Special Article

Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient

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Objective: To update the 2002 version of "Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient."

Design: A Task Force comprising 17 members of the Society of Critical Medicine with particular expertise in the use of neuromuscular-blocking agents; a Grading of Recommendations Assessment, Development, and Evaluation expert; and a medical writer met via teleconference and three face-to-face meetings and communicated via e-mail to examine the evidence and develop these practice guidelines. Annually, all members completed conflict of interest statements; no conflicts were identified. This activity was funded by the Society for Critical Care Medicine, and no industry support was provided.

Methods: Using the Grading of Recommendations Assessment, Development, and Evaluation system, the Grading of Recommendations Assessment, Development, and Evaluation expert on the Task Force created profiles for the evidence related to six of the 21 questions and assigned quality-of-evidence scores to these and the additional 15 questions for which insufficient evidence was available to create a profile. Task Force members reviewed this material and all available evidence and provided recommendations, suggestions, or good practice statements for these 21 questions.

Results: The Task Force developed a single strong recommendation: we recommend scheduled eye care that includes lubricating drops or gel and eyelid closure for patients receiving continuous

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infusions of neuromuscular-blocking agents. The Task Force developed 10 weak recommendations. 1) We suggest that a neuromuscular-blocking agent be administered by continuous intravenous infusion early in the course of acute respiratory distress syndrome for patients with a Pa_{O_2}/Fi_{O_2} less than 150. 2) We suggest against the routine administration of an neuromuscular-blocking agents to mechanically ventilated patients with status asthmaticus. 3) We suggest a trial of a neuromuscular-blocking agents in life-threatening situations associated with profound hypoxemia, respiratory acidosis, or hemodynamic compromise. 4) We suggest that neuromuscular-blocking agents may be used to manage overt shivering in therapeutic hypothermia. 5) We suggest that peripheral nerve stimulation with train-of-four monitoring may be a useful tool for monitoring the depth of neuromuscular blockade but only if it is incorporated into a more inclusive assessment of the patient that includes clinical assessment. 6) We suggest against the use of peripheral nerve stimulation with train of four alone for monitoring the depth of neuromuscular blockade in patients receiving continuous infusion of neuromuscular-blocking agents. 7) We suggest that patients receiving a continuous infusion of neuromuscular-blocking agent receive a structured physiotherapy regimen. 8) We suggest that clinicians target a blood glucose level of less than 180 mg/dL in patients receiving neuromuscular-blocking agents. 9) We suggest that clinicians not use actual body weight and instead use a consistent weight (ideal body weight or adjusted body weight) when calculating neuromuscular-blocking agents doses for obese patients. 10) We suggest that neuromuscular-blocking agents be discontinued at the end of life or when life support is withdrawn. In situations in which evidence was lacking or insufficient and the study results were equivocal or optimal clinical practice varies, the Task Force made no recommendations for nine of the topics. 1) We make no recommendation as to whether neuromuscular blockade is beneficial or harmful when used in patients with acute brain injury and raised intracranial pressure. 2) We make no recommendation on the routine use of neuromuscular-blocking agents for patients undergoing therapeutic hypothermia following cardiac arrest. 3) We make no recommendation on the use of peripheral nerve stimulation to monitor degree of block in patients undergoing therapeutic hypothermia. 4) We make no recommendation on the use of neuromuscular blockade to improve the accuracy of intravascular-volume assessment in mechanically ventilated patients. 5) We make no recommendation concerning the use of electroencephalogram-derived parameters as a measure of sedation during continuous administration of neuromuscular-blocking agents. 6) We make no recommendation regarding nutritional requirements specific to patients receiving infusions of neuromuscular-blocking agents. 7) We make no recommendation concerning the use of one measure of consistent weight over another when calculating neuromuscular-blocking agent doses in obese patients. 8) We make no recommendation on the use of neuromuscular-blocking agents in pregnant patients. 9) We make no recommendation on which muscle group should be monitored in patients with myasthenia gravis receiving neuromuscular-blocking agents. Finally, in situations in which evidence was lacking or insufficient but expert consensus was unanimous, the Task Force developed six good practice statements. 1) If peripheral nerve stimulation is used, optimal clinical practice suggests that it should be done in conjunction with assessment of other clinical findings (e.g., triggering of the ventilator and degree of shivering) to assess the degree of neuromuscular blockade in patients undergoing therapeutic hypothermia. 2) Optimal clinical practice suggests that a protocol should include guidance on neuromuscular-blocking agent administration in patients undergoing therapeutic hypothermia. 3) Optimal clinical practice suggests that analgesic and sedative drugs should be used prior to and during neuromuscular blockade, with the goal of achieving deep sedation. 4) Optimal clinical practice suggests that clinicians at the bedside implement measure to attenuate the risk of unintended extubation in patients receiving neuromuscular-blocking agents. 5) Optimal clinical practice suggests that a reduced dose of an neuromuscular-blocking agent be used for patients with myasthenia gravis and that the dose should be based on peripheral nerve stimulation with train-of-four monitoring. 6) Optimal clinical practice suggests that neuromuscular-blocking agents be discontinued prior to the clinical determination of brain death. (*Crit Care Med* 2016; 44:2079–2103)

Key Words: acute respiratory distress syndrome; asthma; brain death; end of life; myasthenia gravis; neuromuscular-blocking agents; obesity; sedation; therapeutic hypothermia

This document is an update of the previous two guidelines for the use of neuromuscular-blocking agents (NMBAs) in the critically ill adult patient, published in 1995 (1) and 2002 (2). The previous guidelines focused on 1) indications for the use of NMBA, 2) recommendations on specific drugs, and 3) attenuation, if not prevention, of the major complications and adverse effects associated with the use of NMBAs in the critically ill adult patient. This document incorporates new data on the basic science and clinical use of NMBAs in the ICU (3, 4). NMBAs have new uses, such as for attenuation of shivering associated with therapeutic hypothermia in survivors of cardiopulmonary resuscitation (5) and in the treatment of patients with early acute respiratory distress syndrome (ARDS). However, the use of NMBAs has decreased, due to clinician concerns about adverse effects of NMBAs, including ICU-acquired weakness and prolonged duration of mechanical ventilation, thrombosis and thromboembolism, and patient awareness during paralysis (6). After decades of experience with these medications, we recognize that various patient populations have differing responses to NMBAs or require the use of specific monitoring protocols when receiving NMBAs.

The current guidelines have expanded upon the previous two guidelines to include information on the indications and recommendations for use of NMBAs, as well as more information on the nursing management of the critically ill adult receiving NMBAs, on mechanical ventilation management for patients receiving NMBAs, on techniques and therapies to decrease complications and adverse effects related to the use of NMBAs, and on specific patient populations that may benefit from NMBAs.

Most importantly perhaps, in contrast with previous versions of these guidelines, we used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

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methodology to summarize data, assess quality of evidence, and determine the strength of the recommendation when appropriate.

The recommendations are not absolute requirements, and therapy should be tailored to individual patients taking into account patients' values or preferences, site or specific clinician expertise, and equipment availability in a particular ICU. The use of NMBAs requires an appropriate protocol that includes, but is not limited to, management of mechanical ventilation, analgesia, sedation, nursing care, and point-of-care equipment to monitor the degree of neuromuscular blockade. It is possible that individual recommendations based on evidence from a specific patient population may not be generalizable to a larger critical care population. We have factored these considerations into our recommendations and have described important subgroup considerations when deemed appropriate. The release of data from ongoing studies and from future research trials may stimulate the Guidelines Update Committee of the American College of Critical Care Medicine to revise these clinical practice guidelines, but, until such time, guideline application by clinicians should always be modified based on new evidence, as it becomes available.

TARGET PATIENT POPULATION FOR GUIDELINES

These guidelines are targeted, in general, to clinicians who treat adults who are patients in medical and surgical ICUs, with additional information provided, when relevant, on the use of NMBAs in specific patient populations. Data on the use of NMBAs in critically ill neonates, infants, children, and adolescents will not be addressed in this document, although, in a few circumstances, we have reviewed the results of clinical trials in which NMBAs were studied in pediatric patients if the results of those trials were applicable to adult patients.

METHODS

The Guideline Task Force comprised clinicians from North America who are members of the Society of Critical Care Medicine and who have a specific interest in the topic and the guideline process. The Task Force also included a clinician/health-research methodologist (B.R.) from McMaster University who has expertise in evidence synthesis and the GRADE guideline-development process and a medical writer/editor with extensive experience in conducting literature searches (C.F.M.). Task Force members developed a list of clinical questions regarding the use of NMBAs in critically ill adults in the ICU and grouped these questions into five categories: indications for and management of the use of NMBAs; monitoring of NMBAs and sedation; nursing management of the patient receiving an NMBA; adverse events associated with the use of NMBAs in the ICU; and special considerations on the use of NMBAs in specific patient populations. We assigned Task Force members to address each of these categories. Relevant literature was compiled from databases (MedLINE, OVID, Clinicaltrials.gov, CINAHL, Cochrane Central Database, and Medwatch), search engines (PubMed and Google Scholar), reference lists from retrieved publications, and the expertise of the authors. Searches were conducted in November 2012 and included the timeframe of 2001 to November 22, 2012 (to capture literature published since the previous guidelines were created) using the following terms: *neuromuscular blocking agents*, *neuromuscular blockers, cisatracurium, atracurium, rocuronium, vecuronium, pancuronium, succinylcholine,* and *sugammadex*, each alone and in combination with *sedation, analgesia, monitoring, electroencephalogram (EEG), Bispectral Index (BIS), shock, oxygen delivery, oxygen consumption, pregnancy, kidney failure, acute kidney injury,* and *intensive care unit*. Where no data from ICU studies existed to answer a specific question, task force members used the results of studies conducted in the operating room to guide the recommendation, acknowledging the potential decrease in quality of evidence due to indirectness. Randomized controlled trials (RCTs) were preferentially used to formulate evidence summaries. However, if adequate evidence for a specific outcome was not present, we used the best available evidence, including observational studies, to support recommendations.

The Task Force used RevMan2 software (7) to perform pooled analysis of data when appropriate. Published results of clinical trials were used for analysis; abstracts and unpublished studies were excluded. The Task Force used the GRADE system to rate the quality of evidence and strength of the recommendation for each clinical practice question (8). The Task Force selected outcomes of interest for each question based on GRADE methodology (9). The GRADE system classifies the quality of the aggregate body of evidence for each question and for each outcome as high, moderate, low, or very low.

The evidence was evaluated using the following criteria: 1) study design and rigor of its execution (i.e., individual study risk of bias), 2) the extent to which the evidence could be applied to patients of interest (i.e., directness) 3) the consistency of results, 4) the analysis of the results (i.e., precision), and 5) whether there was a likelihood of publication bias. The following three factors, if present, lead to potential upgrading of the quality of evidence: 1) a strong or very strong association between an intervention and the observation of interest, 2) a highly statistically significant relationship between dose and effect, and 3) a plausible confounding variable that could explain a reduced effect or could explain an effect if one was not anticipated. The overall strength of a recommendation was determined by the sum of the quality of evidence, the outcomes studied and their relative importance to patients, the balance between desirable and undesirable effects, the cost, and the feasibility of implementation of the intervention for each individual question. Based on these factors, recommendations were classified as strong or weak. We used the phrasing "we recommend" for strong recommendations and "we suggest" for weak recommendations. Throughout the guideline-development process, we emphasized patient safety and considered this factor in the recommendation for each intervention. If the risk associated with an intervention limited the potential for benefit, or if the evidence for benefit was not strong enough to accept the potential risks, then the recommendation was changed to "weak." It is also important to mention that individual patient or ICU circumstances may influence the applicability of a specific

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recommendation and that even strong recommendations do not necessarily represent standards of care, depending on resources, culture, or individual clinical situations.

In general, if other factors are equal, the higher the quality of the supporting evidence, the more likely it is for the recommendation to be strong. Conversely, if the quality of the evidence is low or very low, a weak recommendation is more likely. Strong recommendations based on low or very low quality evidence are uncommon. There were some clinical questions that the Task Force members thought deserved strong recommendations despite limited evidence and the likelihood existed to support them (e.g., patients receiving NMBAs should have analgesics and anxiolytics administered). In situations such as this, when no clear alternative exists (e.g., not giving analgesics, anxiolytics, or both) and there was consensus among the Task Force members, a strong recommendation was offered with the justification of a "good practice statement" without discrete assessment of the quality of evidence. Clinical questions that lacked adequate evidence to address relevant outcomes of interest and for which the Task Force felt too much uncertainty existed to offer recommendations were clearly indicated with "no recommendation."

Subgroup members wrote the introduction and background for each of the five categories and the recommendations for each of the clinical questions, along with the associated rationale and evidence summary. Evidence profiles were used to present pooled analysis whenever possible. The entire Task Force subsequently reviewed each of the categories and questions. Members' suggestions for improvement and comments were taken into account by each of the subgroups, who were then provided the opportunity to change their recommendations before the entire Task Force subsequently met and evaluated each statement. The wording of individual recommendations, including strength of the recommendations and the quality of evidence upon which the recommendations were based, were agreed upon through consensus of Task Force members after discussing the relevant factors described above. Once the recommendations were compiled, each member again reviewed the guideline document and provided input until consensus was achieved on each of the questions of interest.

Conflicts of Interest

All conflicts of interest were disclosed annually. No Task Force members reported any conflicts of interest during the preparation of the guidelines. External peer review was provided through the Board of Regents of the American College of Critical Care Medicine, the Council of the Society of Critical Care Medicine, the Board of Directors of the American Society of Health-System Pharmacists, and the editorial board of *Critical Care Medicine.*

BACKGROUND

The Neuromuscular Junction

The neuromuscular junction is formed by an unmyelinated presynaptic motor axon in close proximity (30 nm) to a specialized portion of the muscle. Large motor nerve axons divide within skeletal muscle into 5 to 100 smaller nerve fibers that innervate a single myofibril, forming a motor unit (10). Each of the smaller nerve fibers forms a bouton as it terminates within the neuromuscular junction that contains approximately one-half million acetylcholine-filled vesicles. Across the 30-nm gap is the sarcolemma of the muscle fiber, which has folds or invaginations containing as many as 10,000 acetylcholine receptors/μm^2 (11). When a motor neuron is activated, Ca^{++} enters the nerve terminal bouton activating a mechanism by which vesicles within the axon fuse with the neuronal membrane and release acetylcholine into the synaptic cleft. In the cleft, the acetylcholine diffuses to the sarcolemma, binds to a nicotinic receptor opening ligand-gated ion channels, which allows the flow of Na^+ into and K^+ out of the myofibril raising the electrical potential of the adjacent membrane (12). As more receptors are activated, additional membrane is depolarized, Ca^{++} enters the myofibril and stimulates the binding of actin to myosin, and the muscle contracts (13). In addition to the nicotinic receptor, muscarinic acetylcholine receptors on the presynaptic side of the neuromuscular junction, when stimulated by acetylcholine molecules, inhibit the release of more neurotransmitter (14).

Neurophysiology of the Neuromuscular Junction. When the vesicles fuse to the membrane of the nerve terminal, the amount of acetylcholine released into the cleft is several times greater than the amount required to activate nicotinic receptors on the myofibril (15).

The nicotinic receptor in adults is composed of 2 α_1, 1 β_1, 1δ, and 1ε subunits. When one molecule of acetylcholine binds to one of the α_1 subunits, it induces a conformational change at the second α_1 subunit, which increases the affinity of the second α_1 subunit for a second molecule of acetylcholine (16).

