Society of Critical Care Medicine Clinical Practice Guidelines for Rapid Sequence Intubation in the Critically Ill Adult Patient

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RATIONALE: Controversies and practice variations exist related to the pharmacologic and nonpharmacologic management of the airway during rapid sequence intubation (RSI).

OBJECTIVES: To develop evidence-based recommendations on pharmacologic and nonpharmacologic topics related to RSI.

DESIGN: A guideline panel of 20 Society of Critical Care Medicine members with experience with RSI and emergency airway management met virtually at least monthly from the panel's inception in 2018 through 2020 and face-to-face at the 2020 Critical Care Congress. The guideline panel included pharmacists, physicians, a nurse practitioner, and a respiratory therapist with experience in emergency medicine, critical care medicine, anesthesiology, and prehospital medicine; consultation with a methodologist and librarian was available. A formal conflict of interest policy was followed and enforced throughout the guidelines-development process.

METHODS: Panelists created Population, Intervention, Comparison, and Outcome (PICO) questions and voted to select the most clinically relevant questions for inclusion in the guideline. Each question was assigned to a pair of panelists, who refined the PICO wording and reviewed the best available evidence using predetermined search terms. The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework was used throughout and recommendations of "strong" or "conditional" were made for each PICO question based on quality of evidence and panel consensus. Recommendations were provided when evidence was actionable; suggestions, when evidence was equivocal; and best practice statements, when the benefits of the intervention outweighed the risks, but direct evidence to support the intervention did not exist.

RESULTS: From the original 35 proposed PICO questions, 10 were selected. The RSI guideline panel issued one recommendation (strong, low-quality evidence), seven suggestions (all conditional recommendations with moderate-, low-, or very low-quality evidence), and two best practice statements. The panel made two suggestions for a single PICO question and did not make any suggestions for one PICO question due to lack of evidence.

CONCLUSIONS: Using GRADE principles, the interdisciplinary panel found substantial agreement with respect to the evidence supporting recommendations for RSI. The panel also identified literature gaps that might be addressed by future research.

KEY WORDS: etomidate; hypnotics and sedatives; intubation, intratracheal; ketamine; neuromuscular-blocking agents; propofol; rapid sequence induction and intubation; rocuronium; succinylcholine

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full disclaimer for guidelines can be accessed at https://sccm.org/Clinical-Resources/Guidelines/Guidelines. Controversies and practice variations exist related to pharmacologic and nonpharmacologic emergency airway management during rapid sequence intubation (RSI) (1, 2). Therefore, the American College of Critical Care Medicine (ACCM)'s Board of Regents established a guideline panel to review this topic and provide current, systematically developed, recommendations to guide clinical practice.

Emergency airway management is complex and involves decision-making around devices chosen for laryngoscopy, medications used to facilitate intubation, and management after intubation. A common strategy for emergency airway management is RSI, which is defined as the administration of a sedative-hypnotic agent and a neuromuscular-blocking agent (NMBA) in rapid succession and with immediate placement of an endotracheal tube before assisted ventilation (3, 4). RSI is indicated to: 1) reduce the risk of aspiration in at-risk patients (e.g., those with a full stomach, ileus or bowel obstruction, gastroesophageal reflux disease, and increased intra-abdominal pressure) and 2) optimize intubating conditions to reduce the occurrence rate of difficult or failed airways, esophageal tube placement, and complications.

For the purposes of these guidelines, we considered aspects directly related to RSI as pertinent, such as those that occur in the preoxygenation period before RSI and medication selection during RSI. For example, mask ventilation has historically been avoided with RSI to reduce the risk of regurgitation and aspiration of gastric contents, but mask ventilation may reduce the risk of critical hypoxemia. Common themes with conflicting opinions are 1) whether an induction agent should be used and 2) whether an NMBA should be used for emergency airway management in all critically ill patients. We addressed this with two questions involving use of only one pharmacologic agent (either a sedative-hypnotic agent or an NMBA) even though such a recommendation would deviate from the definition of RSI.

Awake intubations, difficult airway management, postintubation sedation, and ventilator management are outside the scope of work for these guidelines. All pharmacologic agents discussed in the guideline are administered via the IV route.

METHODS

Methods related to development of these guidelines can be accessed in **Supplemental Digital Content** (http://links.lww.com/CCM/H378).

TARGET PATIENT POPULATION FOR GUIDELINES

These guidelines are intended for clinicians who treat critically ill adult patients in the emergency department (ED), ICU, or other locations outside the operating room (OR) and who require emergency airway management with endotracheal intubation using RSI.

RESULTS

This clinical practice guideline provides guidance with rationales for one recommendation, seven suggestions, and two best practice statements developed from 10 Population, Intervention, Comparison, and Outcome (PICO) questions (**Table 1**). In one instance, a single PICO produced two suggestions, and, in another, the panel did not find sufficient evidence to answer one PICO question. "Recommendations" were developed when evidence was actionable; "suggestions," when evidence was equivocal; and "best practice statements," when the benefits of the intervention outweighed the risks, but direct evidence to support the intervention did not exist. Evidence summaries with citations of the sources that were evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology, evidence gaps, and future research directions are detailed in each section (5, 6). Evidence profiles and summary of judgments are available in Supplemental Digital Content (http://links.lww.com/CCM/H378).

Positioning

Question 1: In critically ill adults undergoing RSI, is there a difference between the semi-Fowler (head and trunk inclined) position during intubation versus the supine position with respect to first-pass intubation success (FPS) or the incidence of oxygen desaturation or pulmonary aspiration?

Recommendation:

- We suggest use of the head and torso inclined (semi-Fowler) position during RSI (conditional recommendation, very low quality of evidence).

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TABLE 1.
Complete Recommendations and Suggestions for Clinical Practice Guidelines for Rapid Sequence Intubation in the Critically Ill Adult Patient

	Recommendation or Suggestion	Strength of Recommendation	Quality of Evidence
1.Positioning	We suggest use of the head and torso inclined (semi-Fowler) position during RSI	Conditional	Very low
2.Preoxygenation	We suggest preoxygenation with HFNO when laryngoscopy is expected to be challenging We suggest preoxygenation with NIPPV in patients with severe hypoxemia $Pa_{O_2}/F_{IO_2} < 150$	Conditional	Low
3.Medication-assisted preoxygenation	We suggest using medication-assisted preoxygenation to improve preoxygenation in patients undergoing RSI who are not able to tolerate a face mask, NIPPV, or HFNO because of agitation, delirium, or combative behavior	Conditional	Very low
4.Nasogastric tube decompression	We advise nasogastric tube decompression when the benefit outweighs the risk in patients who are undergoing RSI and are at high risk of regurgitation of gastric contents	Best practice statement	Ungraded
5.Peri-intubation vasopressors	There is insufficient evidence to make a recommendation that there is a difference in the incidence of further hypotension or cardiac arrest between the administration of peri-intubation vasopressors or IV fluids for hypotensive critically ill patients undergoing RSI	Insufficient evidence	Not applicable
6.Induction agent use	We advise administering a sedative-hypnotic induction agent when an NMBA is used for intubation	Best practice statement	Ungraded
7.Induction agent selection	We suggest there is no difference between etomidate and other induction agents administered for RSI with respect to mortality or the incidence of hypotension or vasopressor use in the peri-intubation period and through hospital discharge	Conditional	Moderate
8.Etomidate and corticosteroid use	We suggest against administering corticosteroids following RSI with etomidate for the purpose of counteracting etomidate-induced adrenal suppression	Conditional	Low
9.NMBA use	We recommend administering an NMBA when a sedative-hypnotic induction agent is used for intubation	Strong	Low
10.NMBA selection	We suggest administering either rocuronium or succinylcholine for RSI when there are no known contraindications to succinylcholine	Conditional	Low

HFNO = high-flow nasal oxygen, NIPPV = noninvasive positive pressure ventilation, NMBA = neuromuscular-blocking agent, RSI = rapid sequence intubation.

