

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

The decision to treat a patient in the intensive care unit (ICU) with neuromuscular blocking agents (NMBAs) (for reasons other than the placement of an endotracheal tube) is a difficult one that is guided more commonly by individual practitioner preference than by standards based on evidence-based medicine. Commonly cited reasons for the use of NMBAs in the ICU are to facilitate mechanical ventilation or different modes of mechanical ventilation and to manage patients with head trauma or tetanus. Independent of the reasons for using NMBAs, we emphasize that all other modalities to improve the clinical situation must be tried, using NMBAs only as a last resort.

In 1995 the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM) published guidelines for the use of NMBAs in the ICU. The present document is the result of an attempt to reevaluate the literature that has appeared since the last guidelines were published and, based on that review, to update the recommendations for the use of NMBAs in the ICU. Appendix A summarizes our recommendations. Using methods previously described to evaluate the literature and grade the evidence, the task force reviewed the physiology of the neuromuscular receptor, the pharmacology of the NMBAs currently used in the ICU, the means to monitor the degree of blockade, the complications associated with NMBAs, and the economic factors to consider when choosing a drug.

## Neuromuscular Junction in Health and Disease

The neuromuscular junction consists of a motor nerve terminus, the neurotransmitter acetylcholine, and the postsynaptic muscle endplate (Figure 1). The impulse of an action potential causes the release of acetylcholine from synaptic vesicles (each containing about 10,000 molecules of acetylcholine) diffusing across the 20-nm gap to the postsynaptic endplate. The motor endplate contains specialized ligand-gated, nicotinic acetylcholine receptors (nAChRs), which convert the chemical signal (i.e., binding of two acetylcholine molecules) into electrical signals (i.e., a transient permeability change and depolarization in the postsynaptic membrane of striated muscle).

There are depolarizing and nondepolarizing NMBAs. Depolarizing NMBAs physically resemble acetylcholine and, therefore, bind and activate acetylcholine receptors. Succinylcholine is currently the only available depolarizing NMBA and is not used for long-term use in ICUs.

Nondepolarizing NMBAs also bind acetylcholine receptors but do not activate them—they are competitive antagonists. The difference in the mechanism of action also accounts for different effects in certain diseases. If there is a long-term decrease in acetylcholine release, the number of acetylcholine receptors within the muscle increases. This upregulation causes an increased response to depolarizing NMBAs but a resistance to nondepolarizing NMBAs (i.e., more receptors must be blocked). Conditions in which there are fewer acetylcholine receptors (e.g., myasthenia gravis) lead to an increase in sensitivity to nondepolarizing NMBAs.

Adult skeletal muscle retains an ability to synthesize both the mature adult nAChR as well as an immature nAChR variant in which a gamma subunit is substituted for the normal epsilon subunit. Synthesis of immature (fetal) receptors may be triggered in the presence of certain diseases (e.g., Guillain-Barré syndrome, stroke) and other conditions producing loss of nerve function. These immature nAChRs are distinguished by three features. First, immature receptors are not localized to the muscle endplate but migrate across the entire membrane surface.<sup>2</sup> Second, the immature receptors are metabolically short-lived (<24 hours) and more ionically active, having a 2- to 10-fold longer channel “open time.” Lastly, these immature receptors are more sensitive to the depolarizing effects of such drugs as succinylcholine and more resistant to the effects of competitive antagonists, such as pancuronium. This increase in the number of immature acetylcholine receptors may account for the tachyphylaxis seen with NMBAs and some of the complications associated with their use. For the remainder of this document, only nondepolarizing NMBAs will be discussed.

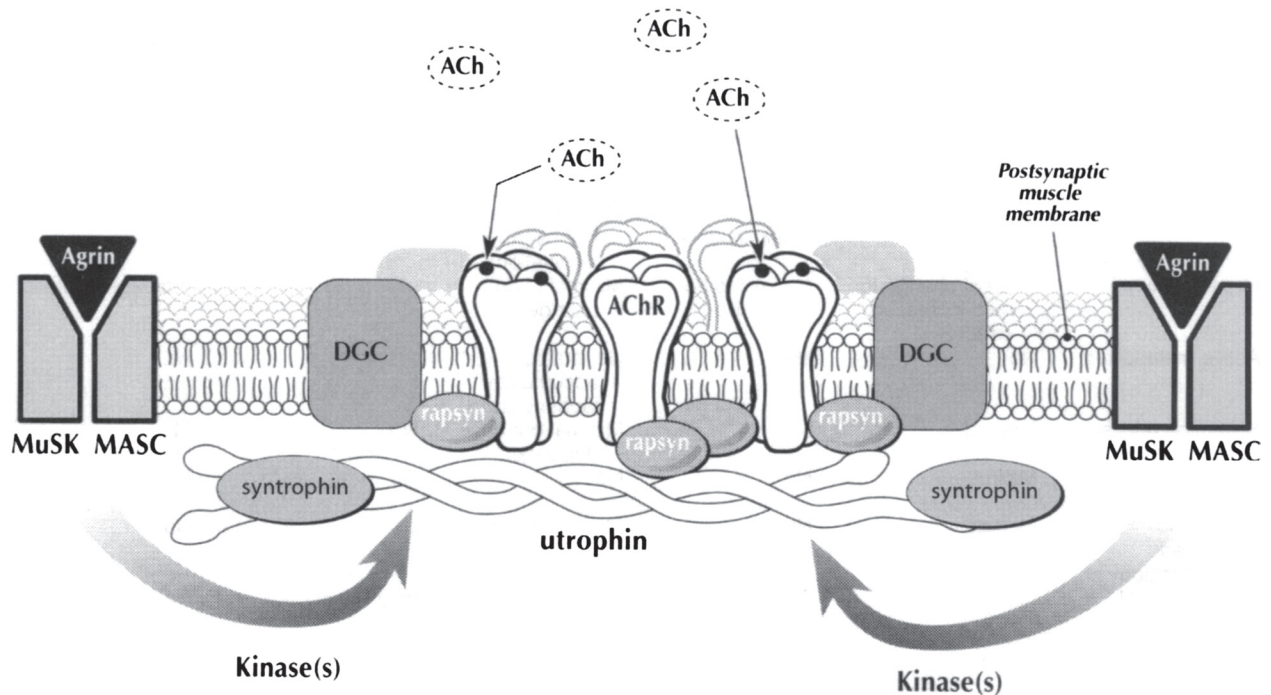
## Pharmacology of Neuromuscular-Receptor Blockers