Acetylcholinesterase. Acetylcholinesterase is an enzyme present in the synaptic cleft that hydrolyzes acetylcholine to choline and acetate, thereby inactivating acetylcholine and terminating muscle contraction (17). Neostigmine, pyridostigmine, and edrophonium all inhibit acetylcholinesterase; the concentration of acetylcholine increases and competes with an NMBA at the nicotinic receptor, thereby antagonizing NMBA action (4). The organophosphate pesticides and the chemical nerve agents (e.g., sarin) bind more permanently to and inhibit acetylcholinesterase, producing weakness, fasciculations, and paralysis due to the unopposed actions of acetylcholine on the nicotinic receptor (18).

Up-Regulation and Down-Regulation. Hypersensitivity and resistance to NMBAs are observed in a number of clinical states. Changes in sensitivity to NMBAs may be due to either 1) an increase in the number or sensitivity of receptors (up-regulation) or 2) a decrease in the number or sensitivity of the receptors (down-regulation) (19). Up-regulation increases the sensitivity to acetylcholine and decreases sensitivity to NMBAs. Up-regulation can lead to release of K^+ from cells after succinylcholine administration in patients with motor neuron lesions, burns, muscle atrophy from disuse, severe trauma or infection and in those who have received NMBAs over a prolonged period in the ICU.

Down-regulation of the nicotinic receptors is manifested by increased sensitivity to NMBAs. In patients with myasthenia gravis, antibodies to the acetylcholine receptor cause the

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neuromuscular junction to function as though fewer receptors are present, leading to enhanced sensitivity to the effects of NMBAs.

Mechanism of Action of NMBAs

The depolarizing NMBA succinylcholine is an agonist at nicotinic receptors; the ion-gated channels open and remain open in the presence of succinylcholine. The initial depolarization is seen clinically as fasciculations and then as paralysis (20). The duration of effect is only 3 to 5 minutes; therefore, succinylcholine is used for short procedures, such as tracheal intubation. Because succinylcholine is not used for prolonged blockade in the ICU, it will not be discussed further.

Nondepolarizing NMBAs are competitive antagonists at nicotinic receptors, binding to the receptor for a longer period of time and preventing acetylcholine from binding to the receptor, which results in prolonged neuromuscular blockade (21). The two classes of nondepolarizing NMBAs—the benzylisoquinolinium and the aminosteroid compounds—have one or more positively charged quaternary ammonium groups in their chemical structure, resulting in an ionized water-soluble drug at physiologic pH. These NMBAs are lipophobic; thus, their ability to cross the blood-brain barrier is limited. The volume of distribution, plasma clearance, and drug elimination are most affected by the presence of renal or hepatic dysfunction. Please refer to any of the standard pharmacology textbooks for a more in-depth discussion of the pharmacokinetic and pharmacodynamics of the currently available NMBAs. Many drugs, elements, conditions, and diseases affect the duration of activity of NMBAs; diuretics, antiarrhythmic agents, aminoglycosides, magnesium, lithium, hypokalemia, hypothermia, acidosis, and myasthenia gravis all increase the potency of nondepolarizing NMBAs (22). The potency of an NMBA is inversely related to its speed of onset (i.e., the lower the potency of a drug, the faster the onset of neuromuscular blockade following administration of an NMBA) (23) Patients with myasthenia gravis are especially sensitive to the effects of NMBAs, and patients with burn injuries are resistant to the effects of NMBAs because of the proliferation (up-regulation) of nicotinic receptors on the sarcolemma.

Monitoring the Action of NMBAs

The dose-response to an NMBA is often monitored clinically with peripheral nerve stimulation (PNS); please refer to any of the basic anesthesiology textbooks for a more thorough description of PNS for monitoring the depth of neuromuscular blockade. In the ICU, PNS is used to deliver four stimuli at 0.5-second intervals, referred to as a train of four (TOF), with assessment of the response of the innervated muscle to the four stimuli. With an increasing dose of an NMBA, the twitches decrease in force. The fourth twitch (T_4) is lost first, followed by the third (T_3), the second (T_2), and finally the first twitch (T_1); if all four twitches are lost, then this is referred to as a TOF of 0 (24). If a single bolus dose of NMBA is given, the twitches return in the reverse order as the drug is metabolized, with T_1 appearing first, followed by T_2, and so on until all four twitches return. Four twitches per se do not indicate return of complete muscle strength. If all four twitches are present, then a TOF ratio (a calculation derived from dividing the amplitude of the fourth twitch response by that of the first twitch response) of 0.9 is currently the standard used to indicate return of muscle strength sufficient for patients to protect their airway and maintain spontaneous ventilation (25) The action of NMBAs can be pharmacologically reversed, which is commonly done in the operating room but rarely in the ICU; please refer to any of the basic anesthesiology textbooks for a description of neuromuscular blockade reversal.

Effects of NMBAs Outside the Neuromuscular Junction

Most of the effects of NMBAs that occur outside the neuromuscular junction are cardiac in nature and are due to histamine release and ganglionic or muscarinic stimulation manifested by vagolytic actions, ganglionic blockade, or sympathetic stimulation. Although pancuronium and atracurium have the greatest potential to cause adverse cardiac effects, all NMBAs may cause these cardiac effects (26).

Cross-Reactivity. All NMBAs potentially react with muscarinic receptors, which can lead to adverse effects, most notably cardiac in origin. In addition, activation of muscarinic type 2 (M_2) receptors can result in bronchodilation, whereas activation of muscarinic type 3 (M_3) receptors can produce the opposite result (i.e., bronchospasm) (27).

Pancuronium exhibits significant blockade at muscarinic M_2 receptors in the parasympathetic nervous system and at presynaptic muscarinic receptors in the peripheral sympathetic nervous system, with the former resulting in vagolytic action and the latter increasing norepinephrine release, both of which cause tachycardia. Rocuronium, more so than vecuronium, has affinity for muscarinic receptors at other sites within the parasympathetic nervous system. The remaining nondepolarizing agents have even weaker affinities for the muscarinic receptor (28–30). The most significant manifestation of these effects is tachycardia; bronchoconstriction is not reported with any frequency, probably because of the equal antagonism between pulmonary M_2 receptors and M_3 receptors (31).

Histamine Release. Originally seen with curare, histamine release is predominantly observed with the use of atracurium (32, 33). Pancuronium causes the release of minimal amounts of histamine (32) and cisatracurium releases virtually none (28). Isolated reports of vecuronium-induced histamine release have not been confirmed, even with high doses (33–36). Hypotension and flushing have been reported after vecuronium administration and may be related to decreased histamine catabolism via inhibition of histamine *N*-methyltransferase (37); histamine release has not been observed with the use of rocuronium (33, 38). Because histamine release is associated with large doses and rapid NMBA administration, it is less likely to occur with the doses typically administered in the ICU. Histamine release, which is typically a direct action of the NMBA on mast cells rather than via IgE-mediated anaphylaxis (28, 39), can be attenuated by slow injection over

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1–3 minutes or by pretreatment with histamine H_1- and H_2-receptor antagonists (40, 41).

Vagolytic Actions. Vagolytic actions are most prominent with pancuronium (28, 29) and result in mild and dose-dependent tachycardia (32). Most clinicians avoid pancuronium in patients with coronary artery disease because of the risk of tachycardia-induced myocardial ischemia (42–45), ventricular ectopy, and cardiovascular collapse (46). Rocuronium also has an affinity for vagal receptors, thereby inhibiting vagal activity (29, 47), and can cause tachycardia in up to 30% of patients (27). Theoretically, this is also true of vecuronium, but to a much lesser degree, and there is little reference to it in the literature (30, 48). Clinically, vecuronium has relatively little effect on the heart (49–52); bradycardia has been reported (53, 54), possibly related to vagal stimulation (47), but a causal relationship has not been established (49). Cisatracurium may also block M_2 vagal receptors, but tachycardia does not appear to be clinically important (55–57).

Ganglionic Blockade. Ganglionic blockade was seen with curare (no longer available), as well as with all other NMBAs if given in large enough doses; pancuronium has weak ganglionic activity at recommended doses (28). Atracurium, cisatracurium, vecuronium, and rocuronium are even more selective and in recommended doses cause minimal, if any, ganglionic blockade (28, 56, 58–60). The effect on heart rate depends on the patient's dominant tone, which, at rest, is generally vagal (M_2 muscarinic), thus resulting in tachycardia (61).

Sympathetic, Ganglionic, or Muscarinic Stimulation. Sympathetic stimulation from pancuronium releases norepinephrine, causing tachycardia (32, 62). Vecuronium causes bradycardia via ganglionic or muscarinic stimulation of the vagus nerve (32, 63).

INDICATIONS FOR THE USE OF NMBAs

Acute ARDS. I. Among adult patients with ARDS, should an NMBA be administered to improve survival?

Recommendation: We suggest that an NMBA be administered by continuous IV infusion early in the course of ARDS for patients with a Pa_{O_2}/F_{IO_2} less than 150 (weak recommendation, moderate quality of evidence; see evidence profile) (**Table 1**).

Rationale: Three multicenter randomized trials (n = 431 patients) have assessed the role for NMBAs in patients with ARDS (64–66). All three trials were originated from the

TABLE 1. Evidence Profile: Neuromuscular-Blocking Agent for Acute Respiratory Distress Syndrome Patients

Quality Assessment						
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations
Mortality (follow-up: 90 d)						
3	Randomized trials	Not seriousa	Not seriousb	Not serious	Not serious	None
Mortality (follow-up: 28 d)						
3	Randomized trials	Not serious[a]	Not serious	Not serious	Not serious	None
ICU mortality						
3	Randomized trials	Not serious[a]	Not serious	Not serious	Not serious	None
Barotrauma (assessed with new pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele)						
3	Randomized trials	Seriousc	Not serious	Not serious	Not serious	None
ICU-acquired weakness (assessed with Medical Research Council scale)						
3	Randomized trials	Very serious [4]	Not serious	Not serious	Serious [5]	None
Duration of mechanical ventilation						
3	Randomized trials	Serious[c]	Not serious	Not serious	Serious [5]	None

RR = relative risk.

[a]Blinding was incomplete; however, this was not considered a source of bias for the outcome of mortality.

[b]I^2 was 0% and results were robust in sensitivity analysis.

[c]Incomplete blinding in included trials.

[d]Rated down two levels for incomplete blinding and ascertainment bias (limited assessment in two of the included trials).

[e]Wide CIs.

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same group of investigators, and each evaluated early use of 48-hour cisatracurium infusions among adult patients with ARDS, mechanically ventilated using volume assist-control mode ventilation with low tidal volumes in ICUs in France (one study included 20 centers). All studies showed significant improvements in oxygenation in patients receiving NMBAs, compared with control groups. Pooling results across trials showed that a 48-hour cisatracurium infusion consistently reduced the risk of death at 28 days and at hospital discharge, reduced the risk of barotrauma, and did not increase the risk of ICU-acquired weakness (67). The quality of evidence across outcomes was moderate, with the primary limitation being the inability to mask caregivers' knowledge of treatment; otherwise, results (for mortality) were large, precise, and consistent across studies. Assuming a baseline mortality rate of 45% for ARDS patients, eight patients would have to be treated with a 48-hour cisatracurium infusion to save one additional life. In a May 2014 publication in the Chinese literature (68), 18 months after our initial literature search was conducted, investigators described the results of their study in which 24 of 48 patients with ARDS and sepsis received vecuronium and 24 assigned to the control group did not. Compared with the control group, the group that received vecuronium had decreased mortality, with an improvement in several other markers of morbidity. The results are consistent with our recommendation and would not have changed our conclusions, the strength of the recommendation, or the quality of the evidence.

The mechanism of benefit of neuromuscular blockade in ARDS remains uncertain; however, neuromuscular blockade prevents ventilator asynchrony and may therefore decrease, to an extent, airway pressures and lung stress. In the largest trial reported to date, an additional bolus of study drug was administered when plateau airway pressure exceeded 32 cm H_2O, in keeping with various randomized trials and systematic reviews suggesting that other interventions to reduce plateau airway pressures can prevent ventilator-associated lung injury and decrease ARDS mortality (69, 70). Current evidence might be extrapolated to support the use of NMBA therapy in adults with ARDS whenever plateau airway pressures exceed 30–35 cm H_2O.

Neuromuscular blockade has been linked to increased risk of ICU-acquired weakness, and this concern is one of the deterrents to its use in patients with ARDS. The most recent and largest trial, which used the validated Medical Research

No. of Patients		Effect			
NMBA Administration	Not Administering NMBA	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
76/223 (34.1%)	98/208 (47.1%)	RR, 0.72 (0.58–0.91)	132 fewer per 1,000 (from 42 fewer to 198 fewer)	⊕⊕⊕⊕ High	Critical
57/223 (25.6%)	81/208 (38.9%)	RR, 0.66 (0.5–0.87)	132 fewer per 1,000 (from 51 fewer to 195 fewer)	⊕⊕⊕⊕ High	Critical
70/223 (31.4%)	93/208 (44.7%)	RR, 0.7 (0.55–0.89)	134 fewer per 1,000 (from 49 fewer to 201 fewer)	⊕⊕⊕⊕ High	Critical
9/223 (4.0%)	20/208 (9.6%)	RR, 0.43 (0.2–0.9)	55 fewer per 1,000 (from 10 fewer to 77 fewer)	⊕⊕⊕○ Moderate	Important
73/223 (32.7%)	62/208 (29.8%)	RR, 1.08 (0.83–1.41)	24 more per 1,000 (from 51 fewer to 122 more)	⊕○○○ Very low	Important
223	208	–	Mean difference, 1.21 lower (4.23 lower to 1.81 higher)	⊕⊕○○ Low	Important

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Council score (71), found identical risks of ICU-acquired weakness at day 28 and at ICU discharge whether or not patients received NMBAs. In keeping with the findings from earlier studies, there was a statistically significant increase in ventilator-free days at 28 days with cisatracurium, which argues against an increased risk of ICU-acquired weakness. Future studies could use measures of neuromuscular function over a more protracted period of time and supplement these assessments with electrophysiologic testing.

There have been no trials of NMBAs other than cisatracurium in patients with ARDS, so whether the results of the above-mentioned studies are unique to cisatracurium is unknown. Likewise, whether longer or shorter infusions of NMBAs would provide additional benefit or change the prevalence of ICU-acquired weakness is unknown.

Status Asthmaticus. II. Among adult patients with status asthmaticus who are intubated and mechanically ventilated, is there a role for the administration of an NMBA to improve survival or hypoxemia?

Recommendation: We suggest against the routine administration of an NMBA to mechanically ventilated patients with status asthmaticus (weak recommendation, very low quality of evidence; see evidence profile) (**Table 2**).

We suggest a trial of an NMBA in life-threatening situations associated with profound hypoxemia, respiratory acidosis, or hemodynamic compromise when other measures such as deep sedation fails. (Weak recommendation, very low quality of evidence)

Rationale: In three retrospective studies of adults ($n = 382$) requiring mechanical ventilation for severe asthma, only six patients (1.6%) died after ICU admission (72–74). In light of the infrequency of death, conducting a prospective study to assess survival benefit would be difficult. Lacking evidence of efficacy, adverse effects of neuromuscular blockade are an important consideration for clinical practice. These three studies, plus an additional retrospective study (total $n = 481$ patients) have investigated the association between NMBA administration and ICU-acquired weakness among adult patients who required mechanical ventilation for the management of acute asthma (72–75) (Table 2). These studies consistently found a positive association between the use of NMBAs and ICU-acquired weakness, as well as between NMBA administration and longer duration of mechanical ventilation. These findings suggest that neuromuscular blockade is associated with more harm than benefit in the routine management of adults with status asthmaticus. However, all studies had a high risk of bias (including group imbalances at baseline, varied high-dose corticosteroid administration, retrospective data capture), and the overall quality of evidence was very low.

