and preoxygenation strategy) resulted in an adjusted OR of 0.83 (95% CI 0.62 to 1.12).

Limitations

Because selection of neuromuscular blocking agents was not randomized, differences in practice patterns and confounding based on indication may bias the associations between the neuromuscular blocking agent received and outcomes. We used multivariable adjustment and a propensity score approach to mitigate confounding, but residual confounding remains possible. Specifically, we were unable to account for information on hyperkalemia, acute or chronic kidney disease, neuromuscular disorders, prolonged immobility, and other potential factors that may have influenced a patient's propensity to receive succinylcholine versus rocuronium because information on these variables was not collected in the data sets for the original trials. Because of its longer half-life, prior studies have suggested that rocuronium may be associated with a greater risk of awareness with paralysis than succinylcholine.[15] Data on awareness about paralysis were not available in this study. Future studies investigating outcomes after receipt of neuromuscular blocking agents should consider incorporating awareness about paralysis. Finally, the parent trials were not designed or powered to detect differences in outcomes based on the choice of neuromuscular blocking agents. Therefore, this secondary analysis with a fixed sample size may be underpowered to detect clinically important differences.

DISCUSSION

Previous research comparing succinylcholine and rocuronium during tracheal intubation has been primarily conducted in out-of-hospital or operating room settings.[6,7]

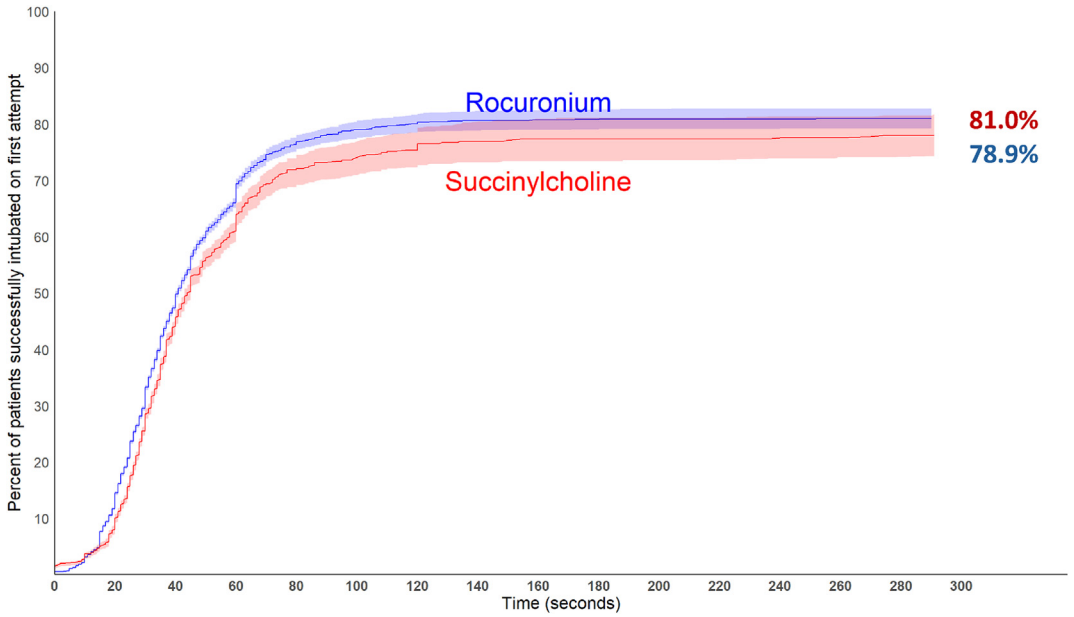

Figure 2. Cumulative incidence of successful intubation on the first attempt. Shown is the unadjusted cumulative incidence and 95% confidence intervals (shaded areas) for successful intubation on the first attempt among patients who received succinylcholine (blue) and patients who received rocuronium (red) relative to the time since the initial insertion of a laryngoscope blade into the mouth. Successful intubation on the first attempt occurred in 375 of 475 patients (78.9%) in the succinylcholine group and 1,509 of 1,864 patients (81.0%) in the rocuronium group.

A randomized trial that compared succinylcholine versus rocuronium among 1,248 patients in the out-of-hospital setting found a higher incidence of successful intubation on the first attempt with succinylcholine (79.4%) compared with rocuronium (74.6%).[7] Severe complications were observed more frequently in the succinylcholine group (23.2% versus 18.2%), which may have been attributable to the increased receipt of sedation and analgesia. However, the incidences of cardiac arrest and death were numerically higher in the rocuronium group. Our study observed a numerically higher incidence of severe complications in the rocuronium group (24.5% versus 14.1%) that was not significant after adjusting for covariates, suggesting that rocuronium may have been preferentially used in sicker patients. The differences between our findings and those of previous trials may be explained by differences in study design, patient population, operator population, or outcome definitions.

Our study combined with prior literature highlights that, for critically ill adults undergoing tracheal intubation in current clinical care, succinylcholine and rocuronium are commonly used medications, each agent has potential risks

Table 2. Adjusted outcomes of tracheal intubation.

Outcome	Succinylcholine No. (%)	Rocuronium No. (%)	Absolute Difference (%)	aOR	95% CI
Primary outcome: successful intubation on the first attempt	375 (78.9)	1,510 (81.0)	−2.1	0.87	0.65-1.15
Secondary outcome: severe complication during intubation	67 (14.1)	456 (24.5)	−10.4	0.88	0.62-1.26
Peripheral oxygen saturation <80%	45 (9.8)	172 (9.6)	0.2	1.13	0.72-1.76
Systolic blood pressure < 65 mmHg	5 (1.1)	71 (4.0)	−2.9	0.42	0.14-1.23
New or increased use of vasopressors	24 (5.1)	303 (16.3)	−11.2	0.62	0.37-1.04
Cardiac arrest	0 (0.0)	13 (0.7)	−0.7	–	–

aOR, adjusted odds ratio.
Displayed are the absolute incidence, unadjusted absolute risk difference, aOR, and 95% CI for the difference between groups in the primary outcome, secondary outcome, and the components of the primary outcome. Adjusted ORs were calculated using a generalized linear mixed-effects model adjusting for prespecified baseline confounders. An aOR could not be calculated for cardiac arrest owing to the limited number of events.

and benefits, and no strong data are available to inform the choice between the 2 agents for intubation in the ED or ICU. To inform optimal care for critically ill adults undergoing intubation in an ED or ICU, a multicenter randomized clinical trial comparing succinylcholine versus rocuronium with regard to successful intubation on the first attempt and severe complications is needed.

In conclusion, in an analysis of 2,339 critically ill adults undergoing emergency tracheal intubation, receipt of succinylcholine versus rocuronium was not associated with differences in successful intubation on the first attempt or severe complications.

Supervising editor: Nicholas M. Mohr, MD, MS. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

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Author contributions: SCD, WHS, JDC, and MWS conceived and helped design the study. SCD drafted the manuscript. All authors critically revised the manuscript for important intellectual content. LW helped with statistical analysis. SCD helped with final approval and held accountability for integrity. SCD takes responsibility for the paper as a whole.

Data sharing statement: The entire deidentified data set for the PREOXI and DEVICE trials are available on request from the date of each respective article publication by contacting Matthew Semler at matthew.w.semler@vumc.org.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: This work was supported in part by grants from the National Institutes of Health (NIH) and the Department of Defense; MWS was supported in part by grants from the NIH/National Center for Advancing Translational Sciences (5UL1TR002243). JDC was supported in part by NIH (K23HL153584). SCD was supported in part by NIH (5T32GM108554). KPS was supported in part by NIH (5T32HL087738). TWR was supported in part by NIH/National Center for Advancing Translational Sciences (UL1TR002243) and NIH/National Heart, Lung, and Blood Institute (UO1 HL123033). NRA was supported in part by grants from NIH and the Department of Defense. AWM is supported by NIH (1K23GM150110) and the American College of Surgeons (C. James Carrico, MD, FACS; Faculty Research Fellowship for the Study of Trauma and Critical Care). DWR was supported in part by NIH/National Heart, Lung, and Blood Institute (1K08HL148514). The Direct versus Video Laryngoscope and the Pragmatic Trial Examining Oxygenation Prior to Intubation trials were supported by

the United States Department of Defense through Defense Health Agency Restoral Funding in collaboration with the 59th Medical Wing (59MDW) of the United States Air Force. The views expressed are those of the authors and do not reflect the official views or policy of the Department of Defense or its components.

SGS has received funding from the Department of Defense in the form of grants to his institution. CGH has received consulting fees for trial steering committee participation from Sedana Medical. AAG receives funding from Seastar and Biomeme unrelated to the present work. ETQ received a teaching fee for teaching bronchoscopy in the ICU for Karl Storz Endoscopy. SHM received travel-related funding support for a research trial from SharpMed.

Publication dates: Received for publication June 6, 2024. Revision received August 15, 2024. Accepted for publication August 23, 2024.

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