Rationale: RSI has traditionally been performed with the patient in neck flexion and head extension ("sniffing position") or neutral head and neck position (if concern for cervical spine injury) together with the torso parallel with the head and neck. However, authors of recently conducted studies have suggested that a head and trunk inclined (semi-Fowler) position may improve FPS through enhanced preoxygenation (denitrogenation) via increased functional residual capacity (FRC) and improved laryngeal view, and reduce the risk of clinically significant aspiration of passively regurgitated gastric contents. Seventeen studies were included that addressed this question (7–23).

Four observational studies, one randomized controlled trial (RCT), and a meta-analysis reported FPS rates (7–12). Three of the four observational studies indicated a benefit from the semi-Fowler position on FPS (7–9), whereas the fourth found no difference compared with supine positioning (10). There was substantial heterogeneity in the definition of semi-Fowler

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position, intubator experience, laryngoscopy technique, and patient subgroup exclusion among these observational studies. The single RCT showed that the semi-Fowler position, compared with the supine sniffing position decreased the FPS rate (76.2% vs 85.4%, $p = 0.02$), increased the incidence of Cormack-Lehane grade 3 or 4 laryngoscopic view (25.4% vs 11.5%, $p = 0.01$), and increased the rate of difficult intubation (laryngoscopy attempts ≥ 3; 12.3% vs 4.6%, $p = 0.04$) (12). Limitations of the RCT include unprotocolized and variable incline degree with the semi-Fowler position, intubations performed by trainees, and the confounding use of direct laryngoscopy in 75% of first-pass attempts. The pooled risk ratio in the meta-analysis (three studies, $n = 513$) for semi-Fowler versus the supine sniffing position was 0.97 (95% CI, 0.86–1.09; $I^2 = 55\%$) but failed to demonstrate that the semi-Fowler position was more favorable compared with supine positioning (12).

Two observational studies (7, 10) and one RCT (11) reported oxygen desaturation and pulmonary aspiration rates. The semi-Fowler position reduced oxygen saturation in the observational studies, and in one study reduced aspiration compared with the supine position (10). The RCT did not find a difference between groups for either oxygen desaturation or aspiration. Differences in the definition of semi-Fowler position, intubator experience, laryngoscopy type, and patient subgroup exclusion contributed to substantial heterogeneity among studies.

Evidence from a cadaveric study (13), simulation trials (14, 15), and surgical patients in the OR (16–23) suggest that the semi-Fowler position is beneficial for improving several intubation-related outcomes, including laryngoscopic view (16–20), time-to-intubation (14, 15), intubation success (20), and time-to-oxygen desaturation (defined as 92% and 95%, respectively, in these studies) (21, 22). In addition, studies in noncritically ill patients showed a benefit with the semi-Fowler position in patients at risk for experiencing difficult intubation (20), including those with morbid obesity (17, 18, 22), and patients at increased risk for aspiration (23). However, none of these studies specifically examined the semi-Fowler position in critically ill patients with these conditions.

The panel determined that head and torso inclined, semi-Fowler position was feasible in most critically ill patients undergoing RSI. Special caveats include patients requiring spine immobilization, a situation in which repositioning for airway management remains unstudied. There is no cost associated with using the semi-Fowler position, and resources for implementation are likely available in most critical care venues. Lastly, semi-Fowler positioning does not preclude incorporation of other optimization techniques and maneuvers, such as the sniffing position.

Evidence Gaps: Future studies should further explore the effectiveness of the semi-Fowler position on meaningful intubation-related outcomes in critically ill patients, including laryngoscopy view, FPS rate, and the incidence of oxygen desaturation and pulmonary aspiration. Further evaluation to ascertain optimal patient prepositioning and the benefits and risks of the semi-Fowler position in select subgroups of critically ill patients (e.g., patients with morbid obesity, hypoxemic respiratory failure, increased aspiration risk; those who are pregnant or require spine immobilization; and patients who have features associated with difficult intubation) is a reasonable next step. To avoid the effects of confounding, future studies of the semi-Fowler position should standardize critical variables, including the angle of semi-Fowler positioning, intubator experience, laryngoscopy technique, and bougie and tracheal tube stylet configuration. Such studies should avoid the risk of bias by using control groups, allocation concealment, and blinding, if possible.

Preoxygenation

Question 2: In critically ill adults undergoing planned RSI, is there a difference preoxygenating with high-flow nasal oxygen (HFNO) (with or without apneic oxygenation) versus using face-mask preoxygenation, bag-mask ventilation, or noninvasive positive pressure ventilation (NIPPV) with respect to occurrence of desaturation, gastric insufflation, or pulmonary aspiration risk?

Recommendation:

- We suggest preoxygenation with HFNO when laryngoscopy is expected to be challenging (conditional recommendation, low quality of evidence).
- We suggest preoxygenation with NIPPV in patients with severe hypoxemia Pao_2/Fio_2 of less than 150 (conditional recommendation, low quality of evidence).

Rationale: Critically ill patients are at high risk of experiencing desaturation, particularly during

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prolonged intubations; thus, preoxygenation is required to prolong the duration of apnea without desaturation (i.e., safe apnea time). Advanced methods of preoxygenation before RSI are often required in patients with acute hypoxemic respiratory failure because they often have reduced FRC and increased ventilation:perfusion mismatch that reduces the efficacy of preoxygenation. HFNO provides heated and humidified oxygen at high-flow rates when using a high-flow nasal cannula system (e.g., Vapotherm, Optiflow) at 100% oxygen. HFNO is often proposed as an option for preoxygenation in critically ill patients because of the physiologic benefits that mimic NIPPV (e.g., end-expiratory lung volume expansion) and because a continuous flow of oxygen can be maintained to provide apneic oxygenation during laryngoscopy. However, concerns exist that continuous oxygen flow of 40–60 L throughout the respiratory cycle may lead to gastric insufflation, which may increase the risk of regurgitation and aspiration. Thirteen studies were included to address this question (24–36).

Eight studies reported oxygen desaturations of less than 80% (24–31). One prospective before-and-after study reported a 14% incidence of desaturation in the face-mask group and 2% in the HFNO group, with HFNO as an independent predictor of preventing desaturation of less than 80% (adjusted odds ratio: 0.17; 95% CI, 0.01–0.90; $p = 0.04$) in a multivariable regression model (24). Another multicenter RCT of patients with more severe underlying hypoxemia (Pao_2/Fio_2 ratio < 150) reported a 25.8% incidence of desaturation for HFNO and 22.3% for face-mask oxygenation (25). A retrospective analysis of prospectively collected data reported a 23% incidence of desaturation for HFNO, compared with 2.5% for NIPPV; however, none of the patients who received HFNO desaturated to less than 70%, compared with 13% of the patients who received NIPPV (26). One recent trial demonstrated desaturation rates of 27% with HFNO and 23% with NIPPV; among patients with a Pao_2/Fio_2 ratio of less than 200, desaturation rates were 35% with HFNO and 24% with NIPPV (27). Another trial demonstrated desaturation rates of 2% with HFNO and 8% with HFNO and face mask (28).