On rare occasions, severe dynamic hyperinflation in the setting of status asthmaticus results in situations that may be imminently life threatening, such as profound and persistent hypoxemia, respiratory acidosis, refractory hypotension, or all 3. There are no comparative studies addressing the effect of NMBAs on mortality in these rare situations. Evidence from case series and clinical experience suggest that neuromuscular blockade can improve oxygenation in the setting of severe refractory hypoxemia (failure to adequately oxygenate with an F_{IO_2} of 1.0) and improve hemodynamics in the setting of severe dynamic hyperinflation causing hemodynamic compromise (72–74). Therefore, in extreme life-threatening situations in which deep sedation is insufficient to manage profound hypoxemia or dynamic hyperinflation, the potential benefit (survival) likely outweighs the potential harm.

III. Among adult patients with acute brain injury and elevated intracranial pressure (ICP), does the administration of an NMBA improve survival?

Recommendation: We make no recommendations as to whether neuromuscular blockade is beneficial or harmful when used in patients with acute brain injury and raised ICP (insufficient evidence).

Rationale: Two observational studies have investigated the ability of neuromuscular blockade to attenuate the rise

TABLE 2. Evidence Profile: Neuromuscular-Blocking Agent for Asthma Patients

Quality Assessment						
No. of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**
Mortality						
1	Observational study	Very serious[a]	Not serious	Not serious	Very serious[b]	None
Clinically significant weakness (assessed with clinical examination, EMG, or both)						
4	Observational studies	Very serious[c]	Seriousd	Serious[e]	Not serious	None

NMBA = neuromuscular-blocking agent, RR = relative risk.

[a]Retrospective observational study.

[b]Very wide CIs that cross unity. Low number of events.

[c]All three studies were retrospective observational studies.

[d]$I^2 = 70\%$.

[e]One of the studies (Kesler) the control group received some NMBA but much less and for a much shorter duration.

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in ICP and the fall in cerebral perfusion pressure (CPP) that can accompany tracheal suctioning in brain-injured patients with elevated ICP (76, 77). In a prospective crossover study of 18 sedated neurosurgical patients (Glasgow Coma Scale score of < 7), vecuronium and atracurium were equally effective in mitigating cough and changes in ICP and CPP during tracheal suctioning (76). A smaller study found that the combination of opioids and NMBA therapy reduced suctioning-induced ICP elevation more than did opioids alone (77). These studies are few in number, small in size, observational in design, and focused on physiologic changes, rather than on clinically important outcomes. Nevertheless, they provide evidence that pretreatment with an NMBA may mitigate procedure-related increases in ICP.

All currently available NMBAs appear to have minimal effects on ICP and systemic blood pressure in most patients when administered as a single dose (78–80). A few patients appear to be sensitive to the vagolytic (pancuronium, rocuronium) or histamine-releasing (atracurium) effects of NMBAs (81), but patients who are sensitive to these effects could be managed with another agent if such problems are noted. Therefore, NMBA choice should be based on patient-specific (e.g., comorbidities) and drug-specific (e.g., onset, offset, route of elimination) factors.

In contrast, two retrospective evaluations of prospective data (82, 83) have investigated NMBAs for the management of intracranial hypertension, with a focus on clinically important outcomes. One study of 514 patients with traumatic brain injury and a Glasgow Coma Scale score of less than 8 found that patients treated with early neuromuscular blockade for more than 12 hours had a higher risk of pneumonia and having a prolonged ICU stay than patients treated with NMBAs for less than 6 hours, even after controlling for age, preresuscitation Glasgow Coma Scale and hypotension, CT findings, and single- versus multiple-system trauma. There was no difference in time with elevated ICP. The use of NMBAs was associated with longer length of stay, more pneumonia, and a higher proportion of survivors with persistent vegetative state or severe disability (82). A similar retrospective evaluation (n = 326) found no difference in mortality or length of stay between patients with traumatic brain injury who did, versus did not, receive an NMBA (83). In summary, although these two studies provide important preliminary data from investigations regarding the role for NMBAs in the management of intracranial hypertension, they do not provide support for evidence-based recommendations to guide clinical practice. The within-study and between-study findings are inconsistent, the studies are retrospective in design, and both studies included a spectrum of patients with mild, moderate, and severe elevations in ICP.

Therapeutic Hypothermia. This guideline does not address neuromuscular blockade used for hypothermia restricted to surgical procedures (e.g., cardiopulmonary bypass), unless the information obtained from studies of such procedures was relevant to therapeutic hypothermia in the ICU.

IV. For patients undergoing therapeutic hypothermia/targeted temperature management (e.g., to improve neurologic outcome following cardiac arrest), should neuromuscular blockade be used to improve survival or secondary outcomes?

Recommendation: We make no recommendation on the routine use of NMBAs for patients undergoing therapeutic hypothermia following cardiac arrest (insufficient evidence).

We suggest that NMBAs can be used to manage overt shivering in therapeutic hypothermia (weak recommendation, very low quality of evidence).

Rationale: The two original studies that established a role for therapeutic hypothermia following cardiac arrest included pancuronium and vecuronium administration, respectively, in combination with sedatives to prevent shivering during the initiation of hypothermia (84, 85). NMBA therapy, itself, may be neuroprotective in this setting by reducing shivering and the associated increased oxygen consumption in the periphery, and time to goal temperature. On the other hand, NMBA therapy may cause harm by obscuring evidence of seizure activity.

No. of Patients		Effect			
NMBA Administration	Not Administering NMBA	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
4/55 (7.3%)	2/46 (4.3%)	RR, 1.67 (0.32–8.72)	29 more per 1000 (from 30 fewer to 336 more)	⊕○○○ Very low	Critical
59/250 (23.6%)	11/214 (5.1%)	RR, 4.81 (2.52–9.17)	196 more per 1000 (from 78 more to 420 more)	⊕○○○ Very low	Critical

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No trials have prospectively evaluated the impact of NMBAs on hypothermia outcomes. Available data are limited to a post hoc analysis of a prospective observational study of 111 adult patients who had experienced a cardiac arrest and who subsequently underwent therapeutic hypothermia (5). The outcome of 18 patients who received an NMBA for a minimum of 24 hours was compared with the outcome of 93 patients who did not receive an NMBA. Those receiving at least 24 hours of NMBA therapy were found to have had a better prognosis at baseline, related to etiology of the cardiac arrest. This group also had improved in-hospital survival (78% vs 41%; $p = 0.004$), even after adjustment for a large number of potential baseline confounders (odds ratio [OR] = 7.23; 95% CI = 1.56–33). Furthermore, these statistically significant findings were consistent in a later reanalysis of the data that compared the outcomes of patients who received NMBAs for a minimum of 24 hours with those who did not receive any NMBA (5, 86). Important limitations of this study are the small sample size, evidence of selection bias, and the additional possibility of selective use of cointerventions. Another retrospective study with similar limitations compared nonrandomized use of cisatracurium and vecuronium for neuromuscular blockade. In multivariable regression analysis, cisatracurium was the only independent predictor of survival with good in-hospital neurologic outcome ($p = 0.014$); however, there was no direct comparison of findings among patients receiving the two alternative agents, and far fewer patients received vecuronium than patients received cisatracurium (36 vs 60), limiting the power to detect a similar benefit of vecuronium therapy (87). Baseline differences in presenting cardiac rhythms likely impacted the investigators' ability to discern a difference related to supportive therapy.

Although the critical outcomes of interest in addressing the role for NMBA in this setting are survival and neurologic recovery, time to target temperature and stability of target temperature are other important considerations. No studies have demonstrated the superiority of NMBA therapy over the use of sedatives or opioids for preventing shivering with respect to these outcomes. However, related research in other populations may be extrapolated to the setting of therapeutic hypothermia following cardiac arrest. In an open-label randomized study of 20 patients following hypothermic cardiopulmonary bypass, vecuronium (0.1 mg/kg bolus followed by 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 4 hr) eliminated shivering in 100% of patients, compared with 50% of patients who received meperidine (25 mg every 15 min until no shivering was observed or a total dose of 75 mg was administered) ($p < 0.05$) (88). Vecuronium eliminated shivering without lowering systolic blood pressure, as occurred with meperidine ($p < 0.02$), and eliminated shivering in the five patients whose shivering was uncontrolled by meperidine. As was noted in nonrandomized studies involving pancuronium for the prevention of shivering in patients following cardiopulmonary bypass (89, 90), vecuronium administration was associated with consistent and statistically significant decreases in oxygen consumption and Co_2 production, effects not seen with opioids.

V. If neuromuscular blockade is used during therapeutic hypothermia, should PNS be used to monitor the degree of block?

Recommendations: We make no recommendation on the use of PNS to monitor degree of block in patients undergoing therapeutic hypothermia (insufficient evidence).

We recommend that, if PNS is used, it be done in conjunction with assessment of other clinical findings (e.g., triggering of the ventilator and degree of shivering) to assess the degree of neuromuscular blockade in patients undergoing therapeutic hypothermia (good practice statement).

Rationale: There is no evidence that the use of PNS to monitor the degree of neuromuscular blockade in conjunction with therapeutic hypothermia leads to improved patient outcomes. The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care recommend that the depth of neuromuscular blockade be monitored by assessing the response to PNS (91). The Guidelines published in 2015 make no reference to the use of NMBAs to achieve targeted temperature management and therefore, no reference to the use of PNS. However, in ICUs in which NMBAs are used during induction of mild hypothermia, studies have shown that cooling of the *adductor pollicis* muscle reduces twitch tension in response to PNS (92). Furthermore, studies in hypothermic patients undergoing anesthesia for extirpation of acoustic nerve neuromas, compared with those who were normothermic, demonstrated substantial variation in the number of posttetanic twitches and in the TOF response measured in adductor pollicis muscles (93). Therefore, PNS to monitor the degree of neuromuscular blockade in patients undergoing therapeutic hypothermia may be unreliable and provide misleading information, as has been shown in a case report (94). If PNS is used, it should be used in conjunction with other clinical parameters (e.g., elimination of shivering) to assess degree of blockade.

VI. In patients undergoing therapeutic hypothermia, should a protocol that includes guidance on NMBA administration be used?

Recommendation: We recommend the use of a protocol that includes guidance on NMBA administration in patients undergoing therapeutic hypothermia (good practice statement).

Rationale: When NMBAs are used in patients undergoing therapeutic hypothermia following cardiac arrest, their use should be guided by a comprehensive protocol. No controlled trials compare protocol- with nonprotocol-guided therapeutic hypothermia, but the lack of such trials is not surprising given the complex nature of the care needed for these patients. In light of the need for appropriate patient selection and the unique monitoring and complicated management considerations that are necessary during the induction, maintenance, and rewarming phases of hypothermia, protocols are recommended to prevent potentially life-threatening problems (e.g., cardiovascular instability, clotting, electrolyte imbalance, infectious complications, and altered drug disposition) associated with the inappropriate implementation of therapeutic hypothermia. The use of such protocols does not guarantee

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positive patient outcomes because it takes time for hospital personnel to gain experience with protocol implementation. In fact, it has been postulated that the inexperience of some investigators with therapeutic hypothermia may account for interinstitutional differences in the efficacy of this intervention in controlled trials (95–97) and may limit the generalizability of the results of these trials (98).

Hemodynamic Indications. VII. In patients who are mechanically ventilated, does neuromuscular blockade improve the accuracy of intravascular-volume assessment (i.e., respiratory-induced variations in hemodynamic indexes)?

Recommendation: We make no recommendation on the use of neuromuscular blockade to improve the accuracy of intravascular-volume assessment in mechanically ventilated patients (insufficient evidence).

Rationale: Trends in the respiratory variation of left ventricular stroke volume or of surrogate markers of stroke volume are considered to be reliable parameters for predicting fluid responsiveness in mechanically ventilated patients with no inspiratory or expiratory efforts (99, 100). Surrogates of stroke volume include arterial pulse pressure, left ventricular outflow tract blood flow, and estimates of stroke volume from arterial pulse contour and pulse pressure analyses, as well as from other minimally and noninvasive methods (100). Quantitative measurements are not generally useful because the magnitude of the change in stroke volume is affected by heart rate, properties of the systemic vascular system, tidal volume, and chest wall and lung compliance (99). The validity of tracking trends is also compromised by the prerequisite of a tidal volume of at least 8 mL/kg (101), a condition that may not be safely maintained in patients with ARDS, for example (102). Although the administration of NMBAs to suppress respiratory effort is reported as part of protocols to assess fluid responsiveness by these various techniques (102–105), we found no study comparing the validity of these measurements made with and without neuromuscular blockade.

Sedation and Analgesia. VIII. Do patients receiving NMBAs require sedation and analgesia?

Recommendation: We recommend that optimal clinical practice requires administering analgesic and sedative drugs prior to and during neuromuscular blockade, with the goal of achieving deep sedation (good practice statement).

Rationale: NMBAs have no analgesic or sedating properties. Because assessing pain and anxiety in patients receiving NMBAs is difficult, if not impossible, clinicians rely on vital signs (heart rate and blood pressure) and the presence of diaphoresis and lacrimation to evaluate pain and anxiety; however, these signs are not reliable and lack specificity (106). Analgesic and sedative medications should not be discontinued while the patient is receiving an NMBA. Bolus NMBA therapy, or scheduled discontinuation of continuous NMBA infusions, permits assessment of the adequacy of analgesia and sedation and the need for ongoing paralysis. Because recall of events during paralysis is not uncommon, patients receiving an NMBA may benefit from frequent verbal reassurance.

No trials have evaluated the need for sedation and analgesia in critically ill patients receiving NMBAs, but several studies have reported unintentional awareness. In small case series, patients who had been paralyzed without receiving adequate sedation reported feeling terrified (107) and experiencing overwhelming panic (108). Wagner et al (109) conducted structured interviews with 11 patients who had been paralyzed. Four patients had recall from the time of paralysis and recalled mostly negative events and experiences, such as sleeplessness, discomfort, pain, anxiety, and inconsistent caregiver communication. Single-drug therapy with propofol and inadequate benzodiazepine dosing was linked to patient recall. In a phenomenologic study of 11 critically ill adult trauma patients who required therapeutic neuromuscular blockade, patients compared their feelings of vagueness to dreaming (110). Few patients recalled pain or painful procedures; however, they remembered having nurses and family members provide emotional support and encouragement. The use of effective pain and sedation protocols may have affected the findings. In interviews with 11 patients, Ballard et al (111) identified two themes. The first theme was a sense of transitioning back and forth between reality and the unreal and between life and death. The second theme was loss of control, with subthemes of fighting or being tied down and being frightened. As in other studies, patients recalled elements of their care while paralyzed. In another study, Arnot-Smith and Smith (112) reviewed 231 patient safety incidents from England and Wales between 2006 and 2008 regarding NMBAs administered during general anesthesia and identified 42 incidents (18%) of possible unintentional awareness under general anesthesia; of these, 11 patients explicitly described awareness.

IX. In critically ill patients on continuous infusions of NMBAs, do electroencephalogram-derived parameters (e.g., Bispectral Index [BIS], E-entropy, Cerebral State Index, and Patient State Index) improve sedation assessment?

Recommendation: We make no recommendation concerning the use of electroencephalogram-derived parameters as a measure of sedation during continuous administration of NMBAs (insufficient evidence).

Rationale: Several devices that analyze cortical electroencephalogram and electromyographic signals to assess the depth of sedation (e.g., BIS, Cerebral State Index, Narcotrend, and E-Entropy) have been studied for their application in critical illness. A Cochrane systematic review concluded that BIS-guided anesthesia significantly reduced the prevalence of intraoperative awareness in surgical patients at high risk of developing awareness, compared with standard practice using either clinical signs or end-tidal anesthetic gas as a guide (OR, 0.24; 95% CI, 0.08–0.69) (113). In contrast, a more recent prospective multicenter randomized trial in 5,713 patients undergoing general anesthesia did not find that a protocol incorporating BIS was superior to standard monitoring of end-tidal anesthetic-agent concentration for the prevention of postoperative awareness (114).

Studies in critically ill patients have also produced conflicting results. In patients not receiving NMBAs, clinically acceptable sedation can produce a broad range of values displayed on these devices (115–118). Analysis of a large database of processed electroencephalogram signals of 44 ICU patients

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receiving continuous sedation (but not receiving NMBAs) showed that these devices were unable to discriminate among light, moderate, and deep sedation, and the score was not altered by the administration of boluses of sedative drugs prior to tracheal suctioning (116). In 40 nonparalyzed patients, Arbour et al (119) found extensive overlap of BIS values at each Sedation Agitation Scale category although they observed a positive BIS/Sedation Agitation Scale correlation ($r = 0.252$; $p < 0.001$). In one study, three awake volunteers who were not receiving sedatives or opioids had a significant reduction in BIS score after administration of an NMBA, and the BIS score failed to detect awareness in completely paralyzed subjects (120). Similarly, patients receiving sedation in other studies had a significant reduction in processed electroencephalogram scores following administration of an NMBA (118, 121–124). However, one study found that deeply sedated patients, compared with more lightly sedated patients, did not exhibit a significant change in the processed electroencephalogram score following administration of an NMBA (123). Dasta et al (125) recorded the bispectral index score in 10 patients receiving continuous sedative, opioid, and NMBA infusions during a period of minimal external stimulation and observed a broad range of BIS values despite minimal electromyographic interference.

Variability in patient response and the confounding influence of electromyography activity reduces the utility of the processed electroencephalogram signal as a reliable monitor of sedation in critically ill patients.

General Care and Monitoring

Monitoring Degree of Blockade. X. Should patients receiving an NMBA by continuous infusion be monitored using PNS with assessment of the TOF response, rather than using clinical assessment alone?

Recommendation: We suggest against the use of PNS with TOF alone for monitoring the depth of neuromuscular blockade in patients on continuous infusion of NMBAs (weak recommendation, very low quality of evidence; see evidence profile) (**Table 3**).

We suggest that PNS with TOF monitoring may be a useful tool for monitoring the depth of neuromuscular blockade but only if it is incorporated into a more inclusive assessment of the patient that includes clinical assessment (weak recommendation, very low quality evidence).

Rationale: The most commonly used method to assess the degree of neuromuscular blockade in the ICU is PNS with monitoring of the TOF response. A number of factors, including the characteristics of the staff using the equipment (e.g., training, experience), the technology itself (different models of PNS devices), or the patient (e.g., edema and hypothermia), may affect the accuracy and interpretation of the results. Baumann et al (126) randomly assigned 30 patients to clinical assessment or TOF monitoring and did not find any differences in outcomes (i.e., mean recovery time, mean total paralysis time, and mean total NMBA dose) between groups (Table 3). Foster et al (127, 128) surveyed acute care facilities in the United States and found that variation in the use of TOF monitoring for patients receiving NMBAs (and concomitant use of analgesia and sedation) was dependent upon the ICU and facility size. Unavailability of equipment, lack of training, and perceived lack of evidence to support the use of TOF monitoring were the primary reasons given for not using this monitoring technique.

Although simple in design, the different brands of PNS devices used to generate the TOF response vary in the amount of current that is delivered and whether or not the precise milliamperes delivered is displayed. Because patients may come

TABLE 3. Evidence Profile: Peripheral Nerve Stimulation Monitoring Versus Clinical Assessment for Continuous Neuromuscular-Blocking Agent Infusions

Quality Assessment						
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations
Paralysis recovery time (higher worse) (assessed with minutes)						
1	Randomized trial	Serious[a]	Not serious	Serious[b]	Serious[c]	None
Mean total paralysis time (higher worse) (assessed with minutes)						
1	Randomized trial	Serious[a]	Not serious	Serious[b]	Serious[c]	None
Mean paralytic dose (higher worse) (assessed with μ g/kg/min)						
1	Randomized trial	Serious[a]	Not serious	Serious[b]	Serious[c]	None

MD = mean difference.
[a]Study intervention was unblinded.
[b]Unclear how important recovery time is to patient important outcomes in generalized ICU population.
[c]Low number of patients included in study ($n = 30$).

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to the ICU with an NMBA already being administered, the baseline level of milliamperes needed for a particular patient may not be documented, resulting in a trial-by-error effort to determine the optimal current.

Patient factors that may influence the results of TOF monitoring include the monitoring site (*orbicularis oculi* vs adductor pollicis), patient temperature, diaphoresis, peripheral edema, and skin resistance. Lagneau et al (129, 130) and Hattori et al (131) demonstrated differing response to PNS at the orbicularis oculi and the adductor pollicis muscles, thought to be due to differences in regional blood flow or peripheral edema. In a case report of a patient receiving an NMBA during therapeutic hypothermia, Mueller et al (94) described an inadequate response to the NMBA (ventilator dyssynchrony) despite TOF of 0/4. As the patient was rewarmed, the accuracy of PNS improved.

Response to PNS differs between not only the adductor pollicis and the orbicularis oculi but also these two sites and the muscles of respiration (chest wall and diaphragm). These differences may arise, not because of variations in the amount of current delivered to the selected nerve, but because of factors intrinsic to the respective muscles (i.e., the number of nicotinic receptors on the muscle). These variations may lead to discrepancies between clinical findings and the degree of neuromuscular blockade. For example, depending on which nerve is being stimulated, a patient with a TOF of 0/4 may still have a cough response or intrinsic respiratory effort. The degree to which clinical goals are being met should guide monitoring and NMBA dose titration.

Peripheral edema may obfuscate external landmarks when using PNS to assess TOF response in the adductor pollicis; therefore, in a patient with edema, palpation to identify the ulnar artery or use of ultrasound may be necessary to locate the ulnar nerve (which lies within the same neurovascular bundle as the ulnar artery) to determine proper electrode placement.

XI. Should patients receiving continuous infusions of an NMBA receive physiotherapy to improve mortality, quality of life, or exercise capacity?

Recommendation: We suggest that patients receiving a continuous infusion of NMBA receive a structured regimen of physiotherapy (weak recommendation, very low quality of evidence; see evidence profile) (**Table 4**).

Rationale: Limited research is available surrounding the use of NMBAs and physiotherapy in critically ill patients. However, indirect evidence is available from evaluations of physiotherapy in sedated, mechanically ventilated patients as a means of preventing complications associated with immobility (132, 133). In a survey of physical therapists working in ICUs across the United States, only 10% of respondents worked in settings with established criteria for initiation of physiotherapy (134). The therapists perceived that patients with traumatic injury, neurologic deficits, or both were more likely to receive physiotherapy, compared with patients in medical ICUs.

Immobility coupled with the use of certain pharmacologic agents (corticosteroids, muscle relaxants, NMBAs, and antibiotics) may lead to impaired neuromuscular transmission, manifested by muscle weakness. Eikermann et al (135) found that, following discontinuation of NMBAs after continuous use over a prolonged period of time, even patients who had recovery of a TOF ratio of 0.9 had decreased strength, which the authors attributed to disuse atrophy. Burtin et al (132) conducted a RCT in a medical–surgical ICU comparing exercise using a bedside cycle ergometer (for subjects who could actively participate) with passive range-of-motion of patients' upper and lower extremities (for sedated subjects who could not participate in

No. of Patients		Effect			
Peripheral Nerve Stimulation Assessment With Train of Four	Clinical Assessment Alone	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
16	14	-	MD, 7 higher (0.48 higher to 13.52 higher)	⊕○○○ Very low	Important
16	14	-	MD, 930 higher (311.72 higher to 1548.28 higher)	⊕○○○ Very low	Important
16	14	-	MD, 0.6 lower (0.74 lower to 0.46 lower)	⊕○○○ Very low	Important

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TABLE 4. Evidence Profile: Physiotherapy for Patients Receiving Neuromuscular-Blocking Agents

Quality Assessment						
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations
Mortality (follow-up: 1 yr)						
1	Randomized trial	Not serious[a]	Not serious	Very serious[b]	Very serious[c]	None
Hospital mortality						
1	Randomized trial	Not serious[a]	Not serious	Very serious[b]	Serious[c]	None
Quality of life (higher number is better) (assessed with Short Form-36 questionnaire)						
1	Randomized trial	Serious[d]	Not serious	Very serious[b]	Not serious	None
ICU length of stay						
1	Randomized trial	Serious[d]	Not serious	Very serious[b]	Serious[c]	None
6-minute walk distance at hospital discharge (higher number is better) (assessed with meters)						
1	Randomized trial	Serious[d]	Not serious	Very serious[b]	Not serious	None

MD = mean difference.
[a]Interventions could not be blinded but felt to be less important for the outcome of mortality.
[b]Only 22% of control patients and 35% of treatment patients were on continuous infusions of neuromuscular-blocking agents.
[c]Wide CIs.
[d]Blinding not possible with intervention.

TABLE 5. Evidence Profile: Lubricating Drops/Gel for Patients Receiving Neuromuscular-Blocking Agent

Quality assessment						
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations
Corneal abrasions						
1	Randomized trial	Serious[a]	Not serious	Not serious	Serious[b]	None

[a]Intervention in this study was unblinded, no mention of randomization procedure. However, each patient acted as own control (one eye intervention, one eye control).
[b]Low number of events, single study.

the active program) (Table 4). The investigators found that early exercise training, even in the sedated subjects, enhanced functional exercise capacity, quality of life, and muscle force at hospital discharge (132). Shortened length of mechanical ventilation and a decrease in overall ICU costs were found in one study of sedated, mechanically ventilated patients who received physiotherapy early in their ICU stay (136).

Although they did not include patients who were receiving NMBAs, Pohlman et al (137) implemented a standard protocol of daily sedation interruption in mechanically ventilated patients and daily physiotherapy in a medical ICU. Sixty-nine percent of the subjects tolerated sitting on the edge of the bed, 33% were able to stand, and 15% were able to ambulate at least 15 feet (137). Barriers to mobilization were identified in 89% of patients and included acute lung injury, delirium, infusions of vasoactive drugs, renal replacement therapy, and body mass index greater than 30 kg/m^2 (137).

A coordinated plan that involves both nursing and physical therapy staff in establishing an early exercise program has several potential benefits, especially in patients who are at risk of developing weakness in association with prolonged use of NMBAs.

XII. Should patients receiving an NMBA by continuous infusion have their eyes lubricated and covered to prevent corneal abrasions?

Recommendation: We recommend scheduled eye care that includes lubricating drops or gel and eyelid closure for patients

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No. of Patients		Effect			
Regular Physical Therapy	Standard of Care	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
3/31 (9.7%)	3/36 (8.3%)	Relative risk, 1.18 (0.22–6.31)	15 more per 1000 (from 65 fewer to 442 more)	⊕○○○ Very low	Critical
0/31 (0.0%)	0/36 (0.0%)	Not estimable	Not estimable	⊕○○○ Very low	Critical
31	36	–	MD, 6 higher (3.84 higher to 8.16 higher)	⊕○○○ Very low	Critical
31	36	–	MD, 2 lower (6.2 lower to 2.2 higher)	⊕○○○ Very low	Important
31	36	–	MD, 53 higher (13.37 higher to 92.63 higher)	⊕○○○ Very low	Important

No. of Patients		Effect			
Scheduled Eye Care	Standard of Care	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
2/50 (4.0%)	11/50 (22.0%)	Relative risk 0.15 (0.03 to 0.71)	187 fewer per 1000 (from 64 fewer to 213 fewer)	⊕⊕○○ Low	Important

receiving continuous infusions of NMBAs. (strong recommendation, low quality of evidence; see evidence profile) (**Table 5**).

Rationale: Because NMBAs impair ocular protective mechanisms (incomplete eyelid closure and absence of corneal reflex), the exposed cornea is at risk of developing ulcerations, infections, and scarring. There is no consensus for the most effective eye-care protocol in patients receiving NMBAs, and clinicians commonly use a combination of petroleum-based ocular lubricants, polyacrylamide gel, and eye-care regimens that include taping the eyelid closed to prevent corneal exposure (138–142). The prevalence of ocular surface disorders (OSD) such as conjunctivitis, exposure keratitis, or corneal erosion occurs in 20–60% of patients who are heavily sedated or receiving NMBAs (138, 140–142). Greater severity of illness increases the potential for the development of OSDs (138, 140–142).

Sorce et al (142) conducted a RCT in three PICUs to assess the prevalence of corneal abrasions in patients receiving NMBAs. Although this study was performed in a pediatric population, the results of the study may be applicable to adults. Subjects' eyes were examined to identify the presence of preexisting corneal abrasions; 7% of subjects (17 of 237) had a corneal abrasion prior to receiving NMBAs. An additional 10% ($n = 21$) developed a corneal abrasion within 2 days of study enrollment. In each case, the subjects served as their own controls, with one eye lubricated with petrolatum white and mineral oil ophthalmic ointment every 6 hours and the eyelid secured closed with tape if needed (control)

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and the opposite eye lubricated with a ribbon of petrolatum white and mineral oil ophthalmologic ointment every 6 hours and plastic film applied over the eye to provide a moisture chamber (experimental condition). The moisture chamber did not significantly reduce the prevalence of corneal abrasion; however, the prevalence of corneal abrasions on initial examination prompted the need to begin prophylactic eye care immediately after the initiation of NMBAs.

Lenart and Garrity (139) conducted a prospective RCT in mechanically ventilated patients receiving either an NMBA or propofol, to compare the effects of artificial-tear ointment and passive eyelid closure on the prevalence of exposure keratitis (Table 5). Nineteen patients (28%) who were screened for the study were excluded due to preexisting exposure keratitis or corneal abrasion. The study sample consisted of 50 patients who served as their own controls—one eye had passive eyelid closure and the other eye had artificial-tear ointment applied. Nine eyes (18% of patients) with passive closure developed exposure keratitis, and two patients (4%) had corneal abrasions in both eyes. Notably, 39 patients(78%) did not develop an OSD in either eye. Artificial-tear ointment was more effective in preventing corneal exposure keratitis than was passive eyelid closure ($p = 0.004$).

In a prospective randomized study in sedated patients in the medical ICU, Sivasankar et al (141) compared an open-chamber method (ocular lubricants plus tape to secure the eyelids closed) and a closed-chamber method (swim goggles plus scheduled moistening of the eyelids with gauze soaked in sterile water) in preventing corneal exposure keratitis or abrasions. Patients were randomly assigned 1:1 to either method. Of the 248 eyes examined, 74 (30%) had incomplete lid closure. More severe exposure keratitis occurred in 32% of subjects' eyes (39 of 122) in the open-chamber group and 8% (10 of 126 eyes) in the closed-chamber group ($p = 0.001$). In those patients with severe exposure keratitis, most corneal lesions developed within the first 48 hours: in 37 of 39 in the open-chamber group (95%) and 8 of 10 in the closed-chamber group (80%). The closed-chamber method was more effective in preventing exposure keratitis and abrasions. Incomplete lid closure and use of an NMBA were predictive factors for development of exposure keratopathy (141).