**Aminosteroidal Compounds.** The aminosteroidal compounds include pancuronium, pipecuronium, vecuronium, and rocuronium (Tables 1 and 2).<sup>3-11</sup>

**Pancuronium.** Pancuronium, one of the original NMBAs used in ICUs, is a long-acting, nondepolarizing compound that is effective after an intravenous bolus dose of 0.06–0.1 mg/kg for up to 90 minutes. Though it is commonly given as an i.v. bolus, it can be used as a continuous infusion<sup>12</sup> by adjusting the dose to the degree of neuromuscular blockade that is desired (Table 1). Pancuronium is vagolytic (more than 90% of ICU patients will have an increase in heart rate of  $\geq 10$  beats/min), which limits its use in patients who cannot tolerate an increase in heart rate.<sup>12</sup> In patients with renal failure or cirrhosis, pancuronium’s neuromuscular blocking effects are prolonged because of its increased elimination half-life and the decreased clearance of its 3-hydroxypancuronium metabolite that has one-third to one-half the activity of pancuronium.

**Pipecuronium.** Pipecuronium is another long-acting NMBA with an elimination half-life of about two hours, similar to pancuronium’s. Khuenl-Brady and colleagues<sup>13</sup> conducted an open-label evaluation of pipecuronium compared with pancuronium in 60 critically ill patients to determine the minimum doses required for ventilatory management. The administration of 8 mg of either drug followed by intermittent boluses of 4–6 mg when needed resulted in optimal paralysis. Patients were paralyzed for a mean duration of 62.6 hours (45–240 hours) and 61.5 hours (46–136 hours) with pancuronium and pipecuronium, respectively. No adverse effects were attributed to either drug. Perhaps because of this lack of difference and because there are no recent studies examining pipecuronium’s use in the ICU, most clinicians continue to use the more familiar drug, pancuronium.

**Figure 1.** Neuromuscular Junction. Schematic model of the organization and structure of the neuromuscular junction, with focus and enlargement on the postsynaptic membrane. Agrin is the nerve-derived protein that triggers receptor clustering during synapse formation. Receptor aggregation appears to occur in distinct steps, however, initiated with acetylcholine receptors (AChR) localized together by rapsyn. Meanwhile, D-dystroglycan, the extracellular component of dystrophin-associated glycoprotein complex (DGC), is the agrin receptor which transduces final AChR clustering. This process utilizes the structural organization of additional proteins like utrophin, which stabilize the mature, immobile domains by interaction with the underlying cytoskeleton (actin). When completed, this process concentrates AChR density 1000-fold compared to typical muscle membrane. ACh = acetylcholine, MuSK = muscle-specific-receptor kinase, MASC = MuSK-accessory specificity component. (Reprinted with permission, from Wall MH, Prielipp RC. Monitoring the neuromuscular junction. In: Lake C, Blitt CD, Hines RL, eds. *Clinical Monitoring: Practical Applications for Anesthesia and Critical Care*. Philadelphia: W.B. Saunders, 2000, Figure 10-3.)



**Vecuronium.** Vecuronium is an intermediate-acting NMBA that is a structural analogue of pancuronium and is not vagolytic. An i.v. bolus dose of vecuronium 0.08–0.1 mg/kg, produces blockade within 60–90 seconds that typically lasts 25–30 minutes. After an i.v. bolus dose, vecuronium is given as a 0.8–1.2- $\mu\text{g}/\text{kg}/\text{min}$  continuous infusion, adjusting the rate to the degree of blockade desired. Because up to 35% of a dose is renally excreted, patients with renal failure will have decreased drug requirements. Similarly, because up to 50% of an injected dose is excreted in bile, patients with hepatic insufficiency will also have decreased drug requirements to maintain adequate blockade. The 3-desacetylvecuronium metabolite has 50% of the pharmacologic activity of the parent compound, so patients with organ dysfunction may have increased plasma concentrations of both the parent compound and the active metabolite, which contributes to the prolongation of blockade if the dose is not adjusted. Vecuronium has been reported to be more commonly associated with prolonged blockade once discontinued, compared with other NMBAs.<sup>9</sup> Members of the task force believe that vecuronium is being used with decreased frequency in the ICU.