Nine studies evaluated desaturation as an outcome, but most evaluated the lowest oxygen saturation (24, 27–29, 32–36). Several studies reported no desaturations of less than 90% (32–34), whereas some studies showed no difference in lowest saturation (29, 35). One study showed no difference in the lowest saturation: 12% desaturated to less than 93% in the face-mask group, whereas, all patients in the HFNO group maintained an oxygen saturation of greater than 93% (35). Two case series reported apnea times (34, 36). Two studies reported reduced desaturation rates with HFNO (24, 28), whereas, a retrospective review of data from a clinical trial showed increased desaturation rates with HFNO (27). Desaturation appeared to be prevented, or at least attenuated, when HFNO was used, as compared with alternatives. In general, the saturation cutoffs were arbitrary numbers. What appears important is that HFNO seemed to reduce the occurrence rate of desaturation, prolonged safe apnea times, and overall limited the degree of desaturation compared with studies of preoxygenation with a face mask, but not necessarily when compared with studies in which NIPPV was used.

Seven studies reported gastric insufflation or aspiration, either directly or when included as a "moderate complication" (24, 25, 27, 28, 30, 33, 35). In general, based on very low-quality evidence, it appears as though HFNO does not affect aspiration risk.

Eight studies reported rates of cardiac arrest (or severe cardiovascular collapse) or severe complications, including cardiac arrest (24, 25, 27, 28, 30, 31, 33, 34). In general, all are very low quality of evidence; therefore, no conclusions could be drawn.

Overall, in patients with severe hypoxemia, NIPPV appears to have the strongest evidence for decreasing the incidence of critical desaturation during RSI. However, HFNO provides the added benefit of continued oxygen flow into the nasopharynx during laryngoscopy. With the recent increased use of HFNO in patients with severe acute respiratory syndrome coronavirus 2 infections, many healthcare providers have gained experience with, and hospitals have purchased, HFNO equipment. However, in some places, providing HFNO may require new equipment and resources but is no less resource-intensive than the best alternative, NIPPV. Many rural hospitals and essentially all prehospital and interfacility transport services cannot provide HFNO due to oxygen-capacity limitations. We considered HFNO to be feasible in all other settings.

Evidence Gaps:. Definitive research is not feasible to determine the optimal method of preoxygenation in patients with difficult airways, prolonged laryngoscopy,

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or severe acute hypoxemic respiratory failure. In some cases, such as evaluating HFNO in patients with difficult or prolonged intubations, a randomized trial with the outcome of duration until desaturation occurred would be unethical in this population. However, evidence is needed on how to optimize each preoxygenation option to stratify patients based on their risk of desaturation. None of the published studies directly evaluated FPS rate as an outcome, and there was significant heterogeneity in how success was reported. Studies with the outcome of desaturation had higher-quality data. However, there was substantial heterogeneity in the patient population that was included in the studies and in the severity of hypoxemia, making a global assessment difficult. The strongest evidence suggests that, in patients with the most severe hypoxemia that needs to be escalated to a noninvasive support modality for preoxygenation, NIPPV appears to decrease the incidence of critical desaturation during RSI.

Medication-Assisted Preoxygenation

Question 3: In critically ill adults in whom RSI is planned but are agitated, delirious, or uncooperative, is there a difference between medication-assisted preoxygenation versus usual care with face-mask preoxygenation, assisted mask ventilation, NIPPV, or HFNO with respect to the incidence of desaturation or hemodynamic instability?

Recommendation:

- We suggest using medication-assisted preoxygenation to improve preoxygenation in patients undergoing RSI who are not able to tolerate a face mask, NIPPV, or HFNO because of agitation, delirium, or combative behavior (conditional recommendation, very low quality of evidence).

Rationale: Preoxygenation is one of the critical steps in airway management to improve the safety of RSI. To appropriately preoxygenate patients, the FRC must be denitrogenated, which requires a high concentration of oxygen delivered commonly via a tight-fitting face mask, face mask with "flush-rate" oxygen, or HFNO system. These methods of preoxygenation generally demand a compliant patient who can tolerate the oxygen delivery device. Preoxygenation, therefore, may be challenging in delirious, agitated, or uncooperative patients. Thus, the clinician must decide whether or not to use sedative-hypnotic medications to facilitate preoxygenation. Medication-assisted preoxygenation, sometimes referred to as delayed sequence intubation, is the latter process, which modifies RSI so that the sedative-hypnotic agent and NMBA are not administered in rapid succession, but a sedative-hypnotic agent is administered to facilitate preoxygenation and once the clinician is satisfied that the patient is adequately preoxygenated, then the NMBA is administered followed by intubation. Data are sparse comparing medication-assisted preoxygenation with other available methods, especially in patients who are hypoxemic.

Two observational studies evaluating the change in oxygen saturation before and after the administration of a sedative-hypnotic medication were identified to address this question (37, 38). The first was a multicenter observational study conducted in the ED that reported a mean oxygenation saturation increase of 8.9% (95% CI, 6.4–10.9%) after ketamine infusion (initial dose 1 mg/kg with 0.5 mg/kg doses until a dissociative state was achieved; mean total dose 1.4 mg/kg) and therefore a higher oxygen saturation level at the time of NMBA administration (98.9% compared with 89.9%) (37). The second was a retrospective observational study in a helicopter-based emergency medical service unit that reported intubation-related outcomes (85% FPS rate, 5% desaturation rate, 5% hypotension rate) with ketamine 1.5 mg/kg (3 min before NMBA administration), but there was no comparison group (38).

Although the overall body of literature is of very low quality, medication-assisted preoxygenation may be useful in a select group of high-risk patients who cannot tolerate a face mask, NIPPV, or HFNO. There is insufficient evidence to suggest using medication-assisted preoxygenation for any other critically ill patient population. Medication-assisted preoxygenation can be implemented using currently available equipment.

Evidence Gaps: Research is needed to fully elucidate the optimal role of medication-assisted preoxygenation for critically ill patients, the ideal medication for this indication, and the most efficacious and safe medication doses. Specifically, the scope of the problem involving agitated, delirious, or uncooperative patients that do not tolerate preoxygenation should be evaluated and procedurally related outcomes, such as FPS, desaturation, aspiration, hemodynamic instability, and cardiac arrest rates, assessed. Additionally, although ketamine was used for medication-assisted preoxygenation at induction doses in the two studies identified,

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other pharmacologic agents or combinations of pharmacologic agents (e.g., dexmedetomidine, fentanyl, remifentanil) may warrant investigation. Within these investigations, considerations of adequate induction with the use of an NMBA to prevent awareness with paralysis must be acknowledged.

Nasogastric Tube Decompression

Question 4: In critically ill adults who are undergoing RSI and are at high risk of aspirating, is there a difference between nasogastric tube (NGT) gastric decompression before intubation versus standard of care (without NGT intervention) with respect to the incidence of vomiting/aspiration?

Best practice statement:

- We advise NGT decompression when the benefit outweighs the risk in patients who are undergoing RSI and are at high risk of regurgitation of gastric contents.

