Chapter 19

Induction Agents for Endotracheal Intubation in Severe Sepsis and Septic Shock

Marie Mullen

Additional information is available at the end of the chapter

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1. Introduction

The management of severe sepsis and septic shock remains to this day one of the great challenges in medical care. These two disease entities represent significant morbidity and mortality and cross the threshold of multiple medical disciplines. Worldwide it is estimated that one in ten intensive care unit (ICU) patients carry the diagnosis of severe sepsis (1). For the year 2020, in the United States alone, the projected number of severe sepsis cases will approach 1.1 million (2). These disease entities are not only common, but lethal. Severe sepsis carries a reported mortality of 28% (2). Septic shock has recorded mortality rates as high as 60% (3).

Sepsis has a strong association with respiratory failure. From an epidemiologic perspective, sepsis and pneumonia are the leading causes of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (4-5). Reported sepsis-related ARDS incidence levels range from 16%-73% in multiple case series (6-9). Pneumonia is consistently documented as the primary inciting infection in the sepsis literature (10-13).

Severe sepsis and septic shock place critically ill patients at risk for respiratory failure and endotracheal intubation. In addition to epidemiologic evidence, there are multiple known complex physiologic variables in sepsis that explain the high potential risk for respiratory failure (14). Sepsis alters the respiratory drive. Early sepsis is particularly associated with an increase respiratory rate and an increase in coinciding energy expenditure. Components of sepsis-related ventilatory failure include a combination of increased respiratory muscle energy requirements with decreased energy availability and impending respiratory muscle fatigue (14).

Additional contributing factors to sepsis-associated respiratory failure include the interaction between the pulmonary and the cardiac system (14). Sepsis decreases pulmonary dynamic compliance, which leads to an increased in pleural pressure variation with each

breath. This change in variation can augment right atrial venous return. A volume-resuscitated patient with sepsis will exhibit a significant increase in right atrial filling pressure. This increased return on the right side can translate to left-sided cardiac dysfunction and contribute to pulmonary edema and cardiac dysfunction (14). Other pulmonary-cardiac interactions include decreased left ventricular dysfunction due to pleural pressure changes. These changes effectively increase cardiac afterload. There is also the added phenomenon of intrinsic myocardial depression that is associated with septic shock (15). The preceding mechanisms for respiratory failure are significant. As severe sepsis and septic shock is a highly complex entity, these physiologic variables are a few of many contributory factors.

As demonstrated, severe sepsis and septic shock place a critically ill patient at high risk for respiratory failure. Correction of this impending failure may require endotracheal intubation. The decision to intubate and ventilate these patients presents significant obstacles as well. Severe sepsis and septic shock patients have potential complex multi-organ dysfunction issues that can create clinical care difficulties before, during, and after the intubation procedure. The choice of pharmacologic agent to facilitate endotracheal intubation should reflect these challenges in care.

2. Intubation in severe sepsis and septic shock

Endotrachael intubation for severe sepsis and septic shock presents multiple hurdles. Prior to intubation, critically ill patients with severe sepsis and septic shock are likely hypoxic. The septic patient is at high risk for oxygen desaturation during the procedure. Figure 1 illustrates the oxyhemoglobin curve and associated desaturation risk based on initial starting oxygen saturation (16). The previously described variables such as increased respiratory effort; increased energy expenditure and respiratory muscle fatigue further increase risk of desaturation despite appropriate maneuvers such as pre-oxygenation (16). Figure 2 further illustrates the effect of critical illness and body habitus on time to oxygen desaturation (17).

Critical illness can further decrease time to profound hypoxia beyond these described desaturation curves (16). Additional desaturation risk can ensue in cases of delayed intubation due to a difficult airway situation. Overall, endotrachael intubation in critically ill patients outside the operating environment is associated with high morbidity and complications (18-20).

The change from negative to positive pressure with intubation and mechanical ventilation represents significant changes in patient hemodynamics. One of the most common hemodynamic changes associated with endotracheal intubation is hypotension. Some studies have reported hypotension occurring in up to 25% of emergency intubations (21).

One notable difficulty element is the associated decrease in venous return with intubation. Venous return reduction occurs from several mechanisms (21). Venous return is a function of the difference of systemic pressure subtracted from right atrial pressure. Vasodilation

from induction agents and reduction of catecholemine-associated vascular tone reduce left sided pressures and venous return. Positive pressure ventilation abruptly increases right atrial pressure. Decreased systemic pressure and increased right atrial pressure create a reduction in venous return that is difficult for a critically ill patient to compensate. Ongoing increased right atrial pressure contributing to persistent decreased venous return will translate to decreased left ventricular preload (22).