Vecuronium has been studied in open-label prospective trials.<sup>14,15</sup> In one of these studies, the mean infusion rate for vecuronium was  $0.9 \pm 0.1 \mu\text{g}/\text{kg}/\text{min}$  for a mean duration of  $80 \pm 7$  hours. Recovery of a train-of-four (TOF) ratio of  $\geq 0.7$  was significantly longer than with cisatracurium.<sup>15</sup> Recovery time averaged 1–2 hours but ranged from  $\leq 30$  minutes to more than 48 hours.

Although Rudis et al.<sup>14</sup> observed no difference in the incidence of prolonged blockade between patients receiving vecuronium with and without concomitant administration of

corticosteroids, the opinion of the task force was that patients receiving vecuronium and corticosteroids were at increased risk of prolonged weakness once the drug was discontinued.

**Rocuronium.** Rocuronium is a newer nondepolarizing NMBA with a monoquaternary steroidal chemistry that has an intermediate duration of action and a very rapid onset. When given as a bolus dose of 0.6–1 mg/kg, blockade is almost always achieved within two minutes, with maximum blockade occurring within three minutes. Continuous infusions are begun at 10  $\mu\text{g}/\text{kg}/\text{min}$ .<sup>8</sup> Rocuronium's metabolite, 17-des-acetylrocuronium, has only 5–10% activity compared with the parent compound.

Sparr, Khuenl-Brady, and colleagues<sup>8,9</sup> studied the dose requirements, recovery times, and pharmacokinetics of rocuronium in 32 critically ill patients, 27 of whom were given intermittent bolus doses, and 5 received a continuous infusion. The median duration of drug administration was 29 hours and 63.4 hours in the bolus dose and infusion groups, respectively. The mean dose of rocuronium required to maintain 80% blockade was 0.34 mg/kg, and the median infusion rate required to maintain one twitch of the TOF was 0.54 mg/kg/hr. The median time from the last bolus dose to the appearance of TOF response was 100 minutes; in the infusion group, the TOF response returned 60 minutes after the infusion was stopped.

**Rapacuronium.** Rapacuronium, a propionate analogue of vecuronium, was marketed as a nondepolarizing NMBA as an alternative to succinylcholine. It was withdrawn from the market on March 27, 2001, because of reports of morbidity (bronchospasm) and mortality associated with its use.

Table 1.

**Selected Neuromuscular Blocking Agents<sup>a</sup> for ICU Use**

Variable	Benzylisoquinolinium Drugs				
	D-Tubocurarine (Curare)	Cisatracurium (Nimbex)	Atracurium (Tracrium)	Doxacurium (Nuromax)	Mivacurium (Mivacron)
Introduced (yr)	1942	1995	1983	1991	1992
ED <sub>95</sub> <sup>b</sup> dose (mg/kg)	0.51	0.05	0.25	0.025–0.03	0.075
Initial dose (mg/kg)	0.1–0.2	0.1–0.2	0.4–0.5	0.025–0.05	0.15–0.25
Duration (min)	80	45–60	25–35	120–150	10–20
Infusion described	...	Yes	Yes	Yes	Yes
Infusion dose (µg/kg/min)	...	2.5–3	4–12	0.3–0.5	9–10
Recovery (min)	80–180	90	40–60	120–180	10–20
% Renal excretion	40–45	Hofmann elimination	5–10 (uses Hofmann elimination)	70	Inactive metabolites
Renal failure	Increased duration	No change	No change	Increased duration	Increased duration
% Biliary excretion	10–40	Hofmann elimination	Minimal (uses Hofmann elimination)	Insufficient data	...
Hepatic failure	Minimal change to mild increased effect	Minimal to no change	Minimal to no change	...	Increased duration
Active metabolites	No	No	No, but can accumulate laudanosine	...	No
Histamine release hypotension	Marked	No	Minimal but dose dependent	No	Minimal but dose dependent
Vagal block tachycardia	Minimal	No	No	No	No
Ganglionic blockade hypotension	Marked	No	Minimal to none	No	No
Prolonged ICU block	...	Rare	Rare	Insufficient data	Insufficient data