Rationale: Gastric decompression with an NGT before RSI was an important component in the description of RSI by Stept and Safar (39) and has been used by others to reduce the risk of aspiration during RSI, although variation in practice exists (3, 40–42). However, the benefit of gastric decompression before RSI has not been evaluated in high-quality clinical trials. When the stomach is decompressed with an NGT, the intragastric pressure and the gastric content volume may be decreased, hence, lowering the likelihood and severity of emesis and pulmonary aspiration during RSI (43). In patients with a full stomach or gastric distention, a clinical assessment, in addition to point-of-care ultrasound, can help to determine the need for and effectiveness of NGT (44–46). The literature suggests an increased risk of regurgitation when point-of-care ultrasound demonstrates the presence of solid gastric contents, an estimated total gastric fluid volume greater than 1.5 mL/kg (with the patient in the right lateral decubitus position), or the presence of clear fluids (with the patient in both supine and lateral decubitus positions) (46). Complications of NGT insertion, including nasal bleeding, gagging and vomiting, esophageal perforation, and tracheal placement can occur and should be factored into the decision-making process (47).

In patients at high risk of regurgitation (i.e., full stomach or intestinal obstruction) during RSI, and when risks are not prohibitive, insertion of an NGT and decompression of the stomach before RSI should be considered. Because the use of an NGT does not guarantee removal of all gastric contents, RSI should proceed with the assumption that the stomach will not be completely empty. Resources required for gastric decompression are readily available in most critical care settings, and the costs are negligible and should not affect implementation.

Evidence Gaps: Further evaluation is warranted to clarify the risks and benefits of gastric decompression in general and in select subgroups of critically ill patients (e.g., those with morbid obesity, who are pregnant, in whom difficult intubation is anticipated, who have coagulopathy).

Peri-intubation Vasopressors

Question 5: In critically ill hypotensive adults undergoing RSI, is there a difference when peri-intubation vasopressors are administered, by infusion or bolus dose, versus fluid resuscitation alone with respect to the incidence of hypotension and cardiac arrest?

Recommendation:

- There is insufficient evidence to make a recommendation that there is a difference in the incidence of further hypotension or cardiac arrest between the administration of peri-intubation vasopressors or IV fluids for hypotensive critically ill patients undergoing RSI (insufficient evidence).

Rationale: Peri-intubation hypotension is associated with ICU mortality (2). Preventing and managing hypotension in this setting has received significant attention, but the best evidence-based intervention has yet to be defined. Four studies were included for evaluation to address this question (48–51). It should be noted that there were no studies identified that directly evaluated vasopressors compared with fluid administration in hypotensive, critically ill adult patients, undergoing RSI.

One prospective trial (48), and two retrospective studies (49, 50) reported blood pressure changes with vasopressor use in the peri-intubation period (given preintubation, intraintubation, or postintubation). These studies were in the ED and ICU settings and used bolus doses of phenylephrine 50–200 μg or ephedrine 5–25 mg (48, 49) or continuous infusions of norepinephrine, epinephrine, vasopressin, dopamine, or phenylephrine as part of an eight-component

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intubation bundle (50). Two studies noted improvement in blood pressure after vasopressor bolus administration (48, 49). A retrospective review of data from 20 patients who were administered bolus doses of phenylephrine in the peri-intubation period in the ED report increased systolic blood pressure (SBP) and diastolic blood pressure (DBP) without a significant increase in heart rate (HR) (48). A retrospective study of 146 patients who received bolus-dose phenylephrine or ephedrine found a 32.5% increase in SBP and 27.2% increase in DBP following bolus administration (49). However, only 59.6% of patients in this study received a vasopressor bolus specifically for peri-intubation hypotension and the remaining administrations were for transient hypotension outside of the RSI setting. A total of 27.9% of patients received concurrent fluid-bolus administration in addition to bolus vasopressors, thus confounding the results. One study evaluated vasopressor use as part of a peri-intubation bundle, resulting in a 12.6% reduction in peri-intubation complications (50); however, this study did not assess vasopressor use in isolation or specifically measure the effect on hypotension or cardiac arrest.

Two studies evaluated the occurrence rate of cardiac arrest; one was the before-and-after trial of an intubation bundle that included vasopressors and fluids and the other was an RCT of a 500 mL crystalloid bolus versus no bolus (50, 51). Neither study identified a difference in cardiac arrest rate; 6.5% (n = 9/138) in the bundle group versus 5.1% (n = 7/137) in the no bundle group and 4.2% (n = 7/168) in the crystalloid bolus group versus 1.2% (n = 2/169) in the no crystalloid bolus group (50, 51).

The recently published PREPARE II trial warrants mention although it was published outside of the date range for inclusion and does not strictly meet criteria as patients were not hypotensive (52). This randomized, controlled, multicenter trial of critically ill patients undergoing RSI (n = 1,067) showed that a crystalloid fluid bolus alone failed to prevent cardiovascular collapse (defined as a combined endpoint of hypotension requiring vasopressors, cardiac arrest, or death) when compared with no fluid bolus. There was no comparison with vasopressor use and again, the study was not conducted in a hypotensive population. One additional trial, INTUBE, also published outside of the date range for inclusion also warrants mention (53). This was a multicenter, prospective cohort study of critically ill patients (n = 2,760) undergoing endotracheal intubation, but was not restricted to those with hypotension and therefore does not strictly meet criteria for this question. Nonetheless, this evaluation identified that vasopressors (OR 1.33; 95% CI, 0.84–2.11) or fluid boluses (OR 1.17; 95% CI, 0.96–1.44) administered before induction did not reduce the occurrence rate of cardiovascular instability/collapse (defined as one of the following events occurring within 30 min from the start of the intubation procedure: systolic arterial pressure < 65 mm Hg once, systolic arterial pressure < 90 mm Hg for > 30 min, new requirement for, or increase of vasopressors, fluid bolus > 15 mL/kg, or cardiac arrest).

Although the literature reviewed demonstrated that vasopressors may increase mean arterial pressure (MAP), some of these studies were not representative of a critically ill, hypotensive population and no studies that solely investigated the use of vasopressors concluded that they had a clinically significant hemodynamic impact, resulted in improved outcomes, or decreased the incidence of cardiac arrest associated with RSI. Furthermore, administration of vasopressors to mitigate the hypotensive effects of RSI medications may be unnecessary in the setting of a reactive sympathetic response to airway instrumentation (54). Because a definitive relationship between the use of vasopressors and improved patient outcomes has not been demonstrated in the peri-intubation period, we cannot be certain that the desirable effects outweigh the undesirable ones. Also, we were unable to identify any studies that evaluated vasopressors compared with fluid administration to ascertain the effect on outcomes.

Regardless, bolus-dose vasopressors are being increasingly used in this setting, but are associated with a high rate of medication errors (commonly incorrect dose or inappropriate use [e.g., use during continuous infusion vasopressor administration or during a normotensive state]) and adverse effects, mostly related to excessive increases in SBP and HR (49). Techniques to promote stable induction should also be optimized (i.e., appropriate resuscitation before RSI, if possible, and consideration of an induction agent with less risk of hypotension) (54). If bolus dose vasopressors are used, they should be reserved for use by clinicians who are familiar with the medications and doses that are used and ideally in collaboration with clinical pharmacists

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to reduce the risk of medication errors (49, 55, 56). Furthermore, medication best practice standards indicate that bolus-dose vasopressors be brought to the bedside in commercially prepared, prefilled syringes to reduce the risk of concentration errors and medication contamination (57).

Evidence Gaps: Future studies are needed to directly compare the use of vasopressors (bolus dose or continuous infusion) to IV fluid boluses to assess the effects on worsening hypotension or cardiac arrest in critically ill, hypotensive patients, undergoing RSI. Additional studies are needed to determine the appropriate vasopressor medication, the optimal peri-intubation dose, and whether bolus doses or continuous infusions are safer and more effective. Further, some populations, such as patients with preexisting right heart failure, pulmonary hypertension, or other physiology bearing special attention, may require different interventions.