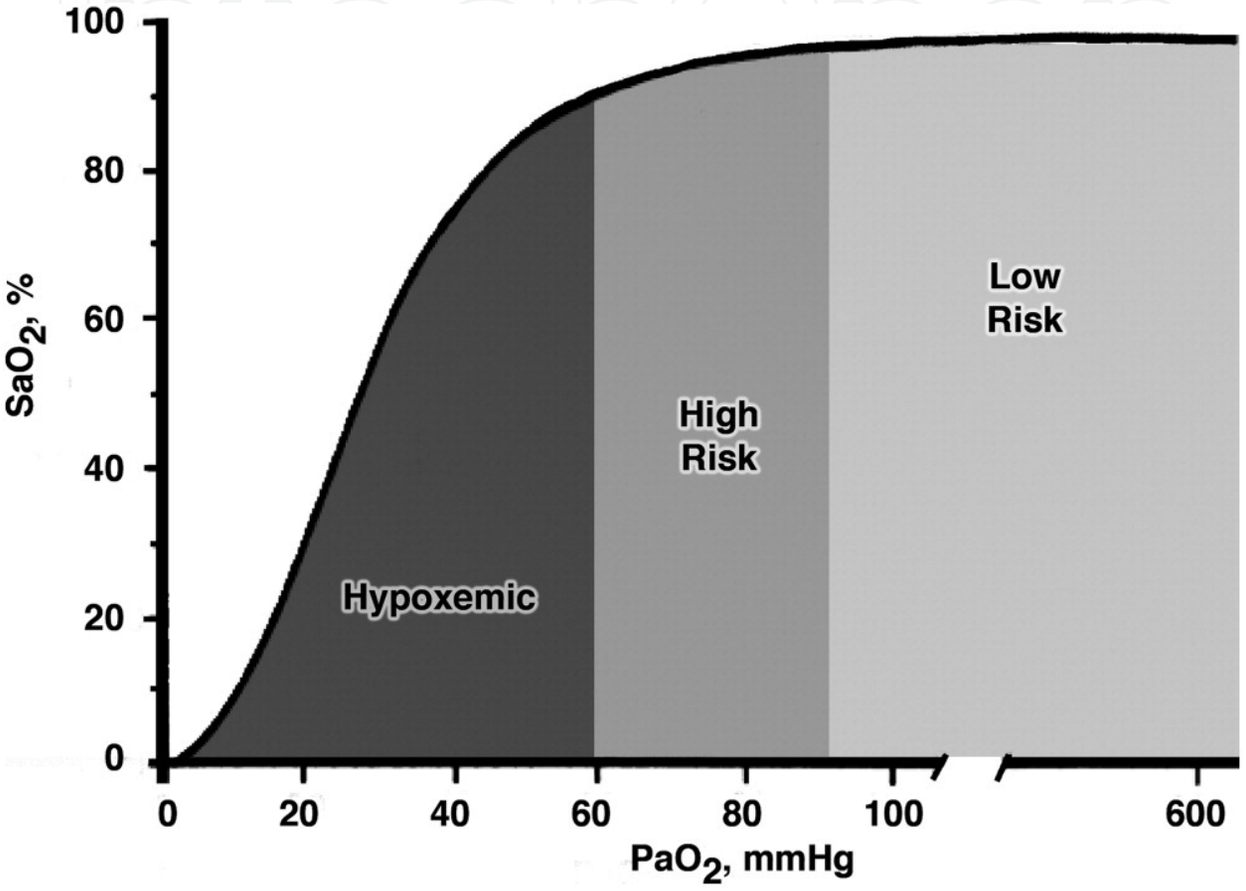

Figure 1. Oxyhemoglobin curve displays risk categories of desaturation (16)

Positive pressure ventilation can further affect left ventricular preload due to the phenomenon of interdependence between the right and left ventricle (22). The increase in thoracic pressure can lead to an increase in pulmonary vascular resistance. This situation results in decreased right ventricular ejection and increasing right ventricular end diastolic volume. Increased right end diastolic volume translates into decreased left end diastolic volume and preload. Mechanical ventilation exerts multiple effects on the cardiopulmonary system that need to be considered when initiating endotracheal intubation. The situation is further complicated in light of the pre-existing cardiopulmonary abnormalities of the sepsis patient (15).

Endotracheal intubation in the severe sepsis and septic shock patient poses many physiologic difficulties. These processes need to be heeded when deciding to intubate and choosing agents to facilitate the procedure.