Variable	Aminosteroidal Drugs			
	Pancuronium (Pavulon)	Vecuronium (Norcuron)	Pipecuronium (Arduan)	Rocuronium (Zemuron)
Introduced (yr)	1972	1984	1991	1994
ED <sub>95</sub> <sup>b</sup> dose (mg/kg)	0.05	0.05	0.05	0.3
Initial dose (mg/kg)	0.06–0.1	0.08–0.1	0.085–0.1	0.6–1
Duration (min)	90–100	35–45	90–100	30
Infusion described	Yes	Yes	No	Yes
Infusion dose (µg/kg/min)	1–2	0.8–1.2	0.5–2	10–12
Recovery (min)	120–180	45–60	55–160	20–30
% Renal excretion	45–70	50	50+	33
Renal failure	Increased effect	Increased effect, especially metabolites	Increased duration	Minimal
% Biliary excretion	10–15	35–50	Minimal	<75
Hepatic failure	Mild increased effect	Variable, mild	Minimal	Moderate
Active metabolites	Yes, 3-OH and 17-OH-pancuronium	Yes, 3-desacetyl-vecuronium	Insufficient data	No
Histamine release hypotension	No	No	No	No
Vagal block tachycardia	Modest to marked	No	No	Some at higher doses
Ganglionic blockade hypotension	No	No	No	No
Prolonged ICU block	Yes	Yes	Insufficient data	Insufficient data

<sup>a</sup>Based on drugs for use in a 70-kg man. Modified with permission from Prielipp and Coursin. Reference 3.

<sup>b</sup>ED<sub>95</sub> = effective dose for 95% of patients studied.

**Benzylisoquinolinium Compounds.** The benzylisoquinolinium compounds include D-tubocurarine, atracurium, cisatracurium, doxacurium, and mivacurium (Tables 1 and 3).<sup>12,15,16,31</sup>

*D-Tubocurarine.* Tubocurarine was the first nondepolarizing NMBA to gain acceptance and usage in the ICU. This long-acting benzylisoquinolinium agent is rarely used in ICUs because it induces histamine release and autonomic

Table 2.  
ICU Studies of Aminosteroidal Drugs<sup>a</sup>

Reference	Type of Study	Patients	Results	Level of Evidence
4	Prospective, observational, cohort	30	Median time to recovery with pancuronium was 3.5 hr in infusion group vs. 6.3 hr in the bolus dose group.	3
5	Prospective, open-label	25 PICU	Increased infusion requirements for pancuronium with anticonvulsants.	3
6	Prospective, open-label	6	Vecuronium clearance increased in 3 and decreased in 2 patients. $V_D$ did not change.	3
7	Survey	...	Neuromuscular blockade monitored clinically with only 8.3% using TOF. All respondents indicated concomitant use of sedatives and/or opioids (75%).	5
8	Prospective, open-label	30 SICU	25 trauma patients received rocuronium 50-mg i.v. bolus dose followed by maintenance doses of 25 mg whenever TOF = 2, five patients were on continuous infusion at 25 mg/hr. Duration 1–5 days, recovery approximately 3 hr, and plasma clearance similar between groups.	3
9	Prospective, open-label	32	An initial dose of rocuronium 50 mg followed by maintenance doses of 25 mg with TOF = 2 ( $n = 27$ ) or by continuous infusion to maintain TOF ( $n = 5$ ). Pharmacokinetic data tabulated. Crossover with patients reported by Khuenl-Brady et al. <sup>8</sup>	3
10	Prospective, randomized, controlled	20 CABG	Pancuronium ( $n = 10$ ) was compared to rocuronium ( $n = 10$ ). Incidence of residual block higher with pancuronium than rocuronium. No effect on time to extubation.	2
11	Prospective, open-label	12 ICU	12 patients, 4 with MODS. Patients given 0.6-mg/kg bolus dose of rocuronium followed by repeated bolus ( $n = 2$ ) or continuous infusion ( $n = 10$ ) started at 10–12 $\mu\text{g}/\text{kg}/\text{min}$ and adjusted to TOF = 1–4. No evidence of prolonged blockade.	3

<sup>a</sup>PICU = pediatric intensive care unit, SICU = surgical intensive care unit, CABG = coronary artery bypass grafting, ICU = intensive care unit, TOF = train-of-four,  $V_D$  = volume of distribution, MODS = multiple organ dysfunction syndrome.

Table 3.  
ICU Studies of Benzylisoquinolinium Drugs<sup>a</sup>

Reference	Type of Study	Patients	Dose	Results	Level of Evidence
16	Review	...	...	Review of pharmacokinetics	5
17	Prospective, open-label, controlled	14 with hepatic failure vs. 11 controls	Cisatracurium 0.1-mg/kg i.v. bolus dose	$V_D$ greater in liver patients but no differences in elimination $t_{1/2}$ or in duration of action	5
18	Prospective, randomized, single-blind	20 ICU	Cisatracurium ( $n = 12$ ) 0.25 mg/kg/hr Atracurium ( $n = 8$ ) 0.62 mg/kg/hr	Similar mean recovery time	2
19	Prospective, randomized	12 ICU	Cisatracurium 0.1-mg/kg bolus dose + 0.18-mg/kg/hr infusion Atracurium: 0.5 mg/kg + 0.6-mg/kg/hr infusion	Measured $V_D$ , Cl, $T_{1/2}$ . Laudanosine concentration was lower in patients on cisatracurium	2
20	Randomized, open-label	61 ICU	Cisatracurium ( $n = 26$ ) 0.1-mg/kg bolus, followed by an infusion of 3 $\mu\text{g}/\text{kg}/\text{min}$ ; 14 pts infusion only Atracurium ( $n = 18$ ) 0.5 mg/kg bolus followed by an infusion of 10 $\mu\text{g}/\text{kg}/\text{min}$ ; 3 pts infusion only Infusion adjusted to one twitch	118 $\pm$ 19 min recovery no change in HR, BP, and ICP with bolus	3