Induction Agent Use

Question 6: In critically ill adults with hemodynamic instability and with a depressed level of consciousness who are undergoing endotracheal intubation, is there a difference between administration of a sedative-hypnotic agent with an NMBA versus an NMBA alone with respect to the incidence of cardiovascular collapse or awareness during paralysis in the peri-intubation period?

Best practice statement:

- We advise administering a sedative-hypnotic induction agent when an NMBA is used for intubation.

Rationale: The purpose of using a sedative-hypnotic agent during RSI is to induce unconsciousness before inducing neuromuscular blockade. In minimally conscious, or unconscious, hemodynamically unstable critically ill patients, there is concern that the use of a sedative-hypnotic agent may worsen hypotension or cause cardiac arrest in patients who are hemodynamically unstable. One secondary analysis of a prospective observational study of patients treated in 13 Japanese EDs was included to address this question (58). This study evaluated intubation with only an NMBA (n = 114) versus a sedative-hypnotic agent administered with an NMBA (n = 738). The primary outcome of this study was FPS, but the intubation success within two attempts and adverse events (cardiopulmonary arrest, esophageal intubation, main bronchial intubation, lip or dental trauma, vomiting, airway trauma, arrhythmia, hypotension, hypoxemia, and death) were also reported. There was no difference in the rate of adverse events—11% in patients who received an NMBA only versus 12% who received an induction agent with an NMBA, but the rates of certain individual adverse events, such as cardiopulmonary arrest, were not reported. Also, the specific time period of intubation-related adverse events was only defined as "during or after intubation," making it difficult to interpret causation. Neither patient awareness nor preintubation conditions were evaluated. Also, there was no analysis evaluating hemodynamically unstable patients.

Although no studies are available to evaluate patient awareness in the setting of using an NMBA only for intubation, there have been reports of awareness when an NMBA is used during general anesthesia. Also, a recent, prospective, observational study identified an incidence of awareness of 2.6% (10/383) in patients intubated in the ED (59). In this study, most patients who had awareness of paralysis received a short-acting sedative-hypnotic induction agent and long-acting NMBA. These results make the situation of using an NMBA only without an induction agent even more concerning. No studies have been conducted in critically ill patients with hemodynamic instability or an altered level of consciousness in which an NMBA was administered alone compared with a sedative-hypnotic agent and an NMBA. Insufficient data are available to evaluate whether the incidence of cardiovascular collapse changes or harm resulting from awareness exists when an NMBA is used alone. Given the widespread availability, low cost, and acceptance into clinical practice, there is no reason to deviate from the practice of administering a sedative-hypnotic agent with an NMBA in critically ill patients for RSI.

Evidence Gaps: Because of the concern for cardiovascular collapse in the peri-intubation period during RSI, this is an important clinical question. However, due to the nature of the patient population (critically ill, hemodynamically unstable, altered level of consciousness) and ethical concerns regarding withholding a sedative-hypnotic agent when an NMBA is administered for intubation, it is likely that only retrospective studies are feasible, which would have inherent selection bias. Research focused on lower doses

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of induction agents may be more feasible and accepted. Any study evaluating this question should include an evaluation of patient awareness.

Induction Agent Selection

Question 7: In critically ill adults undergoing RSI, is there a difference between etomidate versus other induction agents (e.g., ketamine, midazolam, propofol) with respect to mortality or the incidence of hypotension or vasopressor use in the peri-intubation period and through hospital discharge?

Recommendation:

- We suggest there is no difference between etomidate and other induction agents administered for RSI with respect to mortality or the incidence of hypotension or vasopressor use in the peri-intubation period and through hospital discharge (conditional recommendation, moderate quality of evidence).

Rationale: Peri-intubation hypotension is a common event in critically ill patients (2). Hypotension associated with RSI has been associated with organ dysfunction, prolonged duration of mechanical ventilation, prolonged ICU stay, and increased mortality (2). Therefore, the selection of a sedative-hypnotic agent that attenuates hypotension during RSI is desirable. Etomidate has a favorable hemodynamic profile; however, there are concerns with its use in critically ill patients because it is known to inhibit 11-beta-hydroxylase. Whether etomidate-induced adrenal enzyme inhibition results in hypotension, increased vasopressor use, and increased mortality in the peri-intubation and postintubation period is unknown. Ketamine may be a reasonable option for RSI because of its quick onset and short duration of action, its preservation of respiratory drive, and its sympathomimetic properties. However, in critically ill patients with depleted catecholamine stores, there is concern for hypotension and cardiac arrest. Midazolam may be less desirable for RSI as it has a longer onset of action compared with etomidate and ketamine and is a potent venodilator at RSI doses. Propofol, although having a quick onset and short duration of action, has the most profound effect on blood pressure, which may limit its use in critically ill patients. Nine studies were included for evaluation to address this question (60–69).

Three studies were evaluated for the outcome of mortality (60–62). A Cochrane review and meta-analysis comparing bolus-dose etomidate with other induction agents for RSI in critically ill patients evaluated mortality and vasopressor requirements in RCTs published before 2015 (60). Therefore, we only included additional studies that evaluated mortality and vasopressor use that were published after the Cochrane review. The Cochrane review analyzed six studies (n = 772 patients) and did not show increased mortality with etomidate (0.2–0.3 mg/kg) when used as a single dose for RSI, compared with other induction agents, OR 1.17 (95% CI, 0.86–1.60) (moderate quality of evidence) (61). Two retrospective reviews of patients with major trauma who required RSI were also evaluated (61, 62). The first study compared outcomes in 116 patients who were administered etomidate (0.3 mg/kg or 0.15 mg/kg in patients with hemodynamic compromise) and succinylcholine (1.5 mg/kg) and in 145 patients who were administered fentanyl (3 μg/kg), ketamine (2 mg/kg), and rocuronium (1 mg/kg) in a prehospital setting (61). No difference in mortality was found (19% mortality in each group, OR 0.98; 95% CI, 0.51–1.87). In a separate before-and-after study conducted over a 4-year period following an institutional protocol change from etomidate (0.3 mg/kg) (n = 526) to ketamine (1–2 mg/kg) (n = 442), there was no difference in hospital mortality (20% vs 17%; OR 1.41; 95% CI, 0.92–2.16) (62). In addition, a recently published meta-analysis of 29 studies evaluated the relationship of etomidate with 28-day mortality, and the relationship between mortality and severity of illness scores (63). The use of etomidate was associated with an increased overall mortality rate (rr = 1.09; 95% CI, 1.04–1.29) and a meta-regression showed a progressive relative risk of mortality associated with increasing severity of illness. It is difficult to interpret these data; of the 29 studies included in the meta-analysis, only 5 were RCTs (of the remaining, 9 were post hoc analyses and 15 were retrospective evaluations). Three of the five RCTs were also included in the Cochrane analysis described above, and 26 of the 29 studies were published within the timeframe to be screened for inclusion in the Cochrane review. Of the other three, two are incorporated into the discussion below (64, 65), and the other study was an evaluation of two different hydrocortisone regimens in septic shock patients and was not pertinent to the question. Overall, these data are limited by selection bias, which may affect both mortality and the severity of illness correlation.