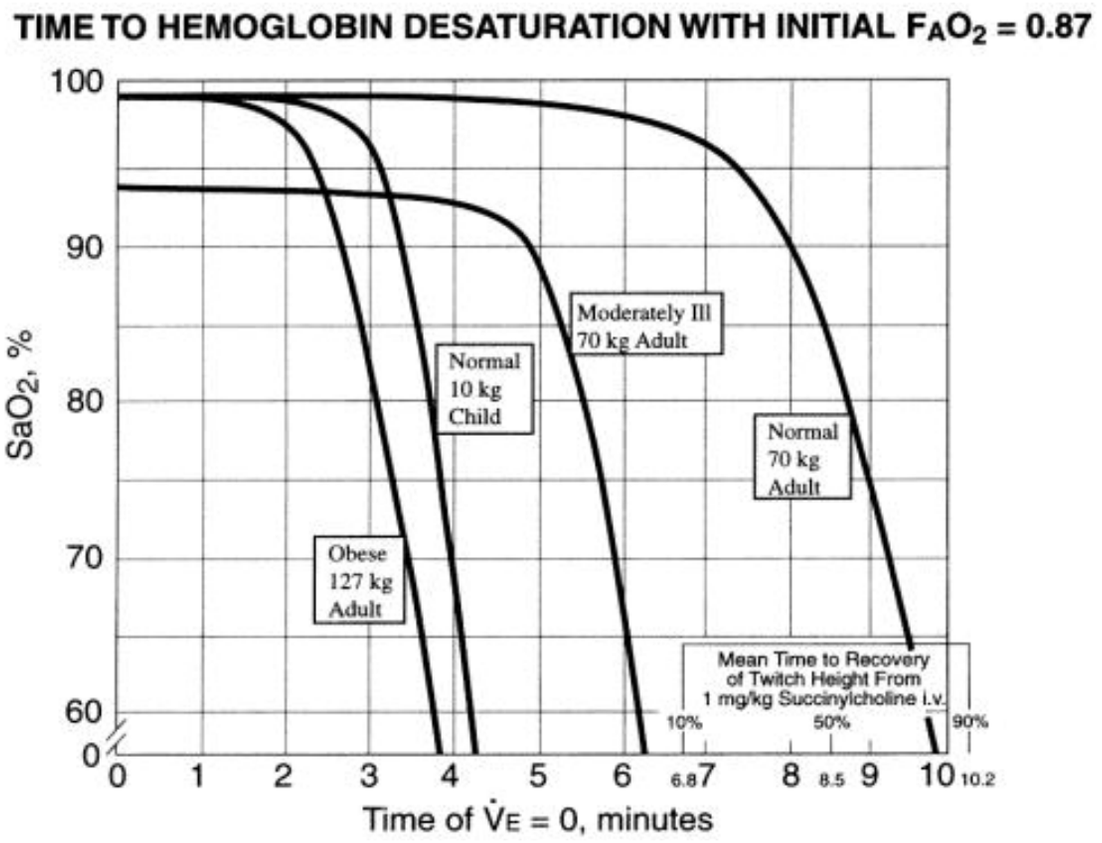

Figure 2. Time to desaturation when apneic with respect to size and medical condition (17)

3. Choosing an induction agent to facilitate intubation

The critically ill severe sepsis and septic shock patient in respiratory failure experiences many physiologic changes. These changes need to be addressed when evaluating the properties of intended induction agents.

As stated, this critically ill population is at high risk for oxygen desaturation. Time of onset for expected effect needs to be considered. An ideal agent would have a short onset of action to prevent undo delay in the procedure. It has been reported that a critically ill patient could theoretically experience serious oxygen desaturation within 23 seconds of apnea (23). This risk of desaturation needs to be evaluated in cases where a paralytic agent in conjunction with an induction agent is the planned intubation strategy.

Septic shock patients are hemodynamically unstable. By definition these patient have fluid-refractory hypotension (24). Induction agents that further contribute to this instability need to be carefully reviewed. The use of induction agents that decrease cardiac output or cause further dilation should be carefully contemplated prior to use. Severe sepsis and septic shock have a documented incidence of myocardial depression (15). Some induction agents may potentiate this cardiac depression as well.

Metabolism of induction agents needs to be examined as well. Severe sepsis and septic shock can exhibit associated organ dysfunction that will potentially affect induction agent

metabolism (25). Organ injury that needs to be especially regarded includes renal and hepatic dysfunction.

4. Review of available induction agents

4.1. Etomidate

Etomidate is a non-barbiturate imidazole compound used for induction in endotracheal intubation. The primary mechanism of action is direct action on the gamma amino butyric acid (GABA) receptor (26). As a sedative hypnotic agent, it exhibits many favorable properties that make it a particularly attractive agent to facilitate intubation. Etomidate has a rapid reliable mechanism of action and duration; has minimal affect on many cardiovascular parameters; is neuroprotective and has other favorable attributes as well.

Etomidate is typically dosed at 0.3 mg/kg in adult patients (27). Reported literature dosing for induction is cited as 0.2-0.4 mg/kg (28). It is also recommended to consider a reduction in dosing in the elderly patient due to delayed metabolic clearance (28).

As stated, etomidate has a rapid onset and duration of action with a single bolus dose. In a standard single induction dose, onset to hypnotic effect is 5-15 seconds (28). Duration of action is rapid as well and is dose dependent. Estimated metabolism is 5-14 minutes. Metabolism of the medication is primarily hepatic and the agent is strongly protein bound. Interestingly, hepatic disease and protein metabolism may alter potency of etomidate, but not timing of clinical actions (28).

The strength of etomidate lies in its cardiovascular effects. Etomidate does not significantly impact systolic blood pressure (SBP), mean arterial blood pressure (MAP), central venous pressure (CVP), heart rate, systemic vascular resistance (SVR), cardiac index (CI), stroke volume (SV) in standard bolus dosing (28). The literature in some cases does report a slight decrease in SBP. At high bolus dosing (>0.4mg/kg), one recorded study reports less than a 15% impact on SBP and MAP (29). Etomidate does not adversely alter hemodynamics in the face of valvular or coronary artery disease (28). The literature also reports improvement of coronary blood flow with the use of etomidate without an increase in oxygen consumption (30). Etomidate seems to offer a significant safety profile for hemodynamically compromised patients.

Other advantageous elements of etomidate include its neuroprotective effects. Etomidate is noted to effectively lower intracranial pressure (ICP) (28). Etomidate is able to lower ICP without adversely affecting hemodynamics. In addition, etomidate appears to independently lower cerebral oxygen consumption by several mechanisms (28). The medication also has the ability to lower intraocular pressure. This induction agent again has many attractive properties when considering its use.

Adverse effects of etomidate should be reviewed. Etomidate is linked to myoclonus. Reported rates of this effect can be as high as 30% (28). The literature regarding this agent and seizures remains mixed (28). There have been reports of decreased seizure potential in

patients with seizure disorders. Overall, etomidate remains a neuroprotective agent. The induction agent has a moderate risk of nausea and vomiting. This may be a consideration in the non-fasted patient. Etomidate also may have a potential to cause peripheral vascular irritation (28).