(Continued on Next Page)

Table 3 (continued)

Reference	Type of Study	Patients	Dose	Results	Level of Evidence
15	Prospective, randomized, double-blind, multicenter	58 ICU	Cisatracurium 2.5- $\mu$ g/kg/min Vecuronium 1- $\mu$ g/kg/min	Recovery profiles were significantly different with more prolonged recovery noted for vecuronium. TOF monitoring could not eliminate prolonged recovery and myopathy	1
21	Prospective, blinded, cross-over	14 with brain injury	Cisatracurium 0.15 mg/kg bolus Atracurium 0.75 mg/kg bolus	No change in ICP, CPP, CBF, MAP, ETCO <sub>2</sub> , and HR and no histamine-related symptoms, with 3xED <sub>95</sub> cisatracurium. With 3xED <sub>95</sub> atracurium, ICP, CPP, CBF, and MAP decreased within 2–4 min. Five patients had typical histamine reaction; excluding these five patients, there was no difference in any variable compared with cisatracurium	2
22	Observational, prospective, open-label	24 with brain injury	0.1 or 0.2-mg/kg cisatracurium bolus dose	No change from baseline in ICP, CPP, MAP, ETCO <sub>2</sub> , HR, and CBF velocity in both groups	5
23	Case	...	...	...	4
24	Case	...	...	...	4
25	Review	...	...	...	4
26	Editorial	...	...	...	4
27	Review	...	...	...	5
28	Review	...	...	...	5
12	Multicenter, prospective, double-blind, randomized	40 critically ill	Doxacurium 0.04-mg/kg bolus dose, 0.025-mg/kg maintenance; pancuronium: 0.07 mg/kg bolus dose, 0.05-mg/kg maintenance	No difference in adverse reactions or onset of blockade; pancuronium had a more prolonged and variable recovery time	1
29	Prospective, open-label	8 mechanical ventilated ICU with HD monitoring and pHi <7.35	Doxacurium: 0.03-mg/kg load; 0.03-mg/kg/hr infusion	DO <sub>2</sub> + VO <sub>2</sub> decreased, pHi increased; VO <sub>2</sub> is decreased and pHi increased. NMBA causes redistribution of blood flow to splanchnic beds	5
30	Prospective, open-label study	8 ICU with traumatic head injury	Doxacurium 0.05 mg/kg then 0.25 $\mu$ g/kg/min	No significant effect in HR, BP, ICP. No adverse effects	5
31	Case report	4 with atracurium tachyphylaxis	Doxacurium 0.25–0.75 $\mu$ g/kg/min	No tachyphylaxis noted	5

<sup>a</sup>ICU = intensive care unit, TOF = train-of-four, V<sub>D</sub> = volume of distribution, HR = heart rate, BP = blood pressure, ICP = intracranial pressure, CPP = cerebral perfusion pressure, CBF = cerebral blood flow, MAP = mean arterial pressure, NMBA = neuromuscular blocking agent, ETCO<sub>2</sub> = end tidal carbon dioxide, ED<sub>95</sub> = effective dose for 95% of patients studied, HD = hemodynamic flow, pHi = gastric mucosal pH, DO<sub>2</sub> = oxygen delivery, VO<sub>2</sub> = oxygen consumption, CBF = cerebral blood flow.

ganglionic blockade. Hypotension is rare, however, when the agent is administered slowly in appropriate dosages (e.g., 0.1–0.2 mg/kg). Metabolism and elimination are affected by both renal and hepatic dysfunction.

**Atracurium.** Atracurium is an intermediate-acting NMBA with minimal cardiovascular adverse effects and is associated with histamine release at higher doses. It is inactivated in plasma by ester hydrolysis and Hofmann elimination so that renal or hepatic dysfunction does not affect the duration of blockade.

Laudanosine is a breakdown product of Hofmann elimination of atracurium and has been associated with central nervous system excitation. This has led to concern about the possibility of precipitating seizures in patients who have received extremely high doses of atracurium or who are in hepatic failure (laudanosine is metabolized by the liver). There has been only one report of a surgical patient who had a seizure while receiving atracurium.<sup>32</sup>

Atracurium has been administered to various critically ill patient populations, including those with liver failure,<sup>17</sup> brain injury,<sup>21</sup> or multiple organ dysfunction syndrome (MODS), to facilitate mechanical ventilation. In these reports, atracurium infusion rates varied widely, but they typically ranged from 10

to 20  $\mu$ g/kg/min with doses adjusted to clinical endpoints or by TOF monitoring. Infusion durations ranged from  $\leq$ 24 hours to >200 hours. Recovery of normal neuromuscular activity usually occurred within one to two hours after stopping the infusions and was independent of organ function. Long-term infusions have been associated with the development of tolerance, necessitating significant dose increases or conversion to other NMBAs.<sup>31,33</sup> Atracurium has been associated with persistent neuromuscular weakness as have other NMBAs.<sup>34–38</sup>