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One other study published outside of the Cochrane Review's inclusion timeframe assessed etomidate (0.2–0.3 mg/kg) compared with ketamine (1–2 mg/kg) in a prospective, randomized, open-label single-center study (66). Seven-day survival but not 28-day survival was higher in those patients randomly assigned to ketamine, although there is no clear explanation for why this was observed. Duration of mechanical ventilation, ICU length of stay, rates of vasopressor use and duration, Sequential Organ Failure Assessment (SOFA) score, and rates of new diagnoses of adrenal insufficiency were not different between groups.

Seven studies evaluated hypotension during the peri-intubation period or during hospitalization (61, 64, 67–71). In a single-center, propensity score-matched evaluation of patients with sepsis, clinical hypotension (defined as MAP decrease > 40% from baseline, MAP < 60 mm Hg, initiation of a vasopressor, or an increase of > 30% of a vasopressor infusion) occurred in 51% of patients who received ketamine (1.3–2.2 mg/kg) and in 73% of patients who received etomidate (0.2–0.4 mg/kg) (OR 0.39; 95% CI, 0.22–0.67) (64). At 6–12 hours and 12–24 hours after RSI, the etomidate group had significantly lower MAPs, compared with the ketamine group. Interestingly, more patients in the ketamine group had septic shock, had higher SOFA scores, and received benzodiazepines, and more patients in the etomidate group received opioids at the time of intubation. Conversely, two evaluations of National Emergency Airway Registry data showed higher rates of hypotension with ketamine, as compared with etomidate (67, 68). An evaluation of 140 patients with sepsis undergoing RSI with ketamine (median dose: 100 mg [interquartile range {IQR} 72.2–150 mg]) compared with 363 patients with sepsis receiving etomidate (median dose: 20 mg [IQR 15–20 mg]) found that post-RSI hypotension occurred more frequently in the ketamine group even after a propensity-adjusted analysis, (OR 2.7; 95% CI, 1.1–6.7) (67). Similarly, peri-intubation hypotension rates in patients in the ED undergoing RSI were 18.3% and 12.4% in those receiving ketamine (n = 738) and etomidate (n = 6,068), respectively (68). Patients in the ketamine group were more likely to have difficult airway characteristics, to undergo intubation with video laryngoscopy, and to have a higher risk for hypotension (OR 1.4; 95% CI, 1.2–1.7). More recent, less-rigorously conducted trials compared etomidate (dose varied based on the study 0.2 mg/kg ± 0.1, mean: 21 mg ± 6) with ketamine, propofol (mean: 127 mg ± 5 mg), thiopental (dose not available), and methohexital (mean: 1 mg/kg ± 0.2) for RSI and did not show a higher rate of hypotension in critically ill or acutely injured patients (61, 69–71). Overall, these studies were dissimilar in regard to patient populations and had significant limitations, such as being retrospective, unblinded, nonrandomized, and self-reporting. The recently published secondary analysis of the INTUBE trial warrants mention although it was published outside of the date range for inclusion (53). This study showed that propofol administered as a sedative-hypnotic agent for RSI in critically ill patients was associated with significantly higher adjusted odds of cardiovascular collapse in multivariate analysis and increased odds of mortality.

Two studies were evaluated for vasopressor requirements (60, 65). One study of 469 patients was included in the Cochrane review and no difference in the duration of vasopressor use was found (60). Similarly, a small RCT of 79 patients in the ICU who received a ketamine/propofol mixture (0.5 mg/kg of each) and 73 who received etomidate (0.15 mg/kg) found no difference in immediate or delayed vasopressor use between groups (65).

Taken as a whole, there was no significant difference between etomidate and other induction agents in the most important outcome, mortality. In addition, most studies demonstrated favorable peri-intubation hemodynamics with etomidate. Because etomidate is often readily available, clinicians have experience with its use, and it has a low cost, it is a reasonable RSI induction agent for critically ill patients.

Evidence Gaps: Because of the lack of evidence that etomidate-induced adrenal insufficiency causes negative clinical outcomes, additional research focused on this topic may be redundant. Patients with certain underlying diseases may be more susceptible to long-term outcomes of hypothalamus-pituitary-adrenal axis suppression; however, this has not been studied adequately. Also, a correlation between mortality rates and degree of severity of illness following etomidate administration is hypothesis generating for a prospective evaluation. Although it is challenging to design a blinded trial due to the pharmacodynamic effects of some induction agents, such a trial may help adequately answer further questions related to RSI sedative-hypnotic agents. Lastly, the optimal doses of

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sedative-hypnotic agents in critically ill patients are unknown and require additional investigation.

Etomidate and Corticosteroid Use

Question 8: In critically ill adults who receive etomidate for induction during RSI, is there a benefit to the coadministration of corticosteroids with respect to mortality, vasopressor use, risk of infection, multiple organ dysfunction, ventilator days, or ICU length of stay?

Recommendation:

- We suggest against administering corticosteroids following RSI with etomidate for the purpose of counteracting etomidate-induced adrenal suppression (conditional recommendation, low quality of evidence).

Rationale: As previously mentioned, it is known that etomidate inhibits 11-beta-hydroxylase, an important enzyme in steroidogenesis. However, it is unclear if exogenous corticosteroids are a reasonable intervention to reduce the incidence of potentially unwanted clinical effects from etomidate. Seven studies were included for evaluation to address this question (72–78).

Of the seven studies, six assessed mortality (72–77); however, the corticosteroid used, dose, frequency, and duration of administration were not consistent across studies. There were two separate RCTs (72, 73). In one study patients received a 42-hour infusion of hydrocortisone 200 mg/day (350 mg total) (72) and in another trial, a 42-hour infusion of hydrocortisone (200 mg total) was administered (73) following etomidate administration for RSI. Mortality rates did not differ between these trials (28-d mortality: 13% [hydrocortisone] vs 12% [control]) (72) and ICU mortality (3% [hydrocortisone] vs 5% [control]) (73). Two prospective, randomized, controlled substudies of patients who received etomidate for RSI evaluated the use of hydrocortisone versus placebo (74, 75). One was a large multicenter study of septic shock patients who were randomly assigned to receive hydrocortisone or placebo (74). The hydrocortisone group received 50 mg every 6 hours for 5 days and the hydrocortisone was then tapered for 6 days. There was no difference in 28-day mortality in the etomidate/hydrocortisone group (46%) compared with the etomidate/placebo group (40%). A nest-cohort study within a randomized double-blind placebo-controlled trial evaluating hydrocortisone in cirrhotic patients with septic shock undergoing RSI assigned patients to receive etomidate/placebo or etomidate/hydrocortisone administered every 6 hours; the hydrocortisone was then tapered over 8 days (75). There was no difference in all-cause 28-day mortality, ICU mortality, or hospital mortality among the 23 patients that received etomidate with or without hydrocortisone (75). Although not conducted in patients undergoing out-of-OR RSI, a retrospective study used propensity score matching (2:1) to evaluate surgical patients who received intraoperative steroids with those who did not receive steroids (76). Among 582 patients who received etomidate/corticosteroids (hydrocortisone, dexamethasone, or methylprednisolone for a median of 6 days, IQR 3–10 d) and 1,023 patients who received etomidate and no steroids, there was no difference in in-hospital mortality (4.6% in each group, OR 1.01 [97.5% CI, 0.58–1.76], $p = 0.97$. Lastly, a retrospective single-center study evaluated patients with septic shock who underwent RSI (77). There were 74 patients that received etomidate and of those 43 patients (58%) received hydrocortisone (hydrocortisone 100 mg every 8 hr). Hospital mortality rates were similar, with etomidate/steroids 32/43 [74%] versus etomidate/no steroids 19/31 [61%], $p = 0.12$ (77).

Three studies evaluated the association between the development of multiple organ dysfunction and the administration of hydrocortisone in patients who received etomidate as an induction agent for RSI (72, 73, 78). One prospective RCT randomized ICU patient to receive etomidate and rocuronium (group 1); etomidate, rocuronium, and methylprednisolone 2 mg/kg IV 2–4 minutes before etomidate administration (group 2); or midazolam and rocuronium (group 3) (78). Within-group comparisons demonstrated decreased SOFA scores at 4 hours compared with baseline in groups 1 and 3, but not in group 2. SOFA scores at 24 hours were significantly lower in all three groups, compared with baseline. The two prospective randomized, double-blind, controlled trials that evaluated the effect of hydrocortisone infused over a 42-hour time period showed that the proportion of patients with a SOFA score of 3 or 4 decreased over time in both the hydrocortisone group and the placebo group (72, 73). There was no difference between groups in the median SOFA score at 48 hours in either study.

Two studies evaluated the effects of hydrocortisone administered to patients who received etomidate for RSI on ventilator-free days (72, 75), three evaluated

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vasopressor use (71–74), and three evaluated ICU length of stay (72, 75, 76). In cirrhotic patients with septic shock who were randomized to hydrocortisone or placebo, there was a difference in ventilator-free days (mean: 3.6 ± 5.6 vs 0.2 ± 0.4, p = 0.04), vasopressor-free days (mean: 4.6 ± 6.9 vs 1.1 ± 3.3, p = 0.05), change in norepinephrine dose between day 1 and 3 (mean: −0.1 ± 0.26 vs 0.31 ± 0.36, p = 0.01), and ICU length of stay (mean: 12.6 ± 7.8 d vs 9.4 ± 5.8 d, p = 0.06) in the etomidate/hydrocortisone versus the etomidate/placebo groups, respectively (75). These findings were not evident in other studies. In the study assessing etomidate/hydrocortisone (42-hr infusion of hydrocortisone 200 mg/d [350 mg total]) compared with etomidate/placebo, there was no difference in ventilator days (median: 2 d [range 1–10] vs 4 d [range 1–10]) (72), duration of norepinephrine administration (median: 2 d [range 1–3] vs 2 d [range 1–4]) (72), time-to-resolution of shock (maintenance of SBP ≥ 90 mm Hg without vasopressor support for ≥ 24 hr) (mean: 3 d [95% CI, 2.5–3.5] vs 3.8 d [95% CI, 3.1–4.4], p = 0.42) (73), or ICU length of stay (mean: 4 d [range 1–10] vs 8 d [range 4–17]), NS (72). In patients who had undergone noncardiac surgery, there was a difference in ICU length of stay after adjusting for history of cardiac disease and year of surgery (hazard ratio: 0.89; 95% CI, 0.8–0.98); however, for obvious reasons, this patient population differs from the general ICU population (76). None of the trials documented adverse events of corticosteroids (i.e., infection) and this outcome could not be evaluated.

Etomidate-related decreases in 11-beta-hydroxylase activity are of unclear clinical significance. The literature evaluating whether corticosteroids should be initiated following RSI with etomidate for the purpose of counteracting etomidate effects is fraught with small sample size, selection bias, heterogeneity in the choice of corticosteroid, dose, frequency of dosing, and duration of administration, homogeneity in the patient populations with septic shock compared with other populations with critical illness, and overall low-quality evidence. Therefore, panelists do not recommend using corticosteroids when etomidate is used for RSI for the purpose of counteracting etomidate-induced adrenal suppression. The recommendation is exclusive to patients already receiving corticosteroids or those requiring corticosteroids for other indications.

Evidence Gaps: Because of the decreasing concerns about the clinical significance of etomidate-induced adrenal insufficiency, additional research focused on corticosteroid administration in patients who receive etomidate for RSI is likely futile. However, certain populations were identified that might benefit from hydrocortisone administration when etomidate is used for RSI, including those with cirrhosis and septic shock and patients who have undergone noncardiac surgery. Prospective research targeting these populations may help determine if corticosteroids should be administered when etomidate is used for RSI.

Neuromuscular-Blocking Agent Use

Question 9: In critically ill adults undergoing endotracheal intubation, is there a difference between the administration of a sedative-hypnotic agent with an NMBA versus a sedative-hypnotic agent alone with respect to FPS, the incidence of respiratory arrest or cardiovascular collapse, need for a surgical airway, or incidence of vomiting/aspiration during the peri-intubation period?

Recommendation:

- We recommend administering an NMBA when a sedative-hypnotic induction agent is used for intubation (strong recommendation, low quality of evidence).

Rationale: Long-standing aversion by some clinicians to NMBA use during intubation has likely come from concerns regarding the risks of awareness and inability to recover from a scenario in which a secure airway is not able to be placed in a timely fashion (i.e., cannot-intubate/cannot-ventilate scenario). Limited evidence demonstrating improved FPS rate and lack of evidence regarding other complications such as respiratory arrest, cardiovascular collapse, aspiration, or need for a surgical airway has also potentially influenced NMBA use during intubation. However, intubations performed without an NMBA may provide less-than-ideal intubating conditions due to the lack of neuromuscular blockade, which may therefore also lead to lower rates of FPS and increased complication rates. Six studies were included for evaluation to address this question (79–84).

Five studies were evaluated that measured FPS, including three observational, prospective studies (79–81) and two observational, retrospective studies (82, 83). The most robust study, which included FPS as the primary outcome, identified a success rate using

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NMBAs of 80.9% (n = 401/496; 95% CI, 77–84) compared with 69.6% (n = 117/168; 95% CI, 62–76, (p = 0.003) when not using an NMBA (79). In a propensity-matched analysis for FPS rate, NMBA use was associated with an OR of 2.37 (95% CI, 1.36–4.88) (79). Overall, FPS rates for patients receiving an NMBA ranged from 72% to 95% compared with 22% to 78% in patients who did not receive an NMBA. Three observational prospective analyses were evaluated for the occurrence rate of respiratory arrest or cardiovascular collapse (79–81). One study that evaluated these outcomes identified no mortality in patients who received an NMBA, compared with a 3% mortality rate in those patients who did not receive an NMBA (p = 0.02) (81). The two remaining studies did not identify any outcomes that were statistically significant (79, 80). In summary, respiratory or cardiovascular collapse rates of 0 to 7.5% were found for those patients who received an NMBA compared with 3% to 24% for those patients who did not receive an NMBA.

The need for a surgical airway was evaluated in one retrospective prehospital analysis of more than 7,500 patients (82). This study identified a less than 1% incidence of need for a surgical airway whether an NMBA was administered, with a composite rate of 0.36% overall.

Five studies addressed the occurrence rate of vomiting or aspiration, with two of the five finding statistical significance favoring the use of an NMBA (79–81, 83, 84). One prospective observational study evaluated aspiration as its primary outcome and found no aspiration in the group receiving an NMBA and 15% in patients who did not receive an NMBA (p < 0.001) (81). A retrospective analysis found rates of vomiting to be 0% in the NMBA group and 24% in the group that did not get an NMBA (p = 0.001) (83). In these two studies there was a 0% chance of vomiting in the patients who received an NMBA and in the other three studies rates of vomiting or aspiration ranged from 0% to 1.8% in patients receiving an NMBA and from 0% to 24% in those not receiving an NMBA (79–81, 83, 84). There was a large effect size that was statistically significant in favor of the administration of an NMBA in two studies, but the quality of evidence was rated low due to the risk of bias and serious imprecision (81, 83).

Current evidence affirms the use of an NMBA will improve FPS with fewer associated complications. Historical concerns precluding its use, such as risk of awareness and inability-to-intubate-or-ventilate scenarios, likely failed to identify the true risk of allowing recovery of spontaneous breathing in critically ill patients who did not receive an NMBA. It is likely that recovery of spontaneous breathing is not actually feasible or safe, and newer intubation techniques as described in this guideline including positioning, preoxygenation, and use of NMBAs themselves have led to improved efficacy and safety. Given the widespread availability and low cost of NMBAs, they should be used for airway management in critically ill patients when a sedative-hypnotic agent is used with the goal of inducing unconsciousness. This assumes that appropriate storage safeguards are in place, trained personnel are available, and education on the use of NMBAs has been completed. The panel recommendation takes into account the high risk of bias and the imprecision of important safety outcomes because of the limited frequency of some events given recent advances in medications and technology. Attempting to further stratify outcomes based on level of experience and variance in airway approaches would likely only highlight differences in practice, and not be significant enough to challenge the large effect size reported in the literature for critical outcomes.

Evidence Gaps: Imprecision exists for rescue surgical airways and the incidence of adverse events deemed critical or important as they relate to using NMBAs. Although larger studies to address these issues should be considered, the likelihood of identifying important differences may not be feasible.

Neuromuscular-Blocking Agent Selection

Question 10: In critically ill adults undergoing RSI, is there a difference between rocuronium versus succinylcholine when used for RSI with respect to mortality, FPS, adverse events, and risk of awareness in the perintubation period and through hospital discharge?

Recommendation:

- We suggest administering either rocuronium or succinylcholine for RSI when there are no known contraindications to succinylcholine (conditional recommendation, low quality of evidence).

Rationale: Succinylcholine is a short-acting depolarizing NMBA traditionally used for RSI. Adverse events, such as hyperkalemia, bradycardia, and malignant hyperthermia, may occur with succinylcholine

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administration, influencing selection for its use in emergent intubations when limited patient information is available. The intermediate-acting NMBA, rocuronium, has gained popularity as an alternative agent not generally associated with these adverse events. However, there are concerns regarding the risk of awareness when rocuronium is used because of its long duration of action (30–60 min), which could potentially mask suboptimal post-RSI analgosedation. Thirty-one studies were included for evaluation to address this question (1, 59, 85–113). One observational single-center study evaluated the effect of the choice of NMBA on mortality in 233 patients undergoing RSI (85). This was a study conducted in a subset of patients with traumatic brain injury (TBI) because succinylcholine may be associated with a transient increase in intracranial pressure (85, 114). The results were stratified based on severity of TBI. Patients with high-severity TBI had an increased risk of mortality when succinylcholine was used for RSI (OR 4.1; 95% CI, 1.2–14.1). Due to the retrospective study design and potential for selection bias, the level of evidence was considered to be very low.

Two RCTs (86, 87) and four observational studies (88–91) evaluated FPS rate with rocuronium and succinylcholine. Both RCTs had a low risk for bias (86, 87). A noninferiority RCT of 1,248 patients who underwent out-of-hospital RSI in France found an FPS rate of 74.6% with rocuronium (1.2 mg/kg) and 79.4% with succinylcholine (1 mg/kg) (difference: −4.8%, one-sided 97.5% CI, −9% to infinity) (86). The results were inconclusive based on a noninferiority margin of 7%. The other RCT, which included 401 patients, was conducted in the ICU setting (87). FPS was a secondary outcome in this trial, which had similar results: FPS rate of 82% in the rocuronium group versus 84% in the succinylcholine group. A pooled analysis of the four observational studies did not show a significant difference with regard to FPS (difference: −2%; 95% CI, −6% to 2%) (88–91).

Eighteen of the 31 studies compared the rate of adverse events in patients treated with these two NMBAs (59, 86–88, 92–106). Several of these studies were RCTs. There was serious heterogeneity and indirectness across the studies. Studies measured different types of adverse events, including hemodynamic changes, oxygen desaturation, postoperative hoarseness, vocal cord injury, sore throat, myalgia, increased intraocular pressure, and hyperkalemia. Most studies had small sample sizes and were inadequately powered to find significant differences in safety outcomes. Also, it was unclear if all of the adverse events could be attributed to the NMBAs.

Three RCTs measured patient awareness in the perintubation period (92–94). The studies were conducted on patients who needed emergency or elective operations. None of the patients in any of the trials reported awareness during the procedure when questioned at a postoperative interview. One observational study measured patient awareness in the intubation and postintubation phases of care in the ED (59). Seven of the 10 patients reporting postintubation awareness during neuromuscular blockade had received a longer-acting NMBA for RSI. One RCT (86) and 10 observational studies (1, 59, 95–97, 107–111) compared the timing or extent of postintubation sedation and analgesia. Most studies reported that postintubation analgosedation was provided more rapidly or to a greater extent when succinylcholine was administered as the NMBA for RSI. The longer duration of action of rocuronium may have prevented patient movement which might have served as a cue for staff to provide analgosedation. Some studies have shown that patient awareness may be mitigated when a clinical pharmacist is involved in the management of RSI (104, 112).

Evidence Gaps: Future studies are needed to compare these two agents in the subset of patients with TBI. One single-center observational study showed that mortality may be increased in patients with severe TBI who receive succinylcholine (85); however, this finding needs to be further evaluated in larger multicenter observational studies or RCTs. The RCT with the most consequential results compared FPS rates in an out-of-hospital setting (86). The findings of this study may not be extrapolated to RSI in the critically ill population in the ED or ICU, where resources are more readily available and video laryngoscopy is more commonly used. Future trials, therefore, should compare these agents in an ED or ICU setting. The effects of the NMBA on outcomes, such as FPS, may be dependent on the dose used for RSI. Thus, the fact that FPS rates were similar with both of the NMBAs should be considered in the context of the doses used in the study (86). Furthermore, pharmacokinetic alterations with poor perfusion or obesity may affect the extent of neuromuscular blockade. The optimal dose in these circumstances requires additional investigation.

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Although RCTs have not shown differences in the incidence of awareness, the evidence highlights that rocuronium may delay the provision of postintubation analgosedation. Future trials examining the incidence of postintubation awareness and potential psychologic sequelae (e.g., posttraumatic stress disorder) are needed if optimal analgosedation cannot be prospectively provided by the healthcare team. Intuitively, institutions should consider the implementation of protocolized care for RSI and incorporate personnel, such as clinical pharmacists, to help improve the timeliness of analgosedation. If postintubation analgosedation provision is optimized with rocuronium, then we would not anticipate differences inpatient awareness after RSI.

CONCLUSIONS

As a multidisciplinary group of clinicians with experience in airway management appointed by ACCM, we aimed to incorporate the most recent and best evidence available at the time of writing to improve the care of critically ill adults undergoing RSI. The recommendations provided are not absolute requirements and should be tailored to individual patients and with available equipment and resources, as appropriate. Particular patient populations, resources, and feasibility were considered and factored into our deliberations and recommendations. The release of data from ongoing studies and future research trials may result in focused updates. Until such time, guideline application by clinicians should always be modified based on new evidence, as it becomes available.

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