The critical care community appropriately expressed concerns about etomidate in regards to its link to critical illness-related corticosteroid insufficiency. Etomidate has a documented ability to inhibit the function of the 11 β-hydroxylase enzyme and subsequently contribute to this phenomenon (31-32). Several retrospective studies or study subsets have even suggested a mortality impact from this suppressive action (33-36).

The literature clearly acknowledges and supports the presence of etomidate-related adrenal insufficiency. The presence of actual mortality remains questionable. Multiple studies retrospective and prospective do not support the presence of increased mortality. Ehrman and Dmello exhibited a lack of mortality in large retrospective cohort studies (37-38).

Prospective studies surrounding the use of etomidate remain encouraging in regards to mortality. Tekwani initially showed no difference in mortality in a prospective observational study of over 100 septic patients receiving etomidate (39). The same author performed a prospective randomized study of etomidate versus midazolam in septic patients, which did not show any increase in length of stay with use (40). A large randomized prospective study comparing etomidate to ketamine in over 400 critically ill patients failed to show a mortality difference between the two agents in regards to administration (41). It should be noted that only 16% of patients in this large cohort carried the diagnosis of sepsis.

Due to the presence of adrenal insufficiency, there is consideration in regards to addition of corticosteroid therapy to patients receiving etomidate. Initial research suggests that in non-shock states this approach may not be effective. A recent prospective study by Payen, et al revealed no significant difference in 28 day mortality, ICU length of stay, ventilator days, or organ failure scales between etomidate treated patients who received moderate dose steroids and those who received a saline control (42). Use of steroids likely should be reserved for septic shock patients with fluid and vasopressor refractory shock (24).

Etomidate remains an attractive induction agent for severe sepsis and septic shock patients. It has a rapid reliable onset and duration of action, which is critical in a highly unstable, hypoxemic patient. The hemodynamic profile is ideal in the setting of hemodynamic instability and potential anticipated clinical decompensation. Vulnerable elderly patients with co-morbidities seem less susceptible to injury with this agent. It has added beneficial effects that do not contribute to potential worsening organ failure.

The issue of adrenal insufficiency continues to give emergency and critical care practitioners pause in regards to use. Based on the most current literature, the corticosteroid insufficiency issue should be acknowledged and respected. At the same time, the current literature does not support an absolute mortality effect. As the intubation procedure under non-operative circumstances can be associated with complications, this reliable medication that preserves hemodynamic reflexes should remain in the induction armamentarium.

4.2. Midazolam

In reviewing available induction agents, midazolam should be included as an option. Midazolam is a member of the benzodiazepine class of medications. As with other benzodiazepines, the medication possesses sedative, hypnotic, amnestic, and anti-anxiolytic properties. The drug specifically is classified as an imidazobenzodiazepine (43). Due its unique structure, midazolam has a significantly rapid onset and short duration of action. These qualities make it an attractive induction medication.

As a benzodiazepine agent, midazolam exerts its influence on the GABA receptor. Midazolam binds to the GABA receptor and potentiates the inhibitory affect of GABA on the receptor (43).

Typical rapid sequence dosing is 0.1-0.3 mg/kg. Onset of action in intravenous dosing is 30-60 seconds. Duration of action is 15-30 minutes (43-45). The lipophilic nature of this drug accounts for its rapid uptake and onset of action. Its rapid metabolism and elimination are subject to several factors.

Midazolam is metabolized through the hepatic system. The cytochrome P450 system is the primary actor in midazolam breakdown. Cytochrome P450-3A4 hydroxylates midazolam to its metabolites, which are ultimately renally excreted (43). This makes midazolam metabolism subject to agents that may interfere with the cytochrome P450 system. Patients taking such agents as ranitidine or macrolide antibiotics may experience a decreased clearance of the medication (43). As elimination is through the renal system, patients with kidney dysfunction may experience a longer sedation period due to slower elimination time (43).

As an induction agent, midazolam has several favorable properties. The rapid action of this medication is a clear advantage. Critically ill patients have a very small respiratory and ventilatory reserve. Rapid action is crucial. The agent has anticonvulsant and muscle relaxant activity. The pharmacology literature has reported that midazolam directly relaxes the muscles of the airway (43). As endotrachael intubation requires optimum conditions, muscle relaxation presents a clear advantage. Midazolam as an agent is also not linked to vomiting and does not have a peripheral vascular irritant effect (45).

Midazolam does have noted cardiovascular effects. Use of midazolam will decrease both systolic and diastolic blood pressure (45). The primary mechanism appears to be vascular dilation and reduction of systemic vascular resistance (SVR) (45). This results in an increase in heart rate as part of the baroreceptor response. Clinicians should expect a lowering of blood pressure and an increase in patient heart rate with the use of this drug. Cardiac index is preserved (45). The degree of blood pressure reduction is not dependent on the presence of cardiac disease, but is more pronounced in cases of volume depletion (45).

The hypotensive effect of midazolam needs to be seriously scrutinized. A case series in the literature revealed at least a 10 percent reduction in systolic blood pressure in patients receiving midazolam for intubation (46). The reduction in blood pressure was doubled for patients age 70 years and older. Reduction in dose still precipitated hypotension in this report (46).

As endotracheal intubation physiologically predisposes a patient to hypotension, midazolam may not be the best induction agent for the severe sepsis and septic shock population. This patient population is often volume depleted and hypotensive prior to the procedure. Midazolam carries the risk of worsening an already tentative hemodynamic situation. Clinician should strongly consider alternative induction agents for this critically ill population.