**Cisatracurium.** Cisatracurium, an isomer of atracurium, is an intermediate-acting benzylisoquinolinium NMBA that is increasingly used in lieu of atracurium. It produces few, if any, cardiovascular effects and has a lesser tendency to produce mast cell degranulation than atracurium. Bolus doses of 0.1–0.2 mg/kg result in paralysis in an average of 2.5 minutes, and recovery begins at approximately 25 minutes; maintenance infusions should be started at 2.5–3  $\mu$ g/kg/min. Cisatracurium is also metabolized by ester hydrolysis and Hofmann elimination, so the duration of blockade should not be affected by renal or hepatic dysfunction. Prolonged weakness has been reported following the use of cisatracurium.<sup>38</sup>

Cisatracurium has been compared with atracurium and vecuronium for facilitating mechanical ventilation in several open-label prospective trials.<sup>15,18–21</sup> Cisatracurium infusion rates ranged from 2 to 8 µg/kg/min and were adjusted to clinical endpoints or to TOF count. Infusion durations varied from 4 to 145 hours. Recovery of a TOF ratio >0.7 occurred within 34–85 minutes after drug discontinuation and was independent of organ function. These recovery times are similar to those seen with atracurium<sup>18,21</sup> and less than those observed with vecuronium.<sup>15</sup>

**Doxacurium.** Doxacurium, a long-acting benzylisoquinolinium agent, is the most potent NMBA currently available. Doxacurium is essentially free of hemodynamic adverse effects. Initial doses of doxacurium 0.05–0.1 mg/kg may be given with maintenance infusions of 0.3–0.5 µg/kg/min and adjusted to the degree of blockade desired. An initial bolus dose lasts an average of 60–80 minutes. Doxacurium is primarily eliminated by renal excretion. In elderly patients and patients with renal dysfunction, a significant prolongation of effect may occur.

Murray and colleagues<sup>12</sup> conducted a prospective, randomized, controlled, multicenter comparison of intermittent doses of doxacurium and pancuronium in 40 critically ill patients requiring neuromuscular blockade to optimize mechanical ventilation or to lower intracranial pressure (ICP). Patients were given another bolus dose based on TOF monitoring and were paralyzed for a mean duration of 2.6 days with doxacurium or 2.2 days with pancuronium. There was a clinically significant increase in heart rate after the initial bolus dose of pancuronium compared with baseline (120 ± 23 versus 109 ± 22 beats/min, respectively) without any differences after the initial dose of doxacurium (107 ± 21 versus 109 ± 21 beats/min, respectively). Once the drugs were discontinued, the pancuronium group had a more prolonged and variable recovery time (279 ± 229 min) than the doxacurium group (135 ± 46 min).

**Mivacurium.** Mivacurium is one of the shortest-acting NMBAs currently available. It consists of multiple stereoisomers and has a half-life of approximately two minutes, allowing for rapid reversal of the blockade. There are little data to support its use as a continuous infusion in the ICU.

## Indications

NMBAs are indicated in a variety of situations (Table 4).<sup>8,9,12–15,17–21,30,39,42</sup> There have been no studies randomizing patients who are considered candidates for NMBAs to a placebo versus an NMBA. We therefore reviewed many studies comparing one NMBA to another to assess the clinical indications for enrolling patients in these studies. The most common indications for long-term administration of NMBAs included facilitation of mechanical ventilation, control of ICP, ablation of muscle spasms associated with tetanus, and decreasing oxygen consumption (Figure 2). NMBAs are often used to facilitate ventilation and ablate muscular activity in patients with elevated ICP or seizures but have no direct effect on either condition. Patients who are being treated for seizures who also take NMBAs should have electroencephalographic monitoring to ensure that they are not actively seizing while paralyzed.

With the exception of atracurium and cisatracurium, which need to be given continuously because of their short half-lives, bolus administration of NMBAs offers potential advantages for controlling tachyphylaxis; monitoring for

accumulation, analgesia, and amnesia; and limiting complications related to prolonged or excessive blockade; and improving economics. However, in many ICUs, NMBAs are administered continuously, achieving adequate paralysis and faster recovery with TOF monitoring.

**Facilitate Mechanical Ventilation.** Numerous reports have described the use of NMBAs to facilitate mechanical ventilation. Most of the reports are limited to case studies, small prospective open-label trials, and small randomized open-label and double-blind trials enrolling a wide variety of critically ill patients to whom NMBAs were given to prevent respiratory dysynchrony, stop spontaneous respiratory efforts and muscle movement, improve gas exchange, and facilitate inverse ratio ventilation. However, none of these reports compared NMBAs to placebos.

**Manage Increased ICP.** The data supporting the use of NMBAs to control ICP are limited to a case report and an open-label trial. Prielipp<sup>30</sup> evaluated doxacurium use in eight patients with severe head injury in an open-label prospective study. NMBAs were given to facilitate ventilation or to manage brain injuries. Patients received an initial bolus injection of doxacurium 0.05 mg/kg followed by a continuous infusion of 0.25 µg/kg/min adjusted to maintain one twitch of the TOF. Doxacurium had no effect on ICP, heart rate, or blood pressure. Infusion rates were similar at the beginning (1 ± 0.1 mg/hr) and at the end (1.3 ± 0.2 mg/hr) of the study. TOF responses returned at 118 minutes; a TOF ratio of 0.7 was measured at 259 ± 24 minutes. No adverse events were reported.

McClelland et al.<sup>40</sup> treated three patients with atracurium for four to six days to manage increased ICP. Patients could undergo a neurologic examination within minutes after discontinuing atracurium. No adverse events were reported. There have been no controlled studies evaluating the role of NMBAs in the routine management of increased ICP.

**Treat Muscle Spasms.** Case studies describe the use of NMBAs in the treatment of muscle contractures associated with tetanus, drug overdoses, and seizures; many were published before 1994.

Anandaciva and Koay<sup>41</sup> administered a continuous rocuronium infusion to control muscle tone in patients with tetanus. Muscle spasms recurred at an infusion rate of 8 µg/kg/min, and neither administering a bolus dose of 0.9 mg/kg nor increasing the infusion rate to 10 µg/kg/min controlled the muscle contractures but did increase heart rate. Switching to a different NMBA could control the spasms.

**Decrease Oxygen Consumption.** Freebairn et al.<sup>42</sup> evaluated the effects of vecuronium on oxygen delivery, oxygen consumption, oxygen extraction ratios, and gastric intramucosal pH in a randomized, placebo-controlled crossover trial in 18 critically ill patients with severe sepsis. Although the infusion of vecuronium achieved an adequate level of paralysis and improved respiratory compliance, it did not alter intramucosal pH, oxygen consumption, oxygen delivery, or oxygen extraction ratios.

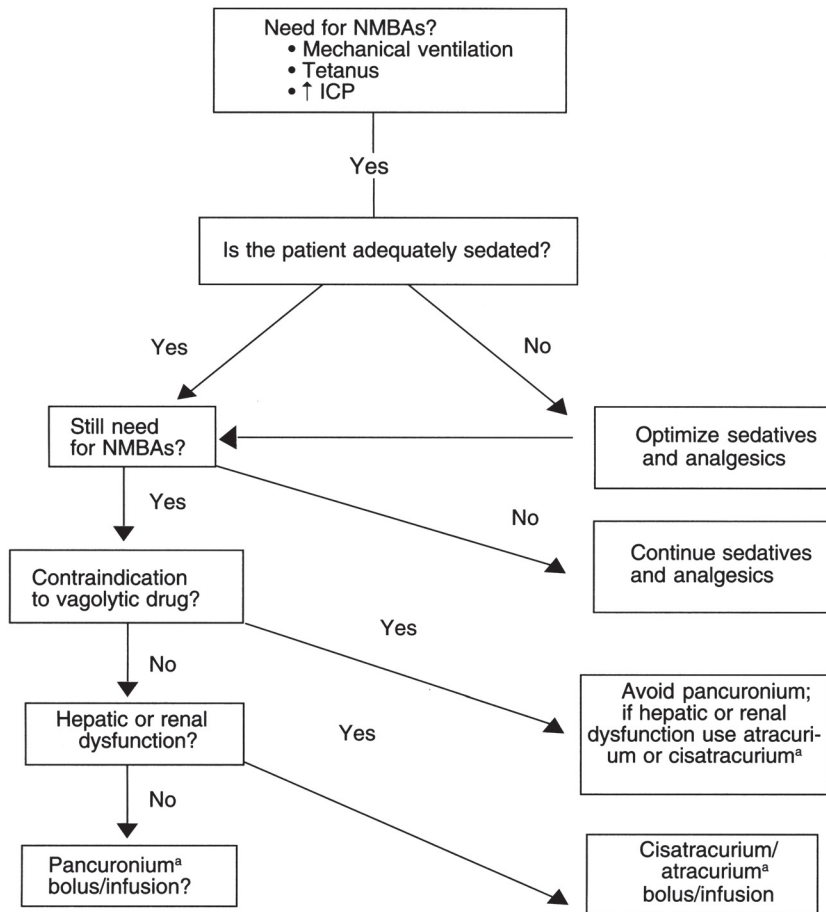
## Recommended Indications

There are no prospective, randomized, controlled trials assigning patients to an NMBA versus a placebo with a goal

Table 4. **Indications for the Long-Term Use of Neuromuscular Blocking Agents in Critically Ill Patients<sup>a</sup>**

Indication	Agents (n)	Study Design	Underlying Diseases	Reference	Level of Evidence
<i>Facilitate Mechanical Ventilation</i>					
Facilitate management	Cisatracurium (40), atracurium (21)	Randomized, open-label	Hepatic failure, sepsis, cardiogenic shock, ARDS	20	2
Beneficial to management	Cisatracurium (12), atracurium (8)	Randomized, single-blind	Cardiac arrest, respiratory failure, postneurosurgery, trauma, multiorgan failure, asthma, cardiogenic shock	18	2
Facilitate management	Cisatracurium (6), atracurium (6)	Randomized, open-label	Multiple	19	2
Facilitate management	Cisatracurium (28), vecuronium (30)	Randomized, double-blind	Head trauma, intracranial hemorrhage, trauma, ARDS, sepsis, hepatic or renal failure, tetanus	15	2
Optimize mechanical ventilation, increase ICP	Doxacurium (19), pancuronium (21)	Prospective, randomized, double-blind	Not reported	12	2
Facilitate mechanical ventilation	Pipecuronium (30), pancuronium (30)	Prospective, open-label	Head injury, multiple trauma, sepsis, multiorgan failure	13	3
Facilitate mechanical ventilation; dose-finding pharmacokinetic study	Rocuronium (32)	Prospective, open-label	Respiratory failure, multiple trauma, blunt brain trauma	9	3
Facilitate mechanical ventilation; dose-finding pharmacokinetic study	Rocuronium (30)	Prospective, open-label	Multiple trauma and/or blunt brain trauma	8	3
Deterioration in gas exchange	Vecuronium and atracurium (1)	Case report	Respiratory failure in a kidney/pancreas transplant patient	39	5
<i>Control ICP</i>					
Facilitate mechanical ventilation and/or management of traumatic brain injury	Doxacurium (8)	Prospective, open-label	Severe head injury	30	3
<i>Control Muscle Spasms</i>					
Control tetanospasms	Atracurium (4)	Case report	Severe head injury	40	5
<i>Decrease Oxygen Consumption</i>					
Determine effect on oxygen delivery, consumption, and gastric intramucosal pH	Rocuronium (1)	Case report	Tetanus	41	5
Determine effect on oxygen delivery, consumption, and gastric intramucosal pH	Vecuronium (18)	Prospective, randomized, controlled, cross-over	Severe sepsis and septic shock	42	2

<sup>a</sup>ARDS = acute respiratory distress syndrome, ICP = intracranial pressure.

**Figure 2.** Use of neuromuscular blocking agents (NMBAs) in the ICU.

<sup>a</sup>Monitor train-of-four ratio, protect eyes, position patient to protect pressure points, and address deep venous thrombosis prophylaxis. Reassess every 12–24 hours for continued NMBA indication.

of documenting if such patients could be managed by means other than NMBA therapy.

*Recommendation: NMBAs should be used for an adult patient in an ICU to manage ventilation, manage increased ICP, treat muscle spasms, and decrease oxygen consumption only when all other means have been tried without success. (Grade of recommendation = C)*

## Recommended Drugs

There has, in essence, been no study since the last guidelines were published that questions the use of pancuronium for the majority of patients in an ICU. Those prospective, randomized, controlled trials (PRCTs) that have been conducted do not clearly show the benefits of using newer agents or any other agents instead of pancuronium.

There are no well-designed studies with sufficient power to make this a level A recommendation, but there is evidence in the literature that patients on pancuronium fare as well as or better than patients receiving any other NMBA.

The two adverse effects of pancuronium that are commented on frequently are vagolysis and an increase in heart rate. Therefore, patients who would not tolerate an increase in heart rate, i.e., those with cardiovascular disease, should probably receive an NMBA other than pancuronium. The indications for the use of an NMBA must outweigh the risk of tachycardia, and

that is based on interpretation of the severity of the patient's underlying cardiovascular disease. For example, a patient with a history of atrial fibrillation now in sinus rhythm and otherwise hemodynamically stable might better tolerate pancuronium than a patient who is hospitalized with cardiogenic pulmonary edema and managed with mechanical ventilation. The clinician should choose an NMBA on the basis of other patient characteristics. Any benzyliisoquinolinium compound or aminosteroidal compound could be substituted for pancuronium in these circumstances.

There are no ideal PRCTs that support this recommendation, but there are data suggesting that patients recover more quickly following administration of cisatracurium or atracurium compared with patients receiving other NMBAs if they have evidence of hepatic or renal disease.

*Recommendations: The majority of patients in an ICU who are prescribed an NMBA can be managed effectively with pancuronium. (Grade of recommendation = B)*

*For patients for whom vagolysis is contraindicated (e.g., those with cardiovascular disease), NMBAs other than pancuronium may be used. (Grade of recommendation = C)*

*Because of their unique metabolism, cisatracurium or atracurium is recommended for patients with significant hepatic or renal disease. (Grade of recommendation = B)*

## Monitoring

Monitoring neuromuscular blockade is recommended (Table 5).<sup>12,14,43–55</sup> Monitoring the depth of neuromuscular blockade may allow use of the lowest NMBA dose and may minimize adverse events. No PRCT has reported that reducing the dose of an NMBA can prevent persistent weakness. Despite this lack of evidence and the lack of a standardized method of monitoring, assessment of the depth of neuromuscular blockade in ICU patients is recommended.<sup>43</sup>

Visual, tactile, or electronic assessment of the patient's muscle tone or some combination of these three is commonly used to monitor the depth of neuromuscular blockade. Observation of skeletal muscