



# Continuous Infusion Neuromuscular Blocking Agents (NMBAs) – Adult – Inpatient Clinical Practice Guideline

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## **Executive Summary**

### **Guideline Overview**

The purpose of this guideline is to serve as a resource for members of multi-disciplinary intensive care teams concerning continuous infusion neuromuscular blocking agent administration considerations

### **Key Revisions (2017 Periodic Review)**

List any MAJOR revisions which were made between full periodic reviews or during last review.

1. Recommendations regarding monitoring sedation in paralyzed patients via BIS were added
2. Information on the reversal agent sugammadex was added

### **Key Practice Recommendations**

1. Indications for the use of neuromuscular blockade include the following:
  - Facilitation of mechanical ventilation (to include ARDS, unconventional ventilatory modes, and significant patient-ventilatory asynchrony)
  - Life threatening status asthmaticus with profound hypoxemia, respiratory acidosis, or hemodynamic compromise
  - To control increased intracranial pressure, reperfusion injury and/or primary graft dysfunction in lung transplant patients
  - Supportive therapy for muscle spasms, tetanus or neuroleptic malignant syndrome
  - To maintain patients' immobility (after certain surgical repairs/devices)
  - To treat shivering with therapeutic hypothermia protocols
  - To help facilitate extracorporeal membrane oxygenation
  - Increased intra-abdominal pressure
  - To accomplish procedures or diagnostic studies such as magnetic resonance imaging (MRI) or computed tomography (CT).
2. NMBA selection: In the absence of hepatic or renal dysfunction, and no concomitant systemic steroid use, vecuronium or rocuronium are the first line NMBAs of choice. If a patient is on systemic steroids, or has hepatic or renal dysfunction, atracurium is the first line NMBA of choice. If, while being treated with atracurium, the patient experiences tachyphylaxis or cardiovascular side effects (e.g., hypotension due to histamine release), it would be appropriate to switch the patient to cisatracurium.
3. Analgesia and sedation: Prior to implementation of neuromuscular blockade, ensure the patient is adequately ventilated and ensure adequate pain control and sedation are achieved prior to neuromuscular blockade. The level of sedation should be monitored using physio-neurologic monitoring—BIS™ (Bispectral Index Monitors).
4. Monitoring: It is recommended that the depth of neuromuscular blockade be monitored with peripheral nerve stimulation (Train of Four (TOF) method) per [UWHC Departmental Policy 8.36AP - Peripheral Nerve Stimulation \(Adult & Pediatric\)](#). Periodic monitoring (Q 48-72 hours) of CK is recommended to prevent prolonged muscle weakness and acute quadriplegic myopathy (AQMS).
5. Supportive care: All patients receiving neuromuscular blocking agents should have the following conditions proactively treated to prevent increased morbidity: venous

thromboembolism (VTE) prophylaxis, scheduled eye lubrication, careful passive range of motion, and pressure points carefully padded and regularly assessed.

### **Companion Documents**

1. [Pharmacokinetic Parameters, Contraindications, and Common Adverse Effects of Neuromuscular Blocking Agents](#)
2. [Neuromuscular Blocking Agent Dose Titration Table](#)
3. [Algorithm for Selection of Neuromuscular Blocking Agent](#)
4. [Key Properties of NMB Reversal Agents](#)
5. [Assessment and Treatment of Pain, Agitation, and Delirium in the Mechanically Ventilated Intensive Care Unit Patient – Adult – Inpatient Clinical Practice Guideline](#)
6. [UWHC Departmental Policy 8.36AP - Peripheral Nerve Stimulation \(Adult & Pediatric\)](#)

### **Scope**

**Disease/Condition(s):** All mechanically ventilated adult patients receiving continuous infusion of neuromuscular blocking agents (NMBAs)

**Clinical Specialty:** Critical care, Nursing, Pharmacy, Respiratory Therapy, Physical Therapy

**Intended Users:** Prescribing Physicians, Advanced Practice Providers, Pharmacists, Registered Nurses, Physical Therapists, & Respiratory Therapists

**Objective(s):** To facilitate the safe and effective use of continuous infusion NMBAs at UW Health

**Target Population:** Adult inpatients (18 years or older) who are intubated.

### **Interventions and Practices Considered:**

- Indication for use of continuous infusion neuromuscular blocker agents
- How to choose the appropriate neuromuscular blocker agent
- Appropriate sedation and supportive care for and monitoring of patients on continuous infusion neuromuscular blocker agents

### **Major Outcomes Considered:**

- Decrease medication errors associated with the use of continuous infusion neuromuscular blocker agents
- Optimize outcomes of patients being treated with continuous infusion neuromuscular blocker agents

### **Methodology**

#### **Methods Used to Collect/Select the Evidence:**

Electronic database searches (e.g., PUBMED) were conducted by the guideline author(s) and workgroup members to collect evidence for review. Expert opinion and clinical experience were also considered during discussions of the evidence.

#### **Methods Used to Formulate the Recommendations:**

The workgroup members agreed to adopt recommendations developed by external organizations and/or arrived at a consensus through discussion of the literature and expert

experience. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees (as appropriate).

**Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:**

Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1** in [Appendix A](#)).

**Rating Scheme for the Strength of the Evidence/Recommendations:**

See [Appendix A](#) for the rating scheme(s) used within this document.

**Recognition of Potential Health Care Disparities:<sup>1</sup> NA**

**Cost Analysis:**

Infusion	Rate	Cost*/day
Vecuronium	1 mcg/kg/min	\$60.48
Rocuronium	10 mcg/kg/min	\$85.78
Atracurium	8 mcg/kg/min	\$125.80
Cisatracurium	5 mcg/kg/min	\$695.72

\*Average Wholesale Price (AWP)

**Definitions**

Neuromuscular blocking agents (NMBAs): medications that paralyze skeletal muscles by blocking the transmission of nerve impulses at the neuromuscular junction

Depolarizing NMBAs: a form of neuromuscular blocker that first causes depolarization and contraction by activating cholinergic receptors, then blocks subsequent neurotransmission, causing paralysis.

Non-depolarizing NMBAs: a form of neuromuscular blocker that does not depolarize the motor end plate but rather exerts its paralytic activity by blocking the activity of acetylcholine at the cholinergic receptors.

Train of Four assessments (TOF): a type of peripheral nerve stimulation monitor that involves electrical stimulation of a peripheral motor nerve with four sequential stimuli over a two second period and observation of the responses of a muscle innervated by the stimulated nerve

Peripheral nerve stimulation monitoring: a process by which stimulators are used to assess neuromuscular transmission when NMBAs are given to block skeletal muscle activity. The muscle twitch response to an electrical stimulus delivered by the peripheral nerve stimulator corresponds to the degree of nerve receptors blocked by NMBAs and assists the clinician in the assessment and titration of medication dosage.

Bispectral Index Monitor (BIS): sedation monitoring device that analyzes a patient's electroencephalogram (EEG), reporting out a compilation of EEG frequency and amplitude. The

BIS monitor is placed on a patient's head during neuromuscular blockade to monitor the level of sedation of the patient when paralyzed. BIS provides a single, dimensionless number from 0 (EEG silence) to 100.

Acute Quadriplegic Myopathy Syndrome (AQMS): an acquired myopathy characterized by diffuse persistent weakness that persists long after NMBAs have been discontinued and any drug metabolites have been eliminated. Both upper and lower extremities are affected, and reflexes are decreased.

Acetylcholinesterase (ACh) inhibitor: a chemical or drug that inhibits the acetylcholinesterase enzyme from breaking down acetylcholine, thereby increasing both the level and duration of action of the neurotransmitter acetylcholine.

## **Introduction**

Patients admitted to the intensive care unit (ICU) may require muscle relaxation with neuromuscular blocking agents (NMBAs) for various indications. Some of these include the facilitation of adequate ventilation, control of intracranial pressure, and allowing for therapeutic hypothermia.<sup>2-5</sup> Due to the complex pharmacokinetic and pharmacodynamic parameters of available agents for the neuromuscular blockade of critically ill adults, continuous infusions and frequent titration are often necessary to achieve therapeutic goals.<sup>4</sup> In determining the need for titration, therapeutic goals are assessed using parameters such as synchrony with ventilator support and train of four (TOF) assessments.<sup>4</sup> The [Neuromuscular Blocking Agent Continuous Infusion – Adult – Inpatient Delegation Protocol](#) has been developed to facilitate the appropriate management of continuous infusions of NMBAs and to delegate authority of titration to nurses. The purpose of this guideline is to provide information and recommendations regarding the safe and effective use of NMBAs in critically ill adults.

## **Recommendations**

### **1. Suggested indications**

- 1.1. Facilitation of mechanical ventilation
  - 1.1.1. Severe acute respiratory distress syndrome (ARDS)<sup>6,7</sup> (*Weak recommendation, moderate quality of evidence*)
  - 1.1.2. Unconventional ventilatory modes (pressure control, inverse I:E ratio, prone ventilation)<sup>8-11</sup> (*Strong recommendation, High quality of evidence*)
  - 1.1.3. Significant patient-ventilatory asynchrony<sup>12</sup> (*Strong recommendation, Moderate quality of evidence*)
- 1.2. Life threatening status asthmaticus with profound hypoxemia, respiratory acidosis, or hemodynamic compromise<sup>7</sup> (*Weak recommendation, very low quality of evidence*)
- 1.3. To control increased intracranial pressure<sup>2,13-15</sup> (*Moderate recommendation, low quality of evidence*)
- 1.4. Reperfusion injury and/or primary graft dysfunction in lung transplant patients<sup>16</sup> (*Weak recommendation, Low quality of evidence*)
- 1.5. Supportive therapy for muscle spasms, tetanus or neuroleptic malignant syndrome<sup>17-19</sup> (*Strong recommendation, Moderate quality of evidence*)
- 1.6. To maintain patients' immobility (after certain surgical repairs/devices) (*Weak recommendation, Low quality of evidence*)
- 1.7. Treat shivering with therapeutic hypothermia protocols<sup>20-26</sup> (*Strong recommendation, Moderate quality of evidence*)
- 1.8. To help facilitate extracorporeal membrane oxygenation (ECMO)<sup>27</sup> (*Weak recommendation, Low quality of evidence*)
- 1.9. Increased intra-abdominal pressure<sup>28-33</sup> (*Weak recommendation, Moderate quality of evidence*)
- 1.10. To accomplish procedures or diagnostic studies such as magnetic resonance imaging (MRI) or computed tomography (CT) (*Weak recommendation, Low quality of evidence*)

### **2. Neuromuscular Blocking Agent Characteristics & Selection**

1. Succinylcholine, the sole depolarizing NMBA, is only used in bolus doses for intubation due to its short duration of action<sup>34</sup> (*Strong recommendation, Moderate quality of evidence*)
2. Most non-depolarizing agents may be used for skeletal muscle relaxation prior to induction of anesthesia and intubation or as a continuous infusion in an ICU setting.<sup>7</sup>
3. In the absence of hepatic or renal dysfunction, and no concomitant systemic steroid use, vecuronium or rocuronium are the first line NMBAs of choice. If a patient is on systemic steroids, or has hepatic or renal dysfunction, atracurium is the first line NMBA of choice. If, while being treated with atracurium, the patient experiences tachyphylaxis or cardiovascular side effects (e.g., hypotension due to histamine release), it would be appropriate to switch the patient to cisatracurium.
  - 3.1. See [Appendix E: Algorithm for Selection of Neuromuscular Blocking Agent](#) for algorithm to guide specific drug selection. If costs for these agents change substantially, algorithm will be updated to reflect cost optimization.
  - 3.2. Although cisatracurium is the primary agent studied for the indication of ARDS, the mortality benefits seen are understood to be a class effect, and cisatracurium should not be used preferentially.<sup>6,33</sup> (*Weak recommendation, Low quality of evidence*)
4. See [Appendix C: Pharmacokinetic Parameters, Contraindications, and Common Adverse Effects of Neuromuscular Blocking Agents](#) for a summary of individual characteristics of NMBAs available.
5. Non-depolarizing NMBAs used for continuous infusion at UWHC include: vecuronium, rocuronium, atracurium, and cisatracurium.
  - 5.1. Vecuronium
    - 5.1.1. Chemical structure: aminosteroid derivative of pancuronium<sup>7</sup>
    - 5.1.2. Pharmacokinetics
      - 5.1.2.1. Duration: intermediate<sup>7</sup>

- 5.1.2.2. Metabolism/excretion: hepatically metabolized to active metabolites with renal (15-35%) and biliary excretion (30-50%).<sup>7,35</sup>
- 5.1.3. Adverse effects
  - 5.1.3.1. Unlike pancuronium, lacks vagolytic effects<sup>7</sup>
  - 5.1.3.2. Similar to atracurium and cisatracurium, has minimal cardiovascular effects.<sup>4</sup>
  - 5.1.3.3. Not associated with histamine release
- 5.1.4. Cautions
  - 5.1.4.1. Patients with renal or hepatic insufficiency may require reduced dosages to maintain appropriate neuromuscular blockade, and may demonstrate prolonged recovery after infusion discontinuation due to increased plasma levels of parent drug and active metabolite.
- 5.1.5. Place in therapy
  - 5.1.5.1. First-line agent for patients without renal (< 30 mL/min) or hepatic impairment (total bilirubin > 2.2 mg/dL, transaminases and alkaline phosphatase > 3 times normal) and not receiving corticosteroid therapy (*Strong recommendation, Low quality of evidence*)
- 5.2. Rocuronium
  - 5.2.1. Chemical structure: aminosteroid derivative with similar chemical structure to vecuronium<sup>36</sup>
  - 5.2.2. Pharmacokinetics
    - 5.2.2.1. Duration: intermediate<sup>36</sup>
    - 5.2.2.2. Metabolism/excretion: Primarily excretion as whole drug via the hepatobiliary route without appreciable hepatic metabolism. Approximately 30% of a dose is excreted unchanged renally.<sup>36,37</sup>
  - 5.2.3. Adverse effects
    - 5.2.3.1. Minimal cardiovascular effects unlike pancuronium<sup>36</sup>
  - 5.2.4. Cautions
    - 5.2.4.1. Patients with renal insufficiency may require reduced dosages to maintain appropriate neuromuscular blockade and may demonstrate prolonged recovery after infusion discontinuation due to increased plasma levels of parent drug.<sup>37</sup>
    - 5.2.4.2. Due to elimination via the hepatobiliary route, extended neuromuscular blockade may occur with patients who have hepatic insufficiency<sup>36,37</sup>
  - 5.2.5. Place in therapy
    - 5.2.5.1. Alternative first-line agent for patients without renal (< 30 mL/min) or hepatic impairment (total bilirubin > 2.2 mg/dL, transaminases and alkaline phosphatase > 3 times normal) and not receiving corticosteroid therapy<sup>7,36</sup> (*Strong recommendation, Moderate quality of evidence*)
- 5.3. Atracurium
  - 5.3.1. Chemical structure: benzylisoquinolinium derivative of tubocurarine
  - 5.3.2. Pharmacokinetics
    - 5.3.2.1. Duration: intermediate
    - 5.3.2.2. Metabolism/excretion: plasma inactivation via Hofmann elimination and ester hydrolysis.<sup>38</sup>
  - 5.3.3. Adverse effects
    - 5.3.3.1. Unlike some of the older NMBA's, atracurium has minimal cardiovascular effects, but may cause histamine release at very high doses (often higher than used clinically) with the potential for resultant hypotension and bronchospasm.<sup>39</sup>
  - 5.3.4. Cautions
    - 5.3.4.1. Atracurium is converted to the inactive metabolite laudanosine which crosses the blood brain barrier and demonstrates a prolonged elimination half-life in hepatic or renal impairment.<sup>40</sup> However, at normal infusion doses of atracurium, this metabolite has not been shown to exhibit toxic effects in humans and dosage modifications in hepatic or renal insufficiency are unnecessary.<sup>41</sup>
    - 5.3.4.2. If a patient develops tachyphylaxis (dose > 12 mcg/kg/min and unable to keep patient adequately paralyzed), a different paralytic agent should be used.<sup>7,42</sup>
  - 5.3.5. Place in therapy

- 5.3.5.1. First-line agent for patients with impaired renal clearance (< 30 mL/min) or hepatic impairment (total bilirubin > 2.2 mg/dL, transaminases and alkaline phosphatase > 3 times normal) or those receiving corticosteroids. (*Strong recommendation, Low quality of evidence*)
- 5.4. Cisatracurium
  - 5.4.1. Chemical structure: the stereoisomer of atracurium, is also a benzyliisoquinolinium agent<sup>39</sup>
  - 5.4.2. Pharmacokinetics
    - 5.4.2.1. Duration: Intermediate<sup>39</sup>
    - 5.4.2.2. Metabolism/excretion: metabolized via Hofmann elimination<sup>39</sup>
  - 5.4.3. Cautions
    - 5.4.3.1. Like atracurium, has very minimal cardiovascular effects as well as is more potent, causes less histamine release, and results in less creation of laudanosine when compared to atracurium<sup>38,39</sup>
  - 5.4.4. Place in therapy
    - 5.4.4.1. Due to costs much higher than atracurium, this agent is recommended only for patients who develop tachyphylaxis to atracurium (dose > 12 mcg/kg/min and unable to keep patient adequately paralyzed). (*Strong recommendation, Level of Evidence IIa*)
- 3. Implementation of Neuromuscular Blockade**
  1. Prior to implementation of neuromuscular blockade the following points should be addressed:
    - 1.1. Provide the patient with adequate ventilation<sup>7-10</sup> (*Strong recommendation, High quality of evidence*)
    - 1.2. Ensure adequate pain control and sedation are achieved prior to neuromuscular blockade<sup>7-10</sup> (*Strong recommendation, High quality of evidence*), evidenced by a Richmond Agitation and Sedation Score (RASS)<sup>43</sup> of -4 to -5 and a Critical Care Pain Observation Tool (CPOT)<sup>44</sup> score of less than 3, according to the [Assessment and Treatment of Pain, Agitation, and Delirium in the Mechanically Ventilated Intensive Care Unit Patient – Adult – Inpatient Clinical Practice Guideline](#).
      - 1.2.1. The use of neuromuscular blocking agents is rare without appropriate and concomitant sedation and analgesia<sup>7</sup>. (*Strong recommendation, Moderate quality of evidence*)
      - 1.2.2. Because dexmedetomidine does not allow for consistent and adequate deep sedation, and does not provide amnestic properties in normal sedative doses, additional sedatives should be used in conjunction with dexmedetomidine. Alternatively, consider sedation with another agent such as propofol or midazolam.<sup>35,45</sup> (*Strong recommendation, Moderate quality of evidence*)
      - 1.2.3. Opioids (including fentanyl, hydromorphone or morphine) are not approved as monotherapy for sedation but should be used as an adjunct with an approved sedative agent.<sup>7</sup> (*Strong recommendation, Low quality of evidence*)
    - 1.3. If an order for an approved and adequate level of a sedative and analgesic agent is not received, the pharmacist and nurse will not implement the order for the neuromuscular agent and notify the prescribing physician that the order was not implemented for this reason. (*Strong recommendation, Low quality of evidence*)
  2. Daily reassessment of the need for ongoing paralysis and termination of the blockade should be performed at the earliest possible time. (*Strong recommendation, Low quality of evidence*)
  3. Smooth muscle is unaffected by NMBAs so enteral feeding still remains an option for nutritional support in critically ill patients receiving NMBAs.<sup>7,46</sup> (*Weak recommendation, Low quality of evidence*).
  4. Increased rates of prolonged weakness and acute quadriplegic myopathy (AQMS) have been associated with the concomitant use of NMBAs and corticosteroids, aminoglycosides, or cyclosporine and the presence of malnutrition, hyperglycemia, metabolic disorders, and hepatic or renal impairment.<sup>7</sup> (*Strong recommendation, Moderate quality of evidence*)
    - 4.1. Patients taking any interacting medications should be evaluated for potential medication discontinuation or change. If the medication cannot be discontinued or changed, patients

- should be followed closely for prolonged weakness and the neuromuscular blocker should be discontinued as early as possible.<sup>7</sup> (*Strong recommendation, Low quality of evidence*)
- 4.2. Incidence of prolonged recovery or weakness may be as high as 30% in patients on concomitant corticosteroids. The risk increases when neuromuscular blockers are used for greater than 2 days and the total daily dose of corticosteroids is in excess of 1 gram/day of methylprednisolone (or equivalent).<sup>7</sup>
    - 4.2.1. If the corticosteroids cannot be discontinued, then benzylisoquinolinium neuromuscular blockers derivatives (atracurium or cisatracurium) should be preferentially used to minimize the risk of prolonged recovery and weakness.<sup>7</sup> (*Strong recommendation, Low quality of evidence*)
  5. All patients receiving neuromuscular blocking agents should have the following conditions proactively treated to prevent increased morbidity:
    - 5.1. Venous thromboembolism (VTE) prophylaxis: VTE prophylaxis should be administered with either low molecular weight heparin or unfractionated heparin if no contraindications exists. Patients are at increased risk for deep venous thrombosis and pulmonary embolism due to immobility.<sup>7</sup> (*Strong recommendation, High quality of evidence*)
    - 5.2. Scheduled eye lubrication: In order to prevent keratitis, corneal abrasions, soft tissue or nerve injury and skin breakdown, artificial tears ophthalmic ointment should be applied as a thin strip to each eye every 4 hours.<sup>7,47-51</sup> (*Strong recommendation, Low quality of evidence*)
      - 5.2.1. Taping eyes shut or using a patch to cover eyes may also be considered in addition to applying eye lubrication<sup>7</sup> (*Strong recommendation, Low quality of evidence*)
    - 5.3. All patients should receive careful passive range of motion.<sup>7</sup> (*Weak recommendation, Very low quality of evidence*)
    - 5.4. All patients should have pressure points carefully padded and regularly assessed. (*Strong recommendation, Low quality of evidence*)
  4. **Titration of Neuromuscular Blocking Agents** ([Appendix D: Neuromuscular Blocking Agent Dose Titration Table](#)) (see [Neuromuscular Blocking Agent Continuous Infusion – Adult – Inpatient delegation protocol](#))
    - 1.1. The rate and frequency of dose titration is dependent upon the patient's individual level of neuromuscular blockade, clinical status, and response to therapy as assessed by the ICU nurse. (*Strong recommendation, Low quality of evidence*)
    - 1.2. The lowest infusion rate that achieves the stated target objective is utilized. Examples: include ventilator synchrony, patient immobility, ICP < goal, or lack of shivering with hypothermia protocol. (*Strong recommendation, Low quality of evidence*)
    - 1.3. The sequence of muscle paralysis progresses from small, rapidly moving muscles (i.e., eyes, jaw and larynx) to limbs / trunk to intercostal muscles and finally to the diaphragm. Recovery of muscles usually occurs in the opposite sequence, with the diaphragm recovering function first.
    - 1.4. Infusion of NMBAs may be discontinued without taper. (*Strong recommendation, Moderate quality of evidence*)
    - 1.5. After discontinuation, peripheral nerve stimulation (TOF) monitoring continues every 2 hours until the patient demonstrates complete return of 4/4 twitches. Respiratory muscle paralysis may still be present to some degree even if a patient has 4/4 twitches. (*Strong recommendation, Low quality of evidence*)
  5. **Monitoring and Documentation**
    1. We suggest patients have the depth of neuromuscular blockade monitored with peripheral nerve stimulation (Train of Four (TOF) method) per [UWHC Departmental Policy 8.36AP - Peripheral Nerve Stimulation \(Adult & Pediatric\)](#).<sup>7,21</sup> (*Strong recommendation, Low quality of evidence*)
      - 1.1. Peripheral nerve stimulation (TOF) should not be used as the goal of titration of neuromuscular blockage, but should be used to titrate the agents to the lowest dose possible while maintaining adequate effect. Neuromuscular blockers should be titrated to clinical effect (e.g. ventilator synchrony, improved oxygenation) with the highest possible TOF. (*Weak recommendation, Very low quality of evidence*)

- 1.2. It is recommended that peripheral nerve stimulation be used with the aminosteroidal derivatives rocuronium and vecuronium<sup>7,21</sup> (*Weak recommendation, Very low quality of evidence*)
- 1.3. Peripheral nerve testing (TOF) will be done prior to initiating the drip (to determine the required milliamperes required to achieve 4 of 4 twitches per [Nursing Policy #8.36 AP](#)), and then after initiation of the drip, once the clinical endpoint has been achieved (i.e., ventilatory synchrony). If TOF is >2, no dose change is needed. If TOF is ≤2, then the dose of the infusion should be decreased, and after 1-2 hours the clinical endpoint and TOF should be reassessed. Once twitches are at the highest possible for 2 consecutive readings while maintaining the clinical endpoint, TOF should be monitoring every 4-8 hours. (*Strong recommendation, Low quality of evidence*). The usual goal for TOF monitoring should be 2-3 out of 4 twitches; however, higher twitch levels (4 out of 4) are appropriate if the patient is still meeting the indication for which the neuromuscular blockers are being used (i.e., ventilator synchrony, no movement). Only in rare circumstances should the goal be 0 out of 4 twitches. (*Strong recommendation, Low quality of evidence*)
- 1.4. The number of twitches (out of four) represents the percentage of neuromuscular blockade as listed below<sup>52</sup>:
  - 1.4.1. 4/4 twitches less than 75% of blockade
  - 1.4.2. 3/4 twitches approximately 75% blockade
  - 1.4.3. 2/4 twitches represents 75-80% blockade
  - 1.4.4. 1/4 twitches represents 90% blockade
  - 1.4.5. 0/4 twitches represents 100% blockade
2. We suggest monitoring level of sedation using physio-neurologic monitoring—BIS™ (Bispectral Index Monitors)<sup>53-55</sup> (*Weak recommendation, Low-quality of evidence*)
  - 2.1. If possible, BIS monitoring should be performed prior to initiation of a NMBA to assess a baseline while a patient is adequately sedated (RAAS of -4 to -5). Initiation of a NMBA continuous infusion may decrease the waveform on the BIS monitor and result in an inappropriate decrease in sedative medications.<sup>53</sup> (*Weak recommendation, Low-quality of evidence*)
  - 2.2. Patients monitored with BIS should be kept in a range from 40-60 to avoid toxicity of sedative medications.<sup>54,55</sup> (*Weak recommendation, Low-quality of evidence*)
    - 2.2.1. BIS Index Range
      - 100 - Awake, responds to normal voice
      - 80 - Light/moderate sedation, may respond to loud commands or mild prodding/shaking
      - 60 - General anesthesia, low probability of explicit recall, unresponsive to verbal stimulus
      - 40 - Deep Hypnotic State
      - 20 - Burst Suppression
      - 0 - Flat line EEG
    - 2.2.2. Caution should be used when titrating down on sedative medications to avoid an awake and paralyzed state (*Weak recommendation, Low-quality of evidence*)
      - 2.2.2.1. A minimum level of sedation should be used for all patients receiving neuromuscular blockade.<sup>56</sup> (*Weak recommendation, Low-quality of evidence*)
        - 2.2.2.1.1. Propofol minimum infusion dose: 20 mcg/kg/min
        - 2.2.2.1.2. Midazolam minimum infusion dose: 2 mg/hour
3. Periodic monitoring (Q 48-72 hours) of CK, total should be considered to monitor the development of prolonged muscle weakness and acute quadriplegic myopathy (AQMS). Increased CK, total levels have been associated with the development of AQMS and are seen in ~50% of patients with this syndrome.<sup>5,7,52</sup> (*Strong recommendation, Moderate quality of evidence*)

## 6. Special Populations

1. Myasthenia Gravis
  - 1.1. Patients with myasthenia gravis may be more sensitive to neuromuscular blockers due to a reduced number of functional nicotinic receptors and may require decreased doses of

neuromuscular blockers. These patients should be monitored with clinical bedside assessment and TOF.<sup>7,57</sup> (*Good practice statement*)

## 7. **Reversing NMBAs**

1. Goal of reversal is to allow patients full use of muscles used in spontaneous ventilation and airway protection<sup>58</sup>
2. Non-depolarizing agents may be reversed by the administration of acetylcholinesterase inhibitors such as neostigmine or pyridostigmine
  - 2.1. Mechanism of acetylcholinesterase inhibitors: acetylcholinesterase inhibitors reversibly inhibit acetylcholinesterase and will increase the concentration of acetylcholine in the neuromuscular junction allowing for the blockade to be overcome<sup>58</sup>
3. The non-depolarizing aminosteroidal agents rocuronium and vecuronium may also be reversed by the modified gamma cyclodextrin sugammadex which is most often used in cases of post-operative prolonged paralysis (see section 4.3) (*Strong recommendation, Low quality of evidence*)
4. Drug-specific considerations (also see [Appendix F: Key Properties of NMB Reversal Agents](#))
  - 4.1. Neostigmine
    - 4.1.1. Typically the reversal agent of choice due to long duration and reliability<sup>59</sup> (*Strong recommendation, Low quality of evidence*)
    - 4.1.2. Dose: 0.03 – 0.07 mg/kg IV per dose or a fixed 0.5 mg dose repeated until reversal achieved or a maximum of 5 mg<sup>59</sup> (*Strong recommendation, Moderate quality of evidence*)
      - 4.1.2.1. 2.5 mg is generally the maximum dose required for reversal<sup>59</sup> (*Strong recommendation, Low quality of evidence*)
    - 4.1.3. Metabolism/excretion: 50% renal, 50% hepatic<sup>59</sup>
    - 4.1.4. Concomitant anticholinergic agents:
      - 4.1.4.1. Glycopyrrolate 0.2 mg IV immediately prior to neostigmine is the agent of choice because of similar onset and duration<sup>59</sup> (*Strong recommendation, Moderate quality of evidence*)
      - 4.1.4.2. Atropine 0.4 mg IV immediately prior to neostigmine may be used, but may result in higher chance of tachycardia and dysrhythmias<sup>59</sup> (*Strong recommendation, Moderate quality of evidence*)
  - 4.2. Pyridostigmine
    - 4.2.1. Less commonly used compared to neostigmine. This agent has a slower onset of action compared to neostigmine and a longer duration of action compared to neostigmine<sup>59</sup> (*Strong recommendation, Low quality of evidence*)
      - 4.2.1.1. Consider use in elderly patients due to potentially fewer autonomic side effects<sup>59</sup> (*Strong recommendation, Low quality of evidence*)
    - 4.2.2. Dose: 0.15 mg/kg IV; may be repeated one time<sup>59</sup> (*Strong recommendation, Moderate quality of evidence*)
    - 4.2.3. Metabolism/excretion: 75% renal, 25% hepatic<sup>59</sup>
    - 4.2.4. Concomitant anticholinergic agent:
      - 4.2.4.1. Glycopyrrolate 0.01 mg/kg IV immediately prior to pyridostigmine is the agent of choice with neostigmine because of similar onset and duration<sup>59</sup> (*Strong recommendation, Moderate quality of evidence*)
      - 4.2.4.2. Atropine 0.007mg/kg (often ~0.45 to 0.57 mg) IV immediately prior to neostigmine may be used, but may result in higher chance of tachycardia and dysrhythmias<sup>59</sup> (*Strong recommendation, Moderate quality of evidence*)
  - 4.3. Sugammadex
    - 4.3.1. Sugammadex is faster than neostigmine in reversing neuromuscular blockage and associated with fewer adverse effects as compared to neostigmine.<sup>60,61</sup>
      - 4.3.1.1. Use of sugammadex at UW Health is restricted to the reversal of aminosteroidal non-depolarizing blocking agents: urgently or emergently when the prescriber determines that any delay of time-critical patient care interventions will be unacceptable OR urgently for monitoring the patient's physical status (e.g. "neuro checks", status epilepticus).<sup>62</sup>

- 4.3.2. Mechanism of action: modified cyclodextrin ring that bind rocuronium and vecuronium in a 1:1 fashion, inhibiting the NMBA from binding to the nicotinic receptors, reversing the neuromuscular blockade.<sup>60,62</sup>
- 4.3.3. Dosing: For routine reversal of rocuronium or vecuronium with TOF 1-2/4, administer 4 mg/kg IV as a single dose. For routine reversal of rocuronium or vecuronium with TOF 3-4/4, administer 2 mg/kg IV as a single dose. For immediate reversal of rocuronium induced blockade, administer 16 mg/kg IV as a single dose. No dose adjustments necessary for hepatic impairment. Use in CrCl < 30 ml/min is not recommended, but no dose adjustment exists for CrCl > 30 ml/min. No dose adjustments for elderly patients. Dosing based on actual body weight.<sup>60,62</sup> (*Strong recommendation, High quality of evidence*)
- 4.3.4. Special dosing considerations: Following dosing of sugammadex for immediate reversal (16 mg/kg), re-dosing with rocuronium and vecuronium should not be attempted for 24 hours. If more immediate neuromuscular blockade is needed, a non-steroidal neuromuscular blocking agent may be used (such as atracurium).<sup>60,62</sup> (*Strong recommendation, High quality of evidence*)
- 4.3.5. Potential adverse effects: pain, nausea, headache, and hypotension. Patients receiving sugammadex should be monitored for hypersensitivity reactions. If a hypersensitivity reaction occurs, sugammadex should be discontinued and the patient should be treated with antihistamines and corticosteroids.<sup>60-62</sup> (*Strong recommendation, High quality of evidence*)
- 4.3.6. The effects of hormonal contraception may be decreased following sugammadex administration. Females who receive sugammadex should be informed to use barrier birth control methods for 7 days following sugammadex administration.<sup>60,62</sup> (*Strong recommendation, High quality of evidence*)
5. Cautions with use of acetylcholinesterase inhibitors
  - 5.1. Asthma<sup>58</sup> (*Strong recommendation, Low quality of evidence*)
  - 5.2. Pre-existing bradycardia<sup>58</sup> (*Strong recommendation, Low quality of evidence*)
  - 5.3. Mechanical obstruction of intestinal or urinary tract<sup>63</sup> (*Strong recommendation, Low quality of evidence*)
6. Adverse effects & Monitoring of reversal agents
  - 6.1. Cholinergic crisis
    - 6.1.1. These agents may cause manifestations of muscarinic excess such as miosis, salivation, bronchial constriction and increased secretions, bradycardia, heart block, nausea, vomiting, and increased gastric motility.<sup>58,63</sup>
    - 6.1.2. May be prevented and/or minimized by administration of anticholinergic concomitantly with antiacetylcholinesterase<sup>59</sup> (*Strong recommendation, Moderate quality of evidence*)
    - 6.1.3. To ameliorate adverse effects, atropine or glycopyrrolate is usually given before the administration of the reversal agent.<sup>58</sup> (*Strong recommendation, Moderate quality of evidence*)
  - 6.2. Recurarization
    - 6.2.1. Occurs when the effects of muscle relaxants extend beyond the effects of the reversal agent, thereby resulting in weakness or re-paralysis and subsequent respiratory depression.<sup>59</sup>
    - 6.2.2. May be managed symptomatically (airway management, oxygen administration, emotional support) or further reversal agents may be titrated to desired effect.<sup>59</sup> (*Strong recommendation, Low quality of evidence*)

## **UW Health Implementation**

### **Potential Benefits:**

- Use of continuous infusion NMBA's for appropriate indications institution-wide
- Staff knowledge of differing characteristics among NMBA options including drug clearance/excretion and adverse effects
- Staff knowledge of appropriate clinical goals for continuous infusion NMBA use

### **Potential Harms:**

- This guideline may not be encompassing of all clinical scenarios. Clinicians should utilize external resources to this document if situations external to this guideline arise
- Given the rapid proliferation of biomedical literature, this guideline may not have considerations to the most current evidence

### **Qualifying Statements:** NA

### **Pertinent UW Health Policies & Procedures**

1. [UW Health Policy #6.1.8: Administration of Intravenous Medications](#)

### **Patient Resources**

None identified

### **Guideline Metrics**

None identified

### **Implementation Plan/Clinical Tools**

1. Guideline will be posted on uConnect in a dedicated location for Clinical Practice Guidelines.
2. Release of the guideline will be advertised in the Physician/APP Briefing newsletter.
3. Content and hyperlinks within clinical tools, documents, or Health Link related to the guideline recommendations will be reviewed for consistency and modified as appropriate.

### **Delegation Protocols**

[Neuromuscular Blocking Agent Continuous Infusion – Adult \[51\]](#)

### **Order Sets & Smart Sets**

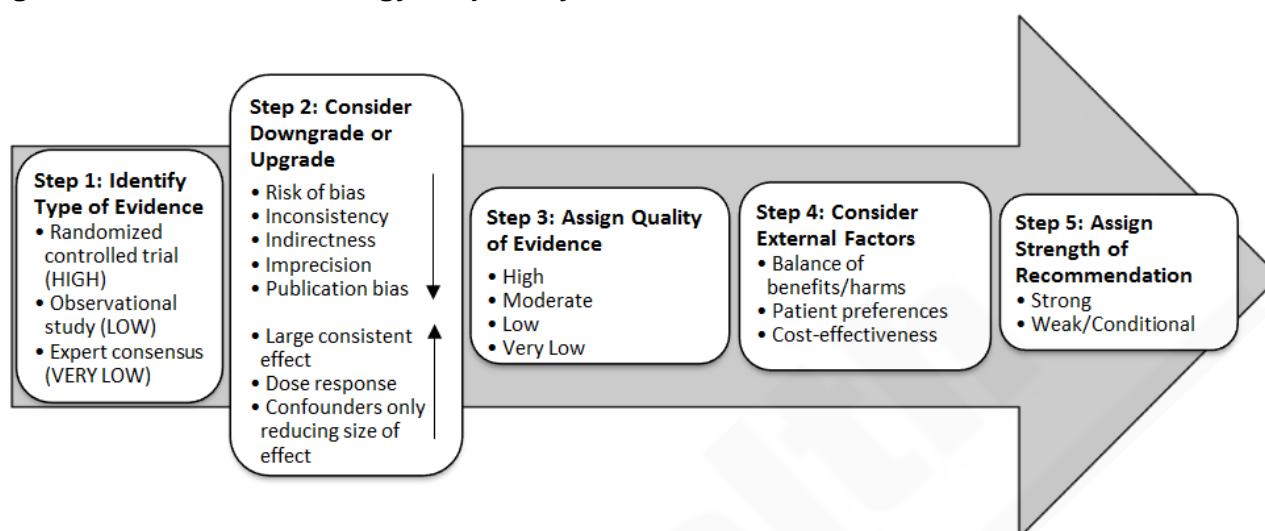
Neuromuscular Blocker Continuous Infusion order set

### **Disclaimer**

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

## Appendix A. Evidence Grading Scheme(s)

Figure 1. GRADE Methodology adapted by UW Health



### GRADE Ranking of Evidence

<b>High</b>	We are confident that the effect in the study reflects the actual effect.
<b>Moderate</b>	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
<b>Low</b>	The true effect may differ significantly from the estimate.
<b>Very Low</b>	The true effect is likely to be substantially different from the estimated effect.

### GRADE Ratings for Recommendations For or Against Practice

<b>Strong</b>	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
<b>Weak/conditional</b>	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

## **Appendix B. Summary of Interim Revisions**

<b>Date</b>	<b>Summary of Interim Revision(s)</b>
07/17	Updated list of appropriate indications
07/17	Updated recommendations regarding enteral feeding during neuromuscular blockade
07/17	Updated recommendation for choice of neuromuscular blocking agent to reinforce class effect for ARDS indication
07/17	Added sugammadex as a reversal agent for rocuronium and vecuronium
07/17	Updated statement regarding sedation and pain control prior to implementing blockade
07/17	Updated information regarding eye lubrication during blockade
07/17	Updated recommendation regarding electroencephalogram monitoring
07/17	Removed first and second notification value for NMBA infusion titration and added a maximum infusion rate
07/17	Updated guideline to reflect most current CCKM standards
07/17	Updated evidence grade to reflect most current CCKM standards

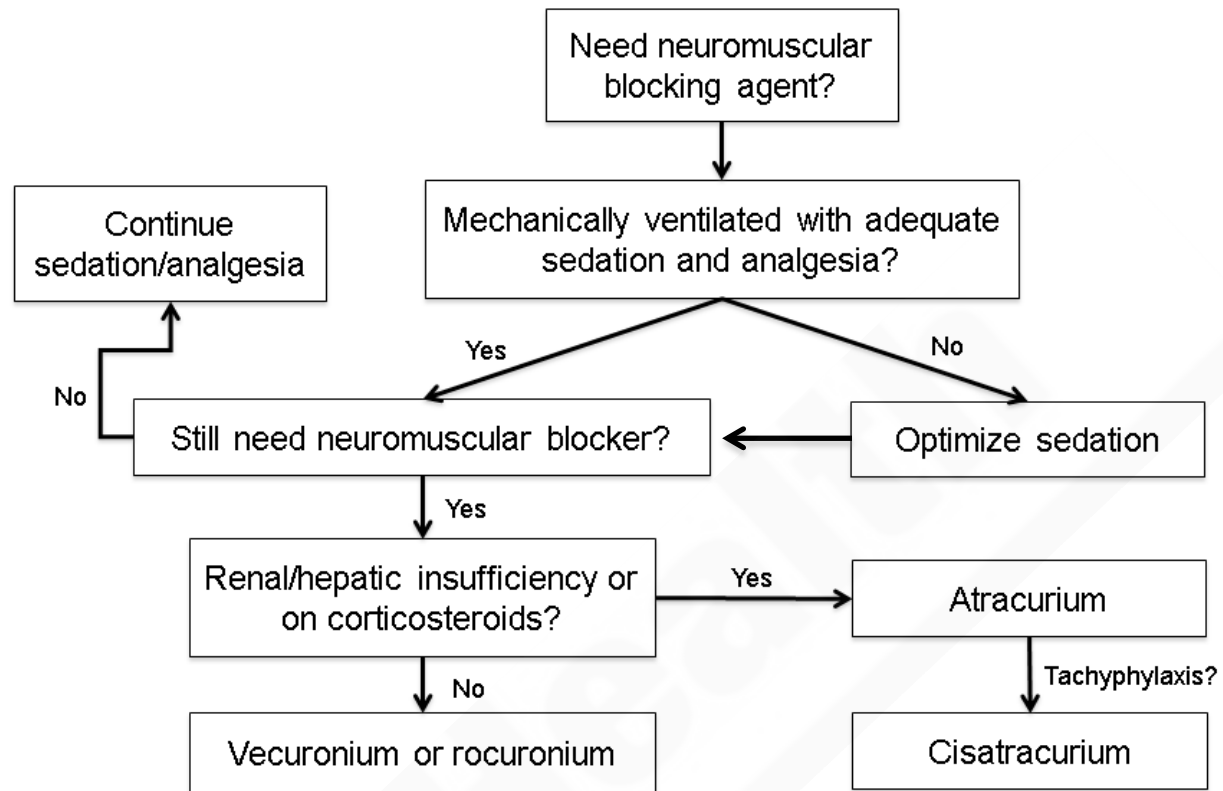
## **Appendix C. Pharmacokinetic Parameters, Contraindications, and Common Adverse Effects of Neuromuscular Blocking Agents** <sup>4,36</sup>

<b>Drug</b>	<b>Onset</b>	<b>Duration</b>	<b>Half-life</b>	<b>Primary route of Elimination</b>	<b>Noteworthy Adverse Effects</b>
Atracurium	2-3 minutes	25-35 minutes	16-20 minutes	Ester hydrolysis	Histamine release at high doses with potential for flushing, bradycardia, hypotension
Cisatracurium	2-8 minutes	45-60 minutes	20-30 minutes	Ester hydrolysis	Transient rare bradycardia, hypotension, or bronchospasm
Rocuronium	1-2 minutes	~25-70 minutes	60-108 minutes	Fecal (50%) & urine (30%); minimal hepatic metabolism	Transient and limited tachycardia (vagolytic effects)
Vecuronium	2-5 minutes	35-45 minutes	50-80 minutes	Hepatic and renal to active metabolites with fecal and renal excretion	Prolonged duration in anephric patients but not usually with other renal impairment

## **Appendix D. Neuromuscular Blocking Agent Dose Titration Table** <sup>4</sup>

<b>Drug</b>	<b>Typical Dose Range</b>	<b>Bolus Dose</b>	<b>Typical Infusion Starting Dose</b>	<b>Titration Dose to Achieve Objective Goal</b>		<b>Rate of Titration</b>	<b>Maximum Dose</b>
Atracurium	4-15 mcg/kg/min	0.4-0.5 mg/kg	4 mcg/kg/min	1 mcg/kg/min		15 minutes	15 mcg/kg/min
Cisatracurium	0.3-10 mcg/kg/min	0.15-0.2 mg/kg	0.3 mcg/kg/min	When Infusion Rate 0.3-1.8 mcg/kg/min: titrate by 0.25 mcg/kg/min	When Infusion Rate > 1.8 mcg/kg/min: titrate by 1 mcg/kg/min	15 minutes	10 mcg/kg/min
Rocuronium	3-12.5 mcg/kg/min	100-1200 mcg/kg	5 mcg/kg/min	1 mcg/kg/min		15 minutes	12.5 mcg/kg/min
Vecuronium	0.4-3 mcg/kg/min	0.04-0.1 mg/kg <sup>4</sup>	1 mcg/kg/min	0.3 mcg/kg/min		15 minutes	3 mcg/kg/min

## Appendix E. Algorithm for Selection of Neuromuscular Blocking Agent



## Appendix F. Key Properties of NMB Reversal Agents <sup>59,60,62,63</sup>

	Neostigmine (1 <sup>st</sup> line)	Pyridostigmine (2 <sup>nd</sup> line)	Sugammadex
<b>Dosage</b>	0.03-0.07 mg/kg IV or 0.5 mg; repeated to max of 5 mg	0.15 mg/kg IV (may be repeated once)	Routine ToF 1-2: 4 mg/kg IV once Routine ToF 3-4: 2 mg/kg IV once Immediate: 16 mg/kg IV once
<b>Peak Onset</b>	7-11 minutes	12-15 minutes	3 minutes
<b>Duration</b>	40-60 minutes	90-137 minutes	120 minutes (prolonged in renal impairment)
<b>Metabolism/excretion</b>	50% renal, 50% hepatic	75% renal, 25% hepatic	Not metabolized, excreted 95% unchanged in the urine
<b>Anticholinergic of Choice*</b>	Glycopyrrolate 0.2 mg IV	Glycopyrrolate 0.01 mg/kg IV	NA
*Use and dose is dependent upon dose of reversal agent. If the patient is profoundly bradycardic, consider atropine as an alternative			

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