4.3. Ketamine

Ketamine is a medication with a unique mechanism of action. Due to its many advantageous properties, this agent merits discussion. Structurally, ketamine resembles the hallucinogenic agent phencyclidine (PCP) (47). Ketamine acts as a dissociative agent. The medication essentially dissociates the thalamus from the limbic system. It is different from the previously discussed agents in that it does not interact with GABA receptors. Its primary mechanism of action is its antagonist effect on the excitatory N-methyl-D-aspartate receptor (NMDA) (48). Ketamine also interacts with opioid and muscarinic receptors, which contribute to its unusual qualities and effects (48). These qualities include sedative, hypnotic, analgesic, bronchodilator and cardiac stimulatory effects.

Dosing of ketamine for induction of intubation is typically 1-2 mg/kg (27,49). The sedative effects are rapid and initiate in approximately 30-60 seconds (27,48-49). Primary sedative effects dissipate within 10-15 minutes.

Ketamine is metabolized in the liver and excreted in urine (47). The primary mechanism of breakdown is through the cytochrome P450 system. Of note, decreased renal function does not effect duration of action as active ketamine metabolites are not excreted in the urine (47,51). Limited ketamine use for induction should not be impacted by renal disease. Induction doses of ketamine have not been well studied in severe liver disease. It is thought that a transient induction dose in liver dysfunction should not have a significant clinical impact (51). Certain medications can interfere with ketamine metabolism including diazepam and halothane (47). Prolonged use of ketamine is linked to elevation of liver enzymes (47).

As stated, ketamine has many favorable effects as an induction agent. It has a rapid onset and duration of action. In a potentially difficult, tenuous airway, where timing is critical, this is an important property. Ketamine has the unique ability to increase blood pressure. It is an actual cardiovascular stimulant (47). Ketamine increases heart rate, blood pressure and systemic vascular resistance (SVR) (47). Ketamine acts to increase these parameters through direct central stimulation of the autonomic nervous system and through indirect inhibition of catecholamine uptake (47, 52).

Unlike other agents, ketamine is not linked to hypotension. As the severe sepsis and septic shock patient is at high risk for hemodynamic instability, this stimulatory effect can be valuable. Ketamine has been reported to show a positive inotropic action. This property may be an advantage, as septic patient tend to have myocardial suppression (15). With increased cardiovascular stimulation, comes increased myocardial oxygen demand.

Clinicians will need to balance ketamine use in the setting of coronary artery disease (47). Overall, ketamine increases mean arterial pressure (MAP), SVR, and cardiac index (CI) (47-48,51-52).

Ketamine exhibits other pertinent abilities that merit consideration. Ketamine preserves airway reflexes and thus minimizes aspiration (51). Ketamine is a known bronchodialtor (47,49,51). In a high-risk airway or a patient with respiratory co-morbidities, these properties can give a care provider an additional benefit. In addition, ketamine has direct analgesic action, which may contribute to patient care during an uncomfortable procedure.

Ketamine has neurologic actions, which have generated controversy. Ketamine has both epileptic and anti-epileptic effects. Ketamine has been noted to change EEG patterns to match epileptiform patterns (47). At the same time, evidence of seizure causation is limited and even contradicted in the literature (53-54). Ketamine's impact on intracranial pressure has generated additional controversy. Initial early ketamine literature did report an increase intracranial pressure (47). A more recent literature review challenges these early reports and suggests a possible neuroprotective role for ketamine (55).

Ketamine does have adverse actions that need to be evaluated. Ketamine is associated with increase oral and airway secretions (47). The clinician needs to consider premedication with atropine or glycopyrrolate to counteract this effect. Ketamine does have a small independent risk factor for larnygospasm. The mechanism seems to be linked to airway sensitivity. Ketamine preserves airway reflexes and may cause increase airway responsiveness to secretions (56). Ketamine is connected to a phenomenon known as reemergence. Patients can experience hallucinations, alarming dreams and delirium. As the patient will be intubated, this phenomenon is less significant. It is also attenuated by concomitant benzodiazepines. Ketamine is associated with nausea and vomiting (51).

In review of ketamine, this medication is an option for severe sepsis and septic shock. It is rapidly acting with a short period of duration. Metabolism does not appear to be a significant concern. It preserves airway reflexes in a potentially high-risk situation. Unlike several agents, it does not cause hypotension. It is linked directly to an increase in blood pressure. This is of particular benefit in hypotensive, hemodynamically unstable patients. Ketamine has been shown to specifically improve hemodynamics in a septic shock case history (57). In a large, randomized, blinded study, ketamine and etomidate were both shown to have a comparable safety profile in critically ill patients (41). This particular cohort of over 400 patients included approximately 16% septic individuals. Clinicians do need to balance known adverse effects such as increased secretions and myocardial oxygen demand.

4.4. Propofol

Propofol is a unique induction mediator. It is an alkyl phenol with sedative, amnestic and anesthetic properties (58). Of note, propofol is highly water-insoluble. This necessitates that its commercial preparation dissolve the medication in a lipid emulsion consisting of soybean oil, egg lecithin and glycerol (59). Despite the egg component in the emulsion, current expert consensus does not indicate that an egg allergy prohibits the use of propofol (59).

At the same time, the lipophilic nature of this unusual drug contributes to its rapid onset and offset of activity (60). Propofol aptly crosses the blood brain barrier to exert its sedating effect. Propofol primarily acts on the GABA receptor and potentiates its activity (50). Induction dosing of propofol ranges from 1.5-3 mg/kg (58). Propofol initiates sedative effects within 20-40 seconds on intravenous administration . Duration of action is 5-10 minutes (58, 60-61).

Metabolism of propofol is through hepatic conjugation (60). The medication is renally excreted. It should be noted that chronic renal or hepatic insufficiency do not significantly affect propofol pharmacokinitcs. The use of prolonged propofol use has not been tested in these populations. The metabolism and elimination of propofol has also not been well studied in cases of acute renal or hepatic failure (58, 60).

There are certain populations to consider when adjusting dosing with propofol. Patients greater than 60 years old have a documented decreased clearance of the drug (58,60). This decreased elimination is thought to be secondary to decreased cardiac output and hepatic blood flow. The obese patients can present a challenge when using this medication as well. Propofol has an increased saturation in fatty tissue and a subsequent decrease in plasma clearance. Use of propofol in obese patients should be dosed according to ideal body weight in the obese patient to insure safety (60).

Propofol as an induction medication has attractive attributes. Its rapid onset of action and short duration of action is a definite benefit for the unstable patient who requires intubation. It also does not seem to be affected by chronic renal or hepatic insufficiency. Propofol has a known bronchodilator ability and has been used in patients with chronic obstructive pulmonary disease with success (60). Propofol also has anti-emetic properties as well (62). Such qualities suggest propofol has good potential as an induction drug.

For a patient with neurologic injury, propofol offers neuroprotective effects. Propofol has been shown to either maintain or reduce intracranial pressure in patients with neurologic injury (60). The medication also has been shown to improve cerebral auto-regulation.

Propofol does have certain qualities that limit its use. Propofol significantly reduces blood pressure. Studies have shown that propofol can reduce blood pressure 30% from baseline (58). Propofol exhibits this suppressive effect to a greater degree than other induction agents including certain barbiturates and midazolam (58, 60). The reduction in blood pressure is presumed to be due to a decrease in systemic vascular resistance and cardiac contractility (60). Propofol also reduces heart rate despite the reduction in blood pressure. The medication has been linked to prolonged bradycardia (58). Elderly patients seem to be particularly susceptible to these effects. Research has shown a decrease in cardiac index in elderly surgical patients who received propofol (58). These effects will give the clinician pause when approaching the hemodynamically unstable, volume depleted, or elderly patient. As severe sepsis and septic shock patients can potentially be included in such categories; propofol appears to be a less ideal medication.

Propofol appears to impact the immune system. The lipid emulsion component of propofol has been shown to have some suppressive affect on the immune system (60). Propofol in one

study exhibited inhibitory effects on neutraphil function (62). Of note, the effect appears to be more significant in cases of prolonged infusion.

Propofol has additional issues to address. Though transient, propofol does cause pain at the site of injection. If a propofol infusion is used after induction, the phenomenon of propofol infusion syndrome needs to be considered. Propofol infusion syndrome is an often-fatal entity that consists of metabolic acidosis, renal failure, cardiac failure and rhabdomyolysis. It is linked to prolonged propofol infusion at higher doses. The disease also is connected to pressor and steroid use in conjunction with propofol (64). This problem will not affect short-term induction use. The clinician does need to be mindful that initiating a propofol infusion may be detrimental to a sepsis patient who may later require vasopressors or steroids.

In general, the unfavorable hemodynamic profile displayed by propofol does not make it an ideal mediator for intubation in severe sepsis and septic shock patients. The negative effects likely outweigh its rapid action and other positive attributes. This is especially pertinent in the light of the hemodynamic changes induced by endotracheal intubation itself.

4.5. Thiopental and methohexital

Thiopental and methohexital are barbiturate sedative induction agents. Due to their rapid onset of action, these two medications are classified as ultra short acting. As barbiturates, thiopental and methohexital exhibit their effect at the level of the inhibitory GABA receptor (50). Thiopental also may have a secondary mechanism of inhibiting the NMDA receptors (50). These processes lead to the expected effect of sedation.

Typical induction dose for thiopental is 3-5 mg/kg (50,65). Methohexital is usually dosed at 1-2 mg/kg (50,66-67). Both agents have a swift onset of action at 10-30 seconds (50). Thiopental is rapidly metabolized and has a duration of 5-10 minutes (50). Methohexital is metabolized 3-4 times more quickly than thiopental and has a duration of action of 4-7 minutes (50,68). The duration of action is comparable despite the faster metabolism of methohexital. This originates from the fact that actual clinical effect is due to redistribution of the medication in the body. In both agents, redistribution to other tissues is swift (50).

Metabolism of both these barbiturates is hepatic with renal elimination. Due to a balance in clearance and elimination, renal insufficiency does not seem to impact thiopental dosing or duration of action. Of note, phenobarbital is one of the few barbiturates affected by renal dysfunction. Plasma clearance of thiopental also remains unaffected by cirrhosis or decreased hepatic blood flow (65). There are factors that do impact duration of action and dosing. Decreased clearance of thiopental in elderly patients indicates a reduction in dose for expected onset of effect. Some authors recommend a reduction in dose of 25-50% for older individuals. Half-life of thiopental is increased in younger females and obese individuals (65).

As an induction drug, both thiopental and methohexital have a rapid onset and short duration of action. These qualities make these medications potential options for critically ill patients with a need for rapid airway management. Thiopental has significant

neuroprotective effects as well. The medication has been shown to decrease intracranial pressure, cerebral oxygen demand , and to decrease the actions of damaging neuro-excitatory transmitters (65). Critically ill patients with brain injury may reap the reward of these beneficial actions.

Thiopental and methohexital do have a marked negative impact on the cardiovascular system. Thiopental has been shown to profoundly lower mean arterial pressure and cardiac output (65). The primary mechanism appears to be vasodilatation. The negative inotropic effect is not entirely defined. There also tends to be a resulting increase in heart rate. Increased heart rate can negatively impact an already tachycardic septic patient or a patient with coronary artery disease. These agents do not appear to offer any benefit to the hemodynamically unstable or volume depleted patient.

There are added negative aspects of barbiturates as induction agents for septic patients. The barbiturates appear to impact immunosuppression. Both thiopental and methohexital were linked to inhibition of granulocyte recruitment and phagocytosis (69). Thiopental has also been linked directly to lymphocyte destruction (70). These agents appear to have a potential negative impact on the immune system response.

Thiopental and methohexital have other concerning attributes. Methohexital has been linked to laryngospasm (68). Both medications have been connected to bronchospasm and are not recommended for patients with asthma (50,65,68,71). Both these agents are contraindicated in cases of porphyria. The medications may increase the activity of γ-aminolevulinic acid synthetase and precipitate an acute episode (50,68).

These agents for multiple reasons do not appear to be ideal induction agents for severe sepsis and septic shock patients. Of note, thiopental is not manufactured in the United States as of 2011.

4.6. Dexmedetomidine

Dexmedetomidine is a newer sedative medication under investigation as an adjunct to intubation. It is currently approved primarily for sedation of critically ill patients in the intensive care environment. As it is a potential intubation facilitator, it will be mentioned in this chapter. It has many potential pitfalls that do not make it ideal for use in severe sepsis and septic shock.

Dexmedetomidine is a centrally acting alpha-2 agonist with sedative, amnestic, and sympatholytic properties. It has the additive effect of preserving airway reflexes (72-74). Due to these properties, it is under evaluation as an adjunct for awake fiberoptic intubation (73).

As an induction agent, dexmedetomidine is not as rapid as the other discussed agents. Use in the intubating environment requires a bolus of 0.5-1 mcg/kg over 10 minutes (73-75). An infusion follows ranging from 0.2-0.7 mcg/kg/hour until the procedure is complete (73, 75). This is not consistent with the rapid acting agents previously discussed. The medication does offers a significant degree of sedation, comfort and airway protection. For the

particularly high-risk airway, this drug creates an environment of "cooperative anesthesia" and has been shown to facilitate the awake intubation (73). The medication again is not as short acting as other medications reviewed. Onset of action is in 5-10 minutes and duration of action extends from 60-120 minutes. When time is critical, dexmedetomidine nay not fit the best pharmacologic profile

Dexmedetomidine is metabolized through the hepatic system. Unlike several of the previously described agents, drug clearance is impacted by hepatic failure and low hepatic blood flow. Elimination is through renal and fecal routes (74). In regards to metabolism, elderly patients have been found to be particularly sensitive to dexmedetomidine. Reduction of bolus dosing in this population is encouraged (74).

As an alpha-2 agonist, dexmedetomidine causes a decrease in mean arterial blood pressure and heart rate. Of note, With the initial bolus, a transient increase of mean arterial pressure can occur (50,74). This is felt to be due to a temporary stimulation of peripheral alpha-2 receptors (50,74). Overall, dexmedetomidine reduces MAP, SVR, cardiac index and heart rate. These attributes are dose dependent and have been diminished with dose reduction or elimination of bolus administration. Dexmedetomidine has been linked to sinus arrest during intubation (74). In a hemodynamically, volume depleted, or inotropically challenged patient this side effect profile is not helpful. As severe sepsis and septic shock patients have many of these attributes, dexmedetomidine may not be the best induction option.

Dexmedetomidine does deserve mention, as it is becoming a select option for induction and sedation. Dexmedetomidine preserves airway integrity, ventilatory response and reduces risk of bronchconstriction (74). In a tenuous airway situation, such qualities are clearly favorable.

While not a first line induction choice, dexmedetomidine may have a role in the sedation of sepsis patients under the appropriate circumstances. Dexmedetomidine appears to have anti-inflammatory properties. In one study, the use of dexmedetomidine reduced the serum levels of tumor necrosis factor (TNF), interleukin-1 and interleukin-6 in comparison to midazolam (76). Use of dexmedetomidine as a sedative agent in another case study reduced delirium, ventilator days, and 28-day mortality in comparison to lorazepam (77). While the medication may not be an optimal emergency intubation agent, future avenues in its use as a sedative are intriguing.

4.7. Methoxycarbonyl-etomidate (MOC-etomidate) and carboetomidate

Etomidate as discussed has a very favorable profile in regards to use in severe sepsis and septic shock. The controversy ensues in regard to etomidate's tendency to suppress the adrenal axis (31-32). In the interest of remaining up to date, it is important to mention etomidate analogues that may resolve the adrenal suppression debate.

Methoxycarbonyl-etomidate is an ultra short-acting analogue of etomidate (78). It was designed to maintain the favorable hemodynamic profile of etomidate and avoid the adrenal axis suppression component. Like etomidate, MOC-etomidate does act at the GABA

receptor. In recent animal studies, this medication exhibited similar sedative potency and was found to have a half-life of 4 minutes as opposed to 40 minutes for etomidate (78). In initial promising research, the drug did not impact adrenal function. This may be due to its extremely swift onset and metabolism. There was some decreased potency in comparison to etomidate and its ultra rapid action will be a factor in future dosing. Multiple questions remain and this data remains extremely preliminary. It is important for the clinician to be aware of the next generation of agents.

Carboetomidate is another analog designed for a better side effect profile as well. Carboetomidate generation focused specifically on adrenal suppression issues (79). The medication was designed to have a reduced affinity for 11 β–hydroxylase. This particular analog maintained a similar hypnotic effect to etomidate, a stable hemodynamic profile, and had a third less adrenal suppression activity. It also did have a slightly less hypnotic effect in regards to etomidate (79). Carboetomidate remains another future potential agent in the care of critically ill patients. Clearly, ongoing research is required.

5. Conclusions

As reviewed, endotracheal intubation of the critically ill septic patient is one of the most significant challenges an emergency medicine or critical care practitioner will face. The intubation procedure itself is associated with profound physiologic changes. Performing this procedure on a patient with underlying hemodynamic, respiratory, and additional organ compromise can be arduous. Agents to rapidly and safely accomplish this procedure need to be chosen. The caregiver needs to be aware of induction agent side effects, mechanism of action, metabolism, and duration of action. This knowledge is as important as the actual procedural skill. Intubation under adverse circumstances can be worsened with poor choice in induction mediator.

Severe sepsis and septic shock is a particularly special circumstance. Critically ill septic patients are literally a maelstrom of organ failure. Induction mediators can help or hinder an already difficult task. This chapter is designed to facilitate the best choices for this particular patient care scenario.

In review of induction medications, rapid onset with short duration of action, preservation of hemodynamic parameters, and low adverse side effect profile are key components for success. Table 1 summarizes the qualities of the previously discussed agents. For severe sepsis and septic shock, two particular candidates rise to the occasion. Ketamine and etomidate appear to be the best current induction options.

The recommendation of etomidate may elicit some controversy. The adrenal suppression effect of this medication is well described in the literature. At the same time, multiple studies continue to show a paucity in mortality impact. The endocrine suppression is evident. The mortality figures are not. For rapid, reliable induction without hemodynamic compromise in a critical moment, etomidate does serve this purpose. Future agents and analogues may make this controversy obsolete.

Induction agent	Class	Dose (IV)	Onset of Action	Duration of Action	Metabolism	Hemodynamic Effects	Special Consideration
Etomidate	Non-barbiturate Sedative hypnotic	0.3mg/kg	5-15 sec	5-14 min	Hepatic	None or slight decrease in MAP Minimal impact on SVR/ CI/ SV	Preservation of hemodynamic status Neuroprotective Adrenal suppression
Midazolam	Benzodiazepine	0.1-0.3 mg/kg	30-60 sec	15-30 min	Hepatic	Decreased MAP/SVR	Risk of hypotension Affected by renal insufficiency
Ketamine	Dissociative	1-2 mg/kg	30-60 sec	10-15 minutes	Hepatic	Increased MAP/ SVR/ CI	Increased myocardial oxygen consumption Increased secretions
Propofol	Non-barbiturate Sedative hypnotic	1.5-3 mg/kg	20-40 sec	5-10 minutes	Hepatic	Decreased MAP/SVR/ CI	Caution with elderly patients Risk of hypotension
Thiopental	Barbiturate	3-5 mg/kg	10-30 sec	5-10 minutes	Hepatic	Decreased MAP/SVR/ CI	Risk of hypotension Vasodilator Immunosuppression
Methohexital	Barbiturate	1-2 mg/kg	10-30 sec	4-7 minutes	Hepatic	Decreased MAP/SVR/ CI	Risk of hypotension Vasodilator Immunosuppression
Dexmedetomidine	Non-barbiturate Sedative hypnotic	0.5-1 mcg/kg over 10 minutes Drip 0.2-0.7 mcg/kg hour	5-10 minutes	60 -120 minutes	Hepatic	Decreased MAP/ SVR/ CI Reduced heart rate	Risk of hypotension Risk of bradycardia

MAP- Mean arterial pressure, SVR- Systemic vascular resistance, CI- Cardiac index, SV- Stroke volume

Table 1. Summary of Induction Agent Attributes

Ketamine is another agent that appears well suited for induction of the severe sepsis and septic shock patient. Ketamine preserves airway reflexes, increases blood pressure and systemic vascular resistance, and serves as a bronchodilator. In a prospective trial, ketamine and etomidate exhibited a similar safety profile for a wide range of critically ill patients; including patients with sepsis (41). Due to increased myocardial oxygen consumption, ketamine may be a less optimal choice for patients with known coronary artery disease.

All other agents discussed suppress the hemodynamic profile to some degree. Best choice for intubation induction for severe sepsis and septic shock remains etomidate and ketamine. Circumstances may preclude the use of these agents. The practicing clinician is cautioned to review the remaining sedation agents carefully in the context of the clinical picture. In the case that the need arises for another drug choice, the most rapid acting medication with the least duration of action and least adverse side effect profile should be administered. The informed clinician needs to be aware of the side effect profile and prepare accordingly.

Successful intubation in severe sepsis and septic shock patients is a critical skill. Choosing the best medication to accomplish this task is a significant component of the battle. The well-informed practitioner can make all the difference in this challenging situation.

Author details

Marie Mullen
Department of Emergency Medicine, University of Massachusetts, Worcester, MA, USA

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