XIII. Do patients receiving sustained NMBA infusions require special nutritional considerations?

Recommendation: We make no recommendation regarding nutritional requirements specific to patients receiving infusions of NMBAs (insufficient evidence).

Rationale: Clinicians often associate gastric dysfunction with the use of an NMBA, but this is not an accurate assumption. Impaired gastric emptying is not related to NMBA use but, rather, to the underlying illness. However, clinicians may need to be more vigilant in assessing bowel function and tolerance of enteral nutrition because prolonged immobility, opioid use, and fluid imbalances are just a few of the factors that decrease intestinal motility. Tamion et al (143) used the paracetamol absorption technique to study gastric function in 20 patients receiving NMBAs and opioids and found no significant differences in peak paracetamol levels, in time to reach peak concentration, or in the paracetamol serum concentration time curve when cisatracurium was added to opiate sedation versus opiate sedation alone. Gut absorption was maintained with NMBA use, and gastric emptying was unaffected. Therefore, evaluating the underlying critical illness will guide the clinician in determining whether the patient has a functional gastrointestinal tract independent of whether or not an NMBA is used (144).

Adverse Events

Safeguards. XIV. In patients receiving NMBAs, should additional safeguards be in place to avoid unplanned extubation (UE)?

Recommendation: We recommend that clinicians at the bedside implement measures to attenuate the risk of UE in patients receiving NMBAs (good practice statement).

Rationale: Investigators have identified risk factors associated with UE that include male sex, younger patient age, sepsis, agitation, benzodiazepine use, physical restraint use, and staffing ratios and experience (145–158). The rate of UE, reported to be between 2% and 22% (145, 146, 153, 154, 157–159),

TABLE 6. Evidence Profile: Intensive Insulin Therapy for Patients Receiving Neuromuscular-Blocking Agent

Quality Assessment						
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations
Clinically significant weakness (assessed with clinical examination ± EMG)						
2	Randomized trials	Serious[a]	Not serious	Serious[b]	Not serious	None
Hypoglycemia						
2	Randomized trials	Serious[a]	Not serious	Serious[b]	Not serious	None

OR = odds ratio.

[a]Intervention was unblinded in these studies.

[b]Not all patients were receiving neuromuscular-blocking agent. Only 36% in one of the studies and 63% in the other. No subgroup outcome data were provided.

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has not significantly changed since prior to 2001, when it was reported to be between 2.6% and 27% (147–150, 160–162). The wide range in prevalence of UE may, in part, be explained by the definition of neuromuscular blockade—if the patient has adequate neuromuscular blockade, UE can only occur when patients are moved by hospital staff; if the patient is inadequately blocked or if emerging from blockade after discontinuation of an NMBA, the patient may be able to self-extubate.

The difficulty in determining "best practices" in this area is due to the paucity of RCTs. In a recent meta-analysis, the authors reported finding no prospective RCTs (152). Multiple retrospective analyses of risk factors have been conducted, but no prospective trials have examined methods to reduce the risk of UE. The site of placement and type of physical restraints and techniques for securing the tracheal tube may be modifiable risk factors for attenuating the risk of UE.

The levels of agitation and sedation of intubated patients have been shown to be associated with UE. Investigators have shown that patients with better level of consciousness are at increased risk for UE (158, 163). The study by Yeh et al (158) was based on a prospective questionnaire, and 65% of patients who had UE were agitated, which corresponds with the results from the retrospective case-control study by Tung et al (163), which demonstrated that 54% of patients experiencing UE were agitated versus 22% of control subjects ($p < 0.05$). Several prospective case-control studies have shown results similar to those of the survey and retrospective study: higher levels of consciousness are associated with increased risk for UE (146, 153, 155). The study by de Groot et al (153) calculated ORs of 30 and 25 for UE, with a Ramsay score of 1 and 2, respectively. These results correspond with the findings of several retrospective cohort-controlled trials, which indicated that increased level of consciousness or a Glasgow Coma Scale score higher than 9 is a risk factor for UE (OR = 1.98; 95% CI, 1.03–3.81) (151, 164, 165). In the work by Chang et al (165), 90.5% of patients experiencing UE had Glasgow Coma Scale scores of 9 to 12. If, as they should be, patients receiving NMBAs are deeply sedated, the level of consciousness should not be a risk factor for UE.

The use of physical restraints may actually be a risk factor for UE. In a retrospective case-control study, Chang et al (165) found restraints to be a risk factor for UE (OR = 3.11; 95% CI, 1.71–5.66; $p < 0.001$). A recent meta-analysis also found a similar correlation between the use of restraints and UE (OR = 3.1; 95% CI, 1.71–5.7) (152). In several retrospective cohort studies, the use of restraints was associated with 42% to 87% of patients having UE (145, 146, 151, 158, 165). In a prospective interventional study, Carrion et al (147) found a 56% reduction in UE when caregivers were instructed to restrain patients' hands farther away than 20 cm from tracheal tubes. This study examined data from all patients in a medical–surgical ICU and was focused on provider awareness and training to reduce UE; this study did not specifically examine the use of restraints as the only intervention.

Patient movement may be the most important factor associated with UE. Kaplow and Bookbinder (166) compared four types of tube holders and taping techniques for securing tracheal tubes; they reported that prolonged gagging and coughing had the highest impact on UE, independent of how the tracheal tube was secured. Cadaver studies have shown that taping techniques (167) and the use of a commercial tube holder (168) have the potential to decrease the rate of UE. Two studies of patients demonstrated that tape was superior to commercial tube holders for securing tracheal tubes (169, 170), but both of these studies were performed more than 20 years ago. In an observational study of tracheal tubes placed by emergency medical personnel, the worst technique was manually holding the tube, and the lowest rates of UE were observed with twill tape use to secure the tracheal tube (171).

Staffing factors have been discussed in the literature. Most UEs occur when patients are cared for by nurses with fewer than 4 years of experience (151, 158). Bouza et al (146) and Curry et al (151) have shown that 59% and 81%, respectively, of UEs occur when the caregiver is not at the bedside.

With such limited data, making specific recommendations to decrease the prevalence of UEs is not possible, but securing the tracheal tube with tape or a tube holder in a deeply sedated

No. of Patients		Effect			
Intensive Insulin Therapy	Liberal Strategy	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
127/389 (32.6%)	216/436 (49.5%)	OR, 0.49 (0.37–0.65)	171 fewer per 1000 (from 106 fewer to 229 fewer)	⊕⊕○○ Low	Important
154/1360 (11.3%)	25/1388 (1.8%)	OR, 6.96 (4.53–10.7)	95 more per 1000 (from 59 more to 146 more)	⊕⊕○○ Low	Important

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patient with staff at the bedside actively surveying for possible UE appears to be best practice.

XV. In critically ill patients receiving NMBAs, has a specific target for blood glucose level been shown to decrease the risk of prolonged weakness?

Recommendation: We suggest that clinicians target a blood glucose level of less than 180 mg/dL in patients receiving NMBAs (weak recommendation, low quality of evidence; see evidence profile) (**Table 6**).

Rationale: Two prospective randomized trials from a single center compared intensive insulin therapy (IIT) to achieve strict glycemic control (blood glucose 80–110 mg/dL, 4.4–6.1 mmol/L) with conventional insulin therapy (172, 173). Subgroup analyses of data from patients who required prolonged mechanical ventilation (≥ 7 days) in surgical (n = 405) and medical (n = 420) ICUs identified similar baseline characteristics except that the patients in the IIT group in the medical ICU had lower scores on the Sequential Organ Failure Assessment and shorter stays in the ICU (174, 175). In the surgical ICU trial, strict glycemic control rather than insulin dose was an independent protective factor for development of critical illness polyneuromyopathy (CIPNM), which was an independent predictor for longer duration of mechanical ventilation. Although a significant reduction in cumulative risk for CIPNM over time was seen with IIT, neither the blood glucose level nor the amount of insulin explained the lower risk of CIPNM in the medical ICU population. Of the 36% of surgical ICU patients who received an NMBA, 5.2% had prolonged treatment with bolus dosing for a median of 5 days. Of the 63.3% of medical ICU patients, 18.1% had prolonged treatment with continuous infusion of an NMBA for a median of 3 days. Prolonged continuous infusion of an NMBA in medical ICU patients was an independent risk factor for at least one abnormal result on an electrophysiologic test for CIPNM. The duration and extent of recovery were not evaluated. In a pooled analysis of both studies (176), patients treated with IIT were less likely to develop CIPNM, as compared with patients treated with conventional insulin therapy (OR = 0.49; 95% CI, 0.37–0.65; $p < 0.0001$). However, hypoglycemic episodes occurred more frequently with IIT than with conventional insulin therapy (11.3% vs 1.8%; $p < 0.0001$).

Additional studies are needed to confirm the appropriate use of IIT to reduce the risk of CIPNM in a broader population and to determine the ideal blood glucose level necessary to decrease morbidity and mortality while still preventing the potential negative consequences associated with severe hypoglycemia. Guidelines for insulin infusion for patients in the ICU suggest maintaining a blood glucose concentration of less than 180 mg/dL (177, 178). Although targeting lower glucose values (e.g., 100–150 mg/dL) may be advantageous in specific populations if it can be done with a minimal risk of hypoglycemia, data are inadequate to make a specific recommendation for or against this lower glucose target (< 150 mg/dL) in patients receiving NMBAs.

Special Populations and End-of-Life Issues

Patients With Myasthenia Gravis. Patients with myasthenia gravis who are treated with cholinesterase inhibitors express a reduced plasma cholinesterase activity and are at risk for experiencing prolonged neuromuscular blockade due to a prolonged inactivation of succinylcholine. Furthermore, pyridostigmine inhibits the metabolism of mivacurium and, therefore, delays recovery from this NMBA (179).

On the other hand, discontinuing the cholinesterase inhibitor on the day of surgery increases the risk of respiratory distress (180).

XVI. In critically ill patients with myasthenic syndromes, are there special dosing considerations when administering NMBAs?

Recommendation: We recommend that a reduced dose of an NMBA be used for patients with myasthenia gravis and that the dose should be based on PNS with TOF monitoring (good practice statement).

Rationale: Myasthenia gravis is characterized by antibodies targeting nicotinic receptors, thereby reducing the number of functional nicotinic receptors. At baseline, therefore, and depending on the severity of the underlying disease, patients with myasthenia gravis may have impaired neuromuscular transmission and a higher sensitivity to the effects of nondepolarizing NMBAs. Assessment of a patient's neuromuscular function before administering an NMBA may uncover impaired neuromuscular transmission, and, therefore, the patient would require a reduced dose of an NMBA to achieve the desired degree of neuromuscular blockade. Sensitivity to NMBAs varies greatly among patients with myasthenia, and individual assessment is necessary (49, 181–183).

XVII. Is there a preferred monitoring approach for patients with myasthenia gravis who are receiving NMBAs?

Recommendation: We make no recommendation on which muscle group should be monitored in patients with myasthenia gravis undergoing treatment with NMBAs (insufficient evidence).

Rationale: In one study (184), 20 patients with myasthenia gravis (10 with ocular disease and 10 with generalized disease) had TOF monitoring of the adductor pollicis muscle. The authors concluded that patients with primarily ocular disease require higher doses of NMBAs than do patients with generalized disease, but the authors did not compare the TOF between the adductor pollicis and the orbicularis oculi muscles.

Obese Patients. XVIII. In critically ill obese patients (body mass index ≥ 30 kg/m^2), should actual body weight, rather than other measures of weight, be used to calculate the dose of NMBAs?

Recommendations: We suggest that clinicians not use actual body weight and instead use a consistent weight (ideal body weight or adjusted body weight) when calculating NMBA doses for obese patients (weak recommendation, low quality of evidence).

We make no recommendation concerning the use of one measure of consistent weight over another when calculating NMBA doses in obese patients (insufficient evidence).

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Rationale: All of the trials evaluating the most appropriate size descriptor for dosing NMBAs in severely obese patients were single-dose studies conducted in the perioperative setting (185–194). The primary endpoint for these studies was either pharmacokinetic or pharmacodynamic (e.g., muscle recovery based on TOF monitoring) in nature. Therefore, no information is available regarding whether the choice of a size descriptor may influence outcomes or length of stay parameters when NMBAs are used on a sustained basis in the ICU setting. Despite these caveats, the results of the studies do provide guidance for weight-based dosing regimens of NMBAs. In a double-blind randomized study (185) involving 20 severely obese patients (body mass index 38–79 kg/m^2) undergoing bariatric surgery, atracurium dosing based on ideal body weight resulted in significantly shorter recovery time by TOF monitoring and less variability in recovery, compared with dosing based on actual body weight. There was a dose-dependent prolongation of recovery time using actual body weight that was not seen with ideal body weight; furthermore, none of the patients in the ideal body weight group required neostigmine at the end of the operation, compared with 70% of patients who were dosed using actual body weight. These results are consistent with findings from other open-label trials involving atracurium, cisatracurium, vecuronium, and rocuronium, all of which suggest that dosing should not be based on actual body weight (189, 190, 192–194). In contrast, small open-label trials that evaluated NMBA dosing in obese versus nonobese patients did not find differences in recovery times (186, 187, 191). However, one of these trials found nonproportional increases in the volume of distribution of atracurium and total clearance with increasing weight, suggesting actual body weight should not be used for dosing (187). In the other trials (186, 191), severely obese patients were not included, making it difficult to detect differences based on weight-based dosing. A final, small (n = 14), open-label trial of pancuronium in morbidly obese and normal-weight patients (188) did not evaluate recovery time and had analysis concerns (195).

The authors of these trials recommended against the use of actual body weight and uniformly recommended using ideal body weight for weight-based dosing of NMBAs. Ideal body weight has the advantage that it is easy to calculate. However, ideal body weight is a surrogate for lean body weight. Lean body weight has been evaluated prospectively for drug-dose prediction in obese patients, but its use requires more complex equations that are far less commonly used in the clinical setting (196). Given other problems related to weight estimates and changes over time in the ICU setting, the continued use of ideal body weight seems reasonable until equations based on lean body weight have been evaluated in critically ill obese patients. An adjusted weight that takes into account a portion of the excess weight might be a reasonable alternative. Importantly, clinicians should strive for consistency in weight measurement and choice of weight among patients and for a single patient when using weight-based dosing for NMBAs (197, 198).

Pregnant Patients. XIX. Can continuous NMBA infusions be used in intubated and mechanically ventilated patients who are pregnant and have an indication for the administration of an NMBA?

Response: We make no recommendation on the use of NMBAs in pregnant patients (insufficient evidence).

Rationale: NMBAs have been used extensively in pregnant patients for obstetrical and nonobstetrical surgeries. Cisatracurium and rocuronium are the only NMBAs that are listed as pregnancy category B drugs. Their use is based on a clinical decision that an NMBA may be justified to save the mother's life or to avoid severe hypoxia for both the mother and the fetus. In the ICU where longer-term use may be encountered, the use of category C drugs should be avoided because category B drugs are available. All NMBAs or their metabolites, with the exception of cisatracurium, cross the placental barrier.

There are no double-blind, randomized, controlled trials comparing NMBAs in pregnant critically ill patients. Most studies of NMBAs administered to pregnant patients have been conducted in patients undergoing cesarean sections or other surgery that requires only one or two doses of an NMBA. An older report associated long-term fetal exposure to NMBAs with arthrogryposis (199). NMBAs are sometimes necessary in the critically ill pregnant patient with ARDS. Critically ill obstetrical patients have increased risk of death from respiratory failure, with an OR of 12.9 for mortality (200), and have a fetal loss rate of 34–52% (200, 201). ARDS alone is associated with a 12% rate of fetal loss (201). Delay in ICU care was found to have an OR of 2.3 for maternal mortality in obstetrical patients (202). Maternal clinical indicators should guide treatment decisions as in these patients. There has been an association between first trimester surgery and low fetal birth weights and increased fetal loss, but no association with any actual drug has been identified (203–205).

The decision to use NMBAs cannot be made purely on whether NMBAs cross the placenta because NMBAs are found in varying concentrations in fetal blood and thus do cross the placenta (206). Historically, succinylcholine was the NMBA of choice for obstetrical procedures because even though it crossed the placenta it had minimal if any clinical effects on the neonate (207). Vecuronium has been shown to have residual clinical effects in the newborn (208), and atracurium and rocuronium also have placental transfer (209, 210). Similar to succinylcholine, pancuronium, atracurium, and vecuronium all cross the placenta and are pregnancy class C, their use should be avoided for long-term infusion, especially in the first trimester (208, 211–214).

Vecuronium, atracurium, and rocuronium do not have a prolonged clinical effect in the pregnant or postpartum patient (208, 210, 215). Cisatracurium has been shown to have a shorter duration of effect in the immediate postpartum patient than in the nonpregnant patient (216). When metabolized, atracurium and cisatracurium produce plasma concentrations of laudanosine, a neuroactive metabolite with the potential to precipitate seizures, but atracurium is associated with much higher levels of laudanosine than cisatracurium (217).

Brain Death. XX. Can clinicians determine brain death in patients receiving NMBAs?

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Recommendation: We recommend that NMBAs be discontinued prior to the clinical determination of brain death (good practice statement).

Rationale: Blinded or controlled studies on the subject of determining brain death are impossible to perform. We have therefore relied on expert opinion, consensus, legal documents, and existing recommendations to formulate our response to this question. In 1968, the Ad Hoc Committee of the Harvard Medical School proposed a definition for irreversible coma (218). This definition included unreceptivity and unresponsivity, no movements or breathing, no reflexes, and a flat electroencephalogram tracing. Legislative action culminated in the Uniform Determination of Death Act, which was approved by the American Medical Association and the American Bar Association in 1980 and 1981, respectively. Under this Act an "individual who has sustained either 1) irreversible cessation of circulatory and respiratory functions or 2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead" (219). Key to this Act is the provision that death is determined in accordance with accepted medical standards, which remains the clinical examination.

In 2009, a commentary on the original 1968 Harvard committee article indicated that the neurologic examination remains the most important concept in determining brain death (220). The presence of NMBA-produced paralysis prevents assessment of the physical examination-based criteria for determining brain death. The American Academy of Neurology lists the first criterion for determining brain death as, "Establish irreversible and proximate cause of coma" and the absence of central nervous system–depressant drugs and NMBAs (221). The physical examination is an integral part of brain death determination and "must be performed with precision" (222), but may be difficult to do in a paralyzed patient, which could lead to a breach of the "Dead Donor Rule," as outlined by Truog (223). We could not locate any studies that described or evaluated other means of reliably determining brain death. Confirmation of brain death, through such means as electroencephalogram, transcranial Doppler, or cerebral perfusion scans, has not been recommended as a replacement for the clinical brain death examination.

Due to the legal definitions and the inherent impossibility of performing an adequate and reliable physical examination when NMBAs are utilized, their continued use during a brain death examination cannot be justified. The clinical diagnosis of brain death in a patient receiving or who has received an NMBA should not be made unless the patient has a TOF of 4/4 as measured using PNS at the maximum current.

End of Life. XXI. In patients receiving NMBAs, should the drugs be discontinued at the end of life or when life support is withdrawn?

Recommendation: We suggest that NMBAs be discontinued at the end of life or when life support is withdrawn (weak recommendation, very low quality of evidence).

Rationale: There are no trials evaluating the use of NMBAs at the end of life, such as when support is withdrawn from a patient. The underlying ethical issue is whether continuing NMBAs provides comfort to the patient and family or instead, constitutes euthanasia, given that use of NMBAs will hasten death.

The principle of doctrine of double effect has been applied to the use of NMBAs when ventilatory support is withdrawn from a patient. Kuhse (224) argues that, even though physicians are not always obligated to preserve life, the use of an NMBA is an intentional causing of death. Others have proposed contrary arguments that NMBAs may alleviate suffering at the end of life. In situations in which patients are medicated with NMBAs and the return of normal muscle activity could take several hours to days, stopping the NMBA infusion may actually increase the suffering of the patient and the family (225, 226). In these cases, it may be acceptable to withdraw support while the patient is still paralyzed. Perkin and Resnik (226, 227) have proposed that giving NMBAs before terminal extubation of a patient can prevent gasping and argue that the muscle contractions associated with gasping increase a patient's suffering.

Others have argued that NMBAs may be an obstacle to this process if the intent is to relieve suffering. A questionnaire study of German physicians reported that NMBAs are occasionally used for terminal extubation because patient comfort cannot be assessed (228). If comfort cannot be clinically assessed, it cannot be treated. For patients dying in the ICU, Hawryluck et al (229) opine that NMBAs mask the signs and symptoms of pain and suffering and recommend against starting them during the dying process. However, if the patient is already receiving an NMBA, the drug maybe continued if the intent is well documented, and adequate analgesia and sedation are provided. Because no placebo-controlled trials have been conducted to evaluate these questions, ensuring that the patient can be clinically assessed seems to be the most defensible position, and use of NMBAs prevents physical examination for signs of discomfort.

There seems to be a near-consensus in this field that analgesics and sedatives fall within purview of the doctrine of double effect and are routinely recommended in guidelines for end-of-life care (223, 229). The use of NMBAs at the end of life will continue to be debated, but alleviating pain and suffering with analgesia and sedation is the standard of care.

CONCLUSION

This document incorporates the best evidence available at the time it was written. As with any guidelines, these recommendations, suggestions, and good practice statements, and their associated strength of evidence should be implemented based upon specific patient factors, clinician experience, and institutional resources and are not intended to be used for all patients in all circumstances. As new agents become available or existing agents are used in new ways, and evidence in support of these changes becomes available, the Society of Critical Care Medicine is committed to updating these guidelines.

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REFERENCES

1. Shapiro BA, Warren J, Egol AB, et al: Practice parameters for sustained neuromuscular blockade in the adult critically ill patient: An executive summary. Society of Critical Care Medicine. *Crit Care Med* 1995; 23:1601–1605
2. Murray MJ, Cowen J, DeBlock H, et al; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists, American College of Chest Physicians: Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med* 2002; 30:142–156
3. Slutsky AS: Neuromuscular blocking agents in ARDS. *N Engl J Med* 2010; 363:1176–1180
4. Warr J, Thiboutot Z, Rose L, et al: Current therapeutic uses, pharmacology, and clinical considerations of neuromuscular blocking agents for critically ill adults. *Ann Pharmacother* 2011; 45:1116–1126
5. Salciccioli JD, Cocchi MN, Rittenberger JC, et al: Continuous neuromuscular blockade is associated with decreased mortality in postcardiac arrest patients. *Resuscitation* 2013; 84:1728–1733
6. Mehta S, Burry L, Fischer S, et al; Canadian Critical Care Trials Group: Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. *Crit Care Med* 2006; 34:374–380
7. Cochrane Collaboration: Cochrane: Review Manager. Edition 5.2. Edited by Centre TNC. Copenhagen, Denmark, Cochrane Collaboration, 2012
8. Kavanagh BP: The GRADE system for rating clinical guidelines. *PLoS Med* 2009; 6:e1000094
9. Guyatt GH, Oxman AD, Kunz R, et al: GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* 2011; 64:395–400
10. Burke RE: Motor unit properties and selective involvement in movement. *Exerc Sport Sci Rev* 1975; 3:31–81
11. Salpeter MM, Loring RH: Nicotinic acetylcholine receptors in vertebrate muscle: Properties, distribution and neural control. *Prog Neurobiol* 1985; 25:297–325
12. Colquhoun D, Sakmann B: Fast events in single-channel currents activated by acetylcholine and its analogues at the frog muscle endplate. *J Physiol* 1985; 369:501–557
13. Ebashi S, Endo M: Calcium ion and muscle contraction. *Prog Biophys Mol Biol* 1968; 18:123–183
14. Colman H, Nabekura J, Lichtman JW: Alterations in synaptic strength preceding axon withdrawal. *Science* 1997; 275:356–361
15. Fonnum F: Radiochemical micro assays for the determination of choline acetyltransferase and acetylcholinesterase activities. *Biochem J* 1969; 115:465–472
16. Volknandt W, Zimmermann H: Acetylcholine, ATP, and proteoglycan are common to synaptic vesicles isolated from the electric organs of electric eel and electric catfish as well as from rat diaphragm. *J Neurochem* 1986; 47:1449–1462
17. Naguib M, Flood P, McArdle JJ, et al: Advances in neurobiology of the neuromuscular junction: Implications for the anesthesiologist. *Anesthesiology* 2002; 96:202–231
18. Bajgar J: Organophosphates/nerve agent poisoning: Mechanism of action, diagnosis, prophylaxis, and treatment. *Adv Clin Chem* 2004; 38:151–216
19. Lindstrom J: Nicotinic acetylcholine receptors in health and disease. *Mol Neurobiol* 1997; 15:193–222
20. Thesleft S: The mode of neuromuscular block caused by acetylcholine, nicotine, decamethonium and succinylcholine. *Acta Physiol Scand* 1955; 34:218–231
21. Paton WD: Mode of action of neuromuscular blocking agents. *Br J Anaesth* 1956; 28:470–480
22. Watling SM, Dasta JF: Prolonged paralysis in intensive care unit patients after the use of neuromuscular blocking agents: A review of the literature. *Crit Care Med* 1994; 22:884–893
23. Minsaas B, Stovner J: Artery-to-muscle onset time for neuromuscular blocking drugs. *Br J Anaesth* 1980; 52:403–407
24. Pino RM, Hassan H: Monitoring of neuromuscular blockade. *Curr Opin Anaesthesiol* 1995; 8:348–350
25. Fuchs-Buder T, Claudius C, Skovgaard LT, et al; 8th International Neuromuscular Meeting: Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: The Stockholm revision. *Acta Anaesthesiol Scand* 2007; 51:789–808
26. McManus MC: Neuromuscular blockers in surgery and intensive care, Part 1. *Am J Health Syst Pharm* 2001; 58:2287–2299
27. Vizi ES, Lendvai B: Side effects of nondepolarizing muscle relaxants: Relationship to their antinicotinic and antimuscarinic actions. *Pharmacol Ther* 1997; 73:75–89
28. Hibbs RE, Zambon AC: Agents acting at the neuromuscular junction and autonomic ganglia. *In*: Goodman & Gilman's The Pharmacological Basis of Therapeutics. Twelfth Edition. Brunton LL, Chabner BA, Knollmann BC (Eds). New York, McGraw-Hill, 2011
29. Hou VY, Hirshman CA, Emala CW: Neuromuscular relaxants as antagonists for M2 and M3 muscarinic receptors. *Anesthesiology* 1999, 88:744–750
30. Lee C: Conformation, action, and mechanism of action of neuromuscular blocking muscle relaxants. *Pharmacol Ther* 2003; 98:143–169
31. Milchert M, Spassov A, Meissner K, et al: Skeletal muscle relaxants inhibit rat tracheal smooth muscle tone *in vitro*. *J Physiol Pharmacol* 2009; 60 Suppl 8:5–11
32. Bevan DR, Donati F: Muscle relaxants. *In*: Clinical Anesthesia. Second Edition. Barash PG, Cullen BF, Stoelting RK (Eds). Philadelphia PA, Lippincott-Raven, 1996, pp 481–508
33. Naguib M, Samarkandi AH, Bakhamees HS, et al: Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine. *Br J Anaesth* 1995; 75:588–592
34. Fahey MR, Morris RB, Miller RD, et al: Clinical pharmacology of ORG NC45 (NorcuronTM): A new nondepolarizing muscle relaxant. *Anesthesiology* 1981; 55:6–11
35. Hilgenberg JC: Comparison of the pharmacology and vecuronium and atracurium with that of other currently available muscle relaxants. *Anesth Analg* 1983; 62:524–531
36. Spence AG, Barnetson RS: Reaction to vecuronium bromide. *Lancet* 1985; 1:979–980
37. Futo J, Kupferberg JP, Moss J: Inhibition of histamine N-methyltransferase (HNMT) *in vitro* by neuromuscular relaxants. *Biochem Pharmacol* 1990; 39:415–420
38. Levy JH, Davis GK, Duggan J, et al: Determination of the hemodynamics and histamine release of rocuronium (Org 9426) when administered in increased doses under N2O/O2-sufentanil anesthesia. *Anesth Analg* 1994; 78:318–321
39. Watkins J: Adverse reaction to neuromuscular blockers: Frequency, investigation, and epidemiology. *Acta Anaesthesiol Scand Suppl* 1994; 102:6–10
40. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium, dimethyl tubocurarine and tubocurarine. *Br J Anaesth* 1983; 55 Suppl 1:105S–106S
41. Scott RP, Savarese JJ, Basta SJ, et al: Atracurium: Clinical strategies for preventing histamine release and attenuating the haemodynamic response. *Br J Anaesth* 1985; 57:550–553
42. Pancuronium bromide. Bethesda, MD, National Library of Medicine. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d705382b-8aa0-4893-ed9e-bcf7c7d9d0a2. Accessed October 15, 2014
43. Cabal LA, Siassi B, Artal R, et al: Cardiovascular and catecholamine changes after administration of pancuronium in distressed neonates. *Pediatrics* 1985; 75:284–287
44. Gyermek L, Cantley EM: Comparison of the onset, spontaneous recovery and train of four fade of the clinical neuromuscular block produced by pancuronium and pipecuronium. *Int J Clin Pharmacol Ther* 1994; 32:600–605
45. Orkin FK, Pegg JR: Cardiac effects of pancuronium bromide. *JAMA* 1973; 224:630
46. Darwish AK, Challen PD: Unexplained death during anaesthesia. *Br J Anaesth* 1977; 49:192–193

Copyright © 2016 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

47. Gordon M: Pharmacology, chemistry and physics for anesthesiology, anesthesia: Implications of co-existing disease. 2013. *Med Pharmacol.* Available at: http://www.anesthesia2000.com/. Accessed October 15, 2014
48. Sugai Y, Sugai K, Hirata T, et al: The interaction of pancuronium and vecuronium with cardiac muscarinic receptors. *Acta Anaesthesiol Scand* 1987; 31:224–226
49. Abel M, Book WJ, Eisenkraft JB: Adverse effects of nondepolarising neuromuscular blocking agents. Incidence, prevention and management. *Drug Saf* 1994; 10:420–438
50. Engbaek J, Ording H, Sørensen B, et al: Cardiac effects of vecuronium and pancuronium during halothane anaesthesia. *Br J Anaesth* 1983; 55:501–505
51. Futo J, Kupferberg JP, Moss J, et al: Vecuronium inhibits histamine N-methyltransferase. *Anesthesiology* 1988; 69:92–96
52. Husby P, Gramstad L, Rosland JH, et al: Haemodynamic effects of high-dose vecuronium compared with pancuronium in beta-blocked patients with coronary artery disease during fentanyl-diazepam-nitrous oxide anaesthesia. *Acta Anaesthesiol Scand* 1996; 40:26–31
53. Inoue K, el-Banayosy A, Stolarski L, et al: Vecuronium induced bradycardia following induction of anaesthesia with etomidate or thiopentone, with or without fentanyl. *Br J Anaesth* 1988; 60:10–17
54. Lines D, Shipton EA: Severe bradycardia and sinus arrest after administration of vecuronium, fentanyl and halothane. A case report. *S Afr Med J* 1991; 80:200–201
55. Cisatracurium besylate. National Bethesda, MD, Library of Medicine. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2ee0358e-2cce-40d3-9fcf-1b9088815c98. Accessed October 15, 2014
56. Jooste E, Klafter F, Hirshman CA, et al: A mechanism for rapacuronium-induced bronchospasm: M2 muscarinic receptor antagonism. *Anesthesiology* 2003; 98:906–911
57. Soukup J, Doenicke A, Hoernecke R, et al: Cardiovascular effects after bolus administration of cisatracurium. A comparison with vecuronium. *Anaesthesist* 1996; 45:1024–1029
58. Bevan DR: Newer neuromuscular blocking agents. *Pharmacol Toxicol* 1994; 74:3–9
59. Booij L: The use of rocuronium in various clinical situations. *Asean J Anaesthesiol* 2005; 6(Suppl 5):5–14
60. Pollard BJ: Interactions involving relaxants. *In*: Applied Neuromuscular Pharmacology. Pollard BJ (Ed). Oxford, UK, Oxford University Press, 1994, pp 202–248
61. Klabunde RE: Electrical activity of the heart. *In* Cardiology Physiology Concepts. Second Edition. Philadelphia, PA, Lippincott, Williams, & Wilkins, 2011, pp 9–40
62. Boehm S, Kubista H: Fine tuning of sympathetic transmitter release via ionotropic and metabotropic presynaptic receptors. *Pharmacol Rev* 2002; 54:43–99
63. Longnecker DE, Murphy FL: Muscle relaxants. *In*: Dripps/Eckenhoff/Vandam: Introduction to Anesthesia. Eighth Edition. Zorab R (Ed). Philadelphia, PA: W. B. Saunders, 1992, 110–124
64. Forel JM, Roch A, Marin V, et al: Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. *Crit Care Med* 2006; 34:2749–2757
65. Gainnier M, Roch A, Forel JM, et al: Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. *Crit Care Med* 2004; 32:113–119
66. Papazian L, Forel JM, Gacouin A, et al; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107–1116
67. Alhazzani W, Alshahrani M, Jaeschke R, et al: Neuromuscular blocking agents in acute respiratory distress syndrome: A systematic review and meta-analysis of randomized controlled trials. *Crit Care* 2013; 17:R43
68. Lyu G, Wang X, Jiang W, et al: Clinical study of early use of neuromuscular blocking agents in patients with severe sepsis and acute respiratory distress syndrome. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2014; 26:325–329
69. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342(18):1301–1308.
70. Burns KE, Adhikari NK, Slutsky AS, et al: Pressure and volume limited ventilation for the ventilatory management of patients with acute lung injury: A systematic review and meta-analysis. *PLoS One* 2011; 6:e14623
71. De Jonghe B, Sharshar T, Lefaucheur JP, et al; Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation: Paresis acquired in the intensive care unit: A prospective multicenter study. *JAMA* 2002; 288:2859–2867
72. Adnet F, Dhissi G, Borron SW, et al: Complication profiles of adult asthmatics requiring paralysis during mechanical ventilation. *Intensive Care Med* 2001; 27:1729–1736
73. Kesler SM, Sprenkle MD, David WS, et al: Severe weakness complicating status asthmaticus despite minimal duration of neuromuscular paralysis. *Intensive Care Med* 2009; 35:157–160
74. Leatherman JW, Fluegel WL, David WS, et al: Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med* 1996; 153:1686–1690
75. Behbehani NA, Al-Mane F, D'yachkova Y, et al: Myopathy following mechanical ventilation for acute severe asthma: The role of muscle relaxants and corticosteroids. *Chest* 1999; 115:1627–1631
76. Werba A, Klezl M, Schramm W, et al: The level of neuromuscular block needed to suppress diaphragmatic movement during tracheal suction in patients with raised intracranial pressure: A study with vecuronium and atracurium. *Anaesthesia* 1993; 48:301–303
77. Kerr ME, Sereika SM, Orndoff P, et al: Effect of neuromuscular blockers and opiates on the cerebrovascular response to endotracheal suctioning in adults with severe head injuries. *Am J Crit Care* 1998; 7:205–217
78. Prielipp RC, Robinson JC, Wilson JA, et al: Dose response, recovery, and cost of doxacurium as a continuous infusion in neurosurgical intensive care unit patients. *Crit Care Med* 1997; 25:1236–1241
79. Schramm WM, Jesenko R, Bartunek A, et al: Effects of cisatracurium on cerebral and cardiovascular hemodynamics in patients with severe brain injury. *Acta Anaesthesiol Scand* 1997; 41:1319–1323
80. Rosa G, Orfei P, Sanfilippo M, et al: The effects of atracurium besylate (Tracrium) on intracranial pressure and cerebral perfusion pressure. *Anesth Analg* 1986; 65:381–384
81. Schramm WM, Strasser K, Bartunek A, et al: Effects of rocuronium and vecuronium on intracranial pressure, mean arterial pressure and heart rate in neurosurgical patients. *Br J Anaesth* 1996; 77:607–611
82. Hsiang JK, Chesnut RM, Crisp CB, et al: Early, routine paralysis for intracranial pressure control in severe head injury: Is it necessary? *Crit Care Med* 1994; 22:1471–1476
83. Juul N, Morris GF, Marshall SB, et al: Neuromuscular blocking agents in neurointensive care. *Acta Neurochir Suppl* 2000; 76:467–470
84. The Hypothermia After Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002, 346(8):549–556
85. Bernard SA, Gray TW, Buist MD, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557–563
86. Salciccioli J, Donnino M: Reply to letter: Continuous neuromuscular blockade is associated with decreased mortality in post-cardiac arrest patients–problems with the data. *Resuscitation* 2014; 85:e3
87. Baker WL, Geronila G, Kallur R, et al: Effect of neuromuscular blockers on outcomes in patients receiving therapeutic hypothermia following cardiac arrest. *Analg Resusc Curr Res* 2013; S1. doi: 10.4172/2324-903X.S1-001
88. Sladen RN, Berend JZ, Fassero JS, et al: Comparison of vecuronium and meperidine on the clinical and metabolic effects of shivering after hypothermic cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1995; 9:147–153
89. Guffin A, Girard D, Kaplan JA: Shivering following cardiac surgery: Hemodynamic changes and reversal. *J Cardiothorac Anesth* 1987; 1:24–28
90. Cruise C, MacKinnon J, Tough J, et al: Comparison of meperidine and pancuronium for the treatment of shivering after cardiac surgery. *Can J Anaesth* 1992; 39:563–568

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91. Peberdy MA, Callaway CW, Neumar RW, et al; American Heart Association: Part 9: Post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122:S768–S786
92. Heier T, Caldwell JE: Impact of hypothermia on the response to neuromuscular blocking drugs. *Anesthesiology* 2006; 104:1070–1080
93. Eriksson LI, Viby-Mogensen J, Lennmarken C: The effect of peripheral hypothermia on a vecuronium-induced neuromuscular block. *Acta Anaesthesiol Scand* 1991; 35:387–392
94. Mueller SW, Winn R, Macht M, et al: Neuromuscular blockade resistance during therapeutic hypothermia. *Ann Pharmacother* 2011; 45:e15
95. Clifton GL, Miller ER, Choi SC, et al: Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 2001; 344:556–563
96. Kupchik NL: Development and implementation of a therapeutic hypothermia protocol. *Crit Care Med* 2009; 37:S279–S284
97. Polderman KH, Herold I: Therapeutic hypothermia and controlled normothermia in the intensive care unit: Practical considerations, side effects, and cooling methods. *Crit Care Med* 2009; 37:1101–1120
98. Marshall LF: Intercenter variance. *J Neurosurg* 2001; 95:733–734
99. Magder S: Clinical usefulness of respiratory variations in arterial pressure. *Am J Respir Crit Care Med* 2004; 169:151–155
100. Monnet X, Rienzo M, Osman D, et al: Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med* 2006; 34:1402–1407
101. De Backer D, Heenen S, Piagnerelli M, et al: Pulse pressure variations to predict fluid responsiveness: Influence of tidal volume. *Intensive Care Med* 2005; 31:517–523
102. Lakhal K, Ehrmann S, Benzekri-Lefèvre D, et al: Respiratory pulse pressure variation fails to predict fluid responsiveness in acute respiratory distress syndrome. *Crit Care* 2011; 15:R85
103. Hofer CK, Senn A, Weibel L, et al: Assessment of stroke volume variation for prediction of fluid responsiveness using the modified FloTrac and PiCCOplus system. *Crit Care* 2008; 12:R82
104. Tavernier B, Makhotine O, Lebuffe G, et al: Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology* 1998; 89:1313–1321
105. Huang CC, Fu JY, Hu HC, et al: Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure. *Crit Care Med* 2008; 36:2810–2816
106. Barr J, Fraser GL, Puntillo K, et al; American College of Critical Care Medicine: Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; 41:263–306
107. Light KP, Lovell AT, Butt H, et al: Adverse effects of neuromuscular blocking agents based on yellow card reporting in the U.K.: Are there differences between males and females? *Pharmacoepidemiol Drug Saf* 2006; 15:151–160
108. Perry SW: Psychological reactions to pancuronium bromide. *Am J Psychiatry* 1985; 142:1390–1391
109. Wagner BK, Zavotsky KE, Sweeney JB, et al: Patient recall of therapeutic paralysis in a surgical critical care unit. *Pharmacotherapy* 1998; 18:358–363
110. Johnson KL, Cheung RB, Johnson SB, et al: Therapeutic paralysis of critically ill trauma patients: Perceptions of patients and their family members. *Am J Crit Care* 1999; 8:490–498
111. Ballard N, Robley L, Barrett D, et al: Patients' recollections of therapeutic paralysis in the intensive care unit. *Am J Crit Care* 2006; 15:86–94; quiz 95
112. Arnot-Smith J, Smith AF: Patient safety incidents involving neuromuscular blockade: Analysis of the UK National Reporting and Learning System data from 2006 to 2008. *Anaesthesia* 2010, 65:1106–1113
113. Punjasawadwong Y, Boonjeungmonkol N, Phongchiewboon A: Bispectral index for improving anaesthetic delivery and postoperative recovery. *Cochrane Database Syst Rev* 2007(4):CD003843
114. Avidan MS, Jacobsohn E, Glick D, et al; BAG-RECALL Research Group: Prevention of intraoperative awareness in a high-risk surgical population. *N Engl J Med* 2011; 365:591–600
115. Arbour R: Impact of bispectral index monitoring on sedation and outcomes in critically ill adults: A case series. *Crit Care Nurs Clin North Am* 2006; 18:227–41, xi
116. Haenggi M, Ypparila-Wolters H, Bieri C, et al: Entropy and bispectral index for assessment of sedation, analgesia and the effects of unpleasant stimuli in critically ill patients: An observational study. *Crit Care* 2008; 12:R119
117. Nasraway SA, Wu EC, Kelleher RM et al: How reliable is the Bispectral Index in critically ill patients? A prospective, comparative, single-blinded observer study. *Crit Care Med* 2002; 30:1483–1487
118. Vivien B, Di Maria S, Ouattara A, et al: Overestimation of Bispectral Index in sedated intensive care unit patients revealed by administration of muscle relaxant. *Anesthesiology* 2003; 99:9–17
119. Arbour R, Waterhouse J, Seckel MA, et al: Correlation between the Sedation-Agitation Scale and the Bispectral Index in ventilated patients in the intensive care unit. *Heart Lung* 2009; 38:336–345
120. Messner M, Beese U, Romstöck J, et al: The bispectral index declines during neuromuscular block in fully awake persons. *Anesth Analg* 2003; 97:488–91, table of contents
121. Aho AJ, Lyytikäinen LP, Yli-Hankala A, et al: Explaining entropy responses after a noxious stimulus, with or without neuromuscular blocking agents, by means of the raw electroencephalographic and electromyographic characteristics. *Br J Anaesth* 2011; 106:69–76
122. Borjian Boroojeny S: The effect of facial muscle contractions on the cerebral state index in an ICU patient: A case report. *Cases J* 2008; 1:167
123. Inoue S, Kawaguchi M, Sasaoka N, et al: Effects of neuromuscular block on systemic and cerebral hemodynamics and bispectral index during moderate or deep sedation in critically ill patients. *Intensive Care Med* 2006; 32:391–397
124. Lu CH, Man KM, Ou-Yang HY, et al: Composite auditory evoked potential index versus bispectral index to estimate the level of sedation in paralyzed critically ill patients: A prospective observational study. *Anesth Analg* 2008; 107:1290–1294
125. Dasta JF, Kane SL, Gerlach AT, et al: Bispectral Index in the intensive care setting. *Crit Care Med* 2003; 31:998; author reply 998–998; author reply 999
126. Baumann MH, McAlpin BW, Brown K, et al: A prospective randomized comparison of train-of-four monitoring and clinical assessment during continuous ICU cisatracurium paralysis. *Chest* 2004; 126:1267–1273
127. Foster JG, Kish SK, Keenan CH: A national survey of critical care nurses' practices related to administration of neuromuscular blocking agents. *Am J Crit Care* 2001; 10:139–145
128. Foster JG, Kish SK, Keenan CH: National practice with assessment and monitoring of neuromuscular blockade. *Crit Care Nurs Q* 2002; 25:27–40
129. Lagneau F, Benayoun L, Plaud B, et al: The interpretation of train-of-four monitoring in intensive care: What about the muscle site and the current intensity? *Intensive Care Med* 2001; 27:1058–1063
130. Lagneau F, Plaud B, Feller M, et al: TOF monitoring is required to achieve effective transient neuromuscular blockade in ICU patients. *Can J Anaesth* 2001; 48:319
131. Hattori H, Saitoh Y, Nakajima H, et al: Visual evaluation of fade in response to facial nerve stimulation at the eyelid. *J Clin Anesth* 2005; 17:276–280
132. Burtin C, Clerckx B, Robbeets C, et al: Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med* 2009; 37:2499–2505
133. Kress JP: Clinical trials of early mobilization of critically ill patients. *Crit Care Med* 2009; 37:S442–S447
134. Hodgin KE, Nordon-Craft A, McFann KK, et al: Physical therapy utilization in intensive care units: Results from a national survey. *Crit Care Med* 2009; 37:561–6; quiz 566
135. Eikermann M, Gerwig M, Hasselmann C, et al: Impaired neuromuscular transmission after recovery of the train-of-four ratio. *Acta Anaesthesiol Scand* 2007; 51:226–234

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136. Kress JP, Hall JB: Cost considerations in sedation, analgesia, and neuromuscular blockade in the intensive care unit. *Semin Respir Crit Care Med* 2001; 22:199–210
137. Pohlman MC, Schweickert WD, Pohlman AS, et al: Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation. *Crit Care Med* 2010; 38:2089–2094
138. Ezra DG, Lewis G, Healy M, et al: Preventing exposure keratopathy in the critically ill: A prospective study comparing eye care regimes. *Br J Ophthalmol* 2005; 89:1068–1069
139. Lenart SB, Garrity JA: Eye care for patients receiving neuromuscular blocking agents or propofol during mechanical ventilation. *Am J Crit Care* 2000; 9:188–191
140. Rosenberg JB, Eisen LA: Eye care in the intensive care unit: Narrative review and meta-analysis. *Crit Care Med* 2008; 36:3151–3155
141. Sivasankar S, Jasper S, Simon S, et al: Eye care in ICU. *Indian J Crit Care Med* 2006; 10(1):11–14
142. Sorce LR, Hamilton SM, Gauvreau K, et al: Preventing corneal abrasions in critically ill children receiving neuromuscular blockade: A randomized, controlled trial. *Pediatr Crit Care Med* 2009; 10:171–175
143. Tamion F, Hamelin K, Duflo A, et al: Gastric emptying in mechanically ventilated critically ill patients: Effect of neuromuscular blocking agent. *Intensive Care Med* 2003; 29:1717–1722
144. Martindale RG, McClave SA, Vanek VW, et al; American College of Critical Care Medicine; A.S.P.E.N. Board of Directors: Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary. *Crit Care Med* 2009; 37:1757–1761
145. Balon JA: Common factors of spontaneous self-extubation in a critical care setting. *Int J Trauma Nurs* 2001; 7:93–99
146. Bouza C, Garcia E, Diaz M, et al: Unplanned extubation in orally intubated medical patients in the intensive care unit: A prospective cohort study. *Heart Lung* 2007; 36:270–276
147. Carrión MI, Ayuso D, Marcos M, et al: Accidental removal of endotracheal and nasogastric tubes and intravascular catheters. *Crit Care Med* 2000; 28:63–66
148. Chevron V, Ménard JF, Richard JC, et al: Unplanned extubation: Risk factors of development and predictive criteria for reintubation. *Crit Care Med* 1998; 26:1049–1053
149. Chiang AA, Lee KC, Lee JC, et al: Effectiveness of a continuous quality improvement program aiming to reduce unplanned extubation: A prospective study. *Intensive Care Med* 1996; 22:1269–1271
150. Coppolo DP, May JJ: Self-extubations. A 12-month experience. *Chest* 1990; 98:165–169
151. Curry K, Cobb S, Kutash M, et al: Characteristics associated with unplanned extubations in a surgical intensive care unit. *Am J Crit Care* 2008; 17:45–51; quiz 52
152. da Silva PS, Fonseca MC: Unplanned endotracheal extubations in the intensive care unit: Systematic review, critical appraisal, and evidence-based recommendations. *Anesth Analg* 2012; 114:1003–1014
153. de Groot RI, Dekkers OM, Herold IH, et al: Risk factors and outcomes after unplanned extubations on the ICU: A case-control study. *Crit Care* 2011; 15:R19
154. de Lassence A, Alberti C, Azoulay E, et al; OUTCOMEREA Study Group: Impact of unplanned extubation and reintubation after weaning on nosocomial pneumonia risk in the intensive care unit: A prospective multicenter study. *Anesthesiology* 2002; 97:148–156
155. Huang YT: Factors leading to self-extubation of endotracheal tubes in the intensive care unit. *Nurs Crit Care* 2009; 14:68–74
156. Moons P, Boriau M, Ferdinande P: Self-extubation risk assessment tool: Predictive validity in a real-life setting. *Nurs Crit Care* 2008; 13:310–314
157. Richmond AL, Jarog DL, Hanson VM: Unplanned extubation in adult critical care. Quality improvement and education payoff. *Crit Care Nurse* 2004; 24:32–37
158. Yeh SH, Lee LN, Ho TH, et al: Implications of nursing care in the occurrence and consequences of unplanned extubation in adult intensive care units. *Int J Nurs Stud* 2004; 41:255–262
159. Krinsley JS, Barone JE: The drive to survive: Unplanned extubation in the ICU. *Chest* 2005; 128:560–566
160. Betbesé AJ, Pérez M, Bak E, et al: A prospective study of unplanned endotracheal extubation in intensive care unit patients. *Crit Care Med* 1998; 26:1180–1186
161. Boulain T: Unplanned extubations in the adult intensive care unit: A prospective multicenter study. Association des Réanimateurs du Centre-Ouest. *Am J Respir Crit Care Med* 1998; 157:1131–1137
162. Whelan J, Simpson SQ, Levy H: Unplanned extubation. Predictors of successful termination of mechanical ventilatory support. *Chest* 1994; 105:1808–1812
163. Tung A, Tadimeti L, Caruana-Montaldo B, et al: The relationship of sedation to deliberate self-extubation. *J Clin Anesth* 2001; 13:24–29
164. Chang LC, Liu PF, Huang YL, et al: Risk factors associated with unplanned endotracheal self-extubation of hospitalized intubated patients: A 3-year retrospective case-control study. *Appl Nurs Res* 2011; 24:188–192
165. Chang LY, Wang KW, Chao YF: Influence of physical restraint on unplanned extubation of adult intensive care patients: A case-control study. *Am J Crit Care* 2008; 17:408–15; quiz 416
166. Kaplow R, Bookbinder M: A comparison of four endotracheal tube holders. *Heart Lung* 1994; 23:59–66
167. Carlson J, Mayrose J, Krause R, et al: Extubation force: Tape versus endotracheal tube holders. *Ann Emerg Med* 2007; 50:686–691
168. Owen R, Castle N, Hann H, et al: Extubation force: A comparison of adhesive tape, non-adhesive tape and a commercial endotracheal tube holder. *Resuscitation* 2009; 80:1296–1300
169. Levy H, Griego L: A comparative study of oral endotracheal tube securing methods. *Chest* 1993; 104:1537–1540
170. Tominaga GT, Rudzwick H, Scannell G, et al: Decreasing unplanned extubations in the surgical intensive care unit. *Am J Surg* 1995; 170:586–589
171. Kupas DF, Kauffman KF, Wang HE: Effect of airway-securing method on prehospital endotracheal tube dislodgment. *Prehosp Emerg Care* 2010; 14:26–30
172. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359–1367
173. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461
174. Van den Berghe G, Schoonheydt K, Becx P, et al: Insulin therapy protects the central and peripheral nervous system of intensive care patients. *Neurology* 2005; 64:1348–1353
175. Hermans G, Wilmer A, Meersseman W, et al: Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. *Am J Respir Crit Care Med* 2007; 175:480–489
176. Van den Berghe G, Wilmer A, Milants I, et al: Intensive insulin therapy in mixed medical/surgical intensive care units: Benefit versus harm. *Diabetes* 2006; 55:3151–3159
177. Dellinger RP, Levy MM, Carlet JM, et al; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296–327
178. Jacobi J, Bircher N, Krinsley J, et al: Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med* 2012; 40:3251–3276
179. Paterson IG, Hood JR, Russell SH, et al: Mivacurium in the myasthenic patient. *Br J Anaesth* 1994; 73:494–498

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180. Tripathi SS, Hunter JM: Neuromuscular blocking drugs in the critically ill. *Contin Educ Anaesth Crit Care Pain* 2006; 6:117–123
181. Baraka A: Anesthesia and myasthenia gravis. *Middle East J Anaesthesiol* 1993; 12:9–35
182. Blichfeldt-Lauridsen L, Hansen BD: Anesthesia and myasthenia gravis. *Acta Anaesthesiol Scand* 2012; 56:17–22
183. Eisenkraft JB, Book WJ, Papatestas AE: Sensitivity to vecuronium in myasthenia gravis: A dose-response study. *Can J Anaesth* 1990; 37:301–306
184. Itoh H, Shibata K, Nitta S: Difference in sensitivity to vecuronium between patients with ocular and generalized myasthenia gravis. *Br J Anaesth* 2001; 87:885–889
185. van Kralingen S, van de Garde EM, Knibbe CA, et al: Comparative evaluation of atracurium dosed on ideal body weight vs. total body weight in morbidly obese patients. *Br J Clin Pharmacol* 2011; 71:34–40
186. Weinstein JA, Matteo RS, Ornstein E, et al: Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. *Anesth Analg* 1988; 67:1149–1153
187. Varin F, Ducharme J, Théorêt Y, et al: Influence of extreme obesity on the body disposition and neuromuscular blocking effect of atracurium. *Clin Pharmacol Ther* 1990; 48:18–25
188. Tsueda K, Warren JE, McCafferty LA, et al: Pancuronium bromide requirement during anesthesia for the morbidly obese. *Anesthesiology* 1978; 48:438–439
189. Schwartz AE, Matteo RS, Ornstein E, et al: Pharmacokinetics and pharmacodynamics of vecuronium in the obese surgical patient. *Anesth Analg* 1992; 74:515–518
190. Salihoĝlu Z, Demiroluk S, Köse Y, et al: Neuromuscular effects of cisatracurium in morbidly obese patients. *Middle East J Anaesthesiol* 2008; 19:831–839
191. Pühringer FK, Keller C, Kleinsasser A, et al: Pharmacokinetics of rocuronium bromide in obese female patients. *Eur J Anaesthesiol* 1999; 16:507–510
192. Leykin Y, Pellis T, Lucca M, et al: The pharmacodynamic effects of rocuronium when dosed according to real body weight or ideal body weight in morbidly obese patients. *Anesth Analg* 2004; 99:1086–1089, table of contents
193. Leykin Y, Pellis T, Lucca M, et al: The effects of cisatracurium on morbidly obese women. *Anesth Analg* 2004; 99:1090–1094, table of contents
194. Kirkegaard-Nielsen H, Helbo-Hansen HS, Lindholm P, et al: Anthropometric variables as predictors for duration of action of atracurium-induced neuromuscular block. *Anesth Analg* 1996; 83:1076–1080
195. Feingold A: Pancuronium requirements of the morbidly obese. *Anesthesiology* 1979; 50:269–270
196. Janmahasatian S, Duffull SB, Ash S, et al: Quantification of lean bodyweight. *Clin Pharmacokinet* 2005; 44:1051–1065
197. Bloomfield R, Steel E, MacLennan G, et al: Accuracy of weight and height estimation in an intensive care unit: Implications for clinical practice and research. *Crit Care Med* 2006; 34:2153–2157
198. Jensen GL, Friedmann JM, Henry DK, et al: Noncompliance with body weight measurement in tertiary care teaching hospitals. *JPEN J Parenter Enteral Nutr* 2003; 27:89–90
199. Jago RH: Arthrogryposis following treatment of maternal tetanus with muscle relaxants. *Arch Dis Child* 1970; 45:277–279
200. Karnad DR, Guntupalli KK: Critical illness and pregnancy: Review of a global problem. *Crit Care Clin* 2004; 20:555–76, vii
201. Cartin-Ceba R, Gajic O, Iyer VN, et al: Fetal outcomes of critically ill pregnant women admitted to the intensive care unit for nonobstetric causes. *Crit Care Med* 2008; 36:2746–2751
202. Karnad DR, Lapsia V, Krishnan A, et al: Prognostic factors in obstetric patients admitted to an Indian intensive care unit. *Crit Care Med* 2004; 32:1294–1299
203. Duncan PG, Pope WD, Cohen MM, et al: Fetal risk of anesthesia and surgery during pregnancy. *Anesthesiology* 1986; 64:790–794
204. Mazze RI, Källén B: Reproductive outcome after anesthesia and operation during pregnancy: A registry study of 5405 cases. *Am J Obstet Gynecol* 1989; 161:1178–1185
205. Mazze RI, Källén B: Appendectomy during pregnancy: A Swedish registry study of 778 cases. *Obstet Gynecol* 1991; 77:835–840
206. Guay J, Grenier Y, Varin F: Clinical pharmacokinetics of neuromuscular relaxants in pregnancy. *Clin Pharmacokinet* 1998; 34:483
207. Sharp LM, Levy DM: Rapid sequence induction in obstetrics revisited. *Curr Opin Anaesthesiol* 2009; 22:357–361
208. Hawkins JL, Johnson TD, Kubicek MA, et al: Vecuronium for rapid-sequence intubation for cesarean section. *Anesth Analg* 1990; 71:185–190
209. Shearer ES, Fahy LT, O'Sullivan EP, et al: Transplacental distribution of atracurium, laudanosine and monoquaternary alcohol during elective caesarean section. *Br J Anaesth* 1991; 66:551–556
210. Abouleish E, Abboud T, Lechevalier T, et al: Rocuronium (Org 9426) for caesarean section. *Br J Anaesth* 1994; 73:336–341
211. Cherala SR, Eddie DN, Sechzer PH: Placental transfer of succinylcholine causing transient respiratory depression in the newborn. *Anaesth Intensive Care* 1989; 17:202–204
212. Dailey PA, Fisher DM, Shnider SM, et al: Pharmacokinetics, placental transfer, and neonatal effects of vecuronium and pancuronium administered during cesarean section. *Anesthesiology* 1984; 60:569–574
213. Duvaldestin P, Demetriou M, Henzel D, et al: The placental transfer of pancuronium and its pharmacokinetics during caesarian section. *Acta Anaesthesiol Scand* 1978; 22:327–333
214. Fodale V, Santamaria LB: Laudanosine, an atracurium and cisatracurium metabolite. *Eur J Anaesthesiol* 2002; 19:466–473
215. Khuenl-Brady KS, Koller J, Mair P, et al: Comparison of vecuronium- and atracurium-induced neuromuscular blockade in postpartum and nonpregnant patients. *Anesth Analg* 1991; 72:110–113
216. Pan PH, Moore C: Comparison of cisatracurium-induced neuromuscular blockade between immediate postpartum and nonpregnant patients. *J Clin Anesth* 2001; 13:112–117
217. Smith CE, van Miert MM, Parker CJ, et al: A comparison of the infusion pharmacokinetics and pharmacodynamics of cisatracurium, the 1R-cis 1'R-cis isomer of atracurium, with atracurium besylate in healthy patients. *Anaesthesia* 1997; 52:833–841
218. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. *JAMA* 1968; 205:337–340
219. Guidelines for the determination of death. Report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *JAMA* 1981; 246:2184–2186.
220. Rosenberg RN: Consciousness, coma, and brain death–2009. *JAMA* 2009; 301:1172–1174
221. Wijdicks EF, Pfeifer EA: Neuropathology of brain death in the modern transplant era. *Neurology* 2008; 70:1234–1237
222. Wijdicks EF: The diagnosis of brain death. *N Engl J Med* 2001; 344:1215–1221
223. Truog RD: Brain death - too flawed to endure, too ingrained to abandon. *J Law Med Ethics* 2007; 35:273–281
224. Kuhse H: Response to Ronald M Perkin and David B Resnik: The agony of trying to match sanctity of life and patient-centred medical care. *J Med Ethics* 2002; 28:270–272
225. Riddick CA, Schneiderman LJ: Distinguishing between effect and benefit. *J Clin Ethics* 1994; 5:41–43
226. Perkin RM, Resnik DB: The agony of agonal respiration: Is the last gasp necessary? *J Med Ethics* 2002; 28:164–169
227. Perkin RM, Resnik DB: Response to Kuhse. *J Med Ethics* 2002; 28:273–4; discussion 274
228. Faber-Langendoen K: The clinical management of dying patients receiving mechanical ventilation. A survey of physician practice. *Chest* 1994; 106:880–888
229. Hawryluck LA, Harvey WR, Lemieux-Charles L, et al: Consensus guidelines on analgesia and sedation in dying intensive care unit patients. *BMC Med Ethics* 2002; 3:E3
230. Forel JM, Roch A, Papazian L: Paralytics in critical care: Not always the bad guy. *Curr Opin Crit Care* 2009; 15:59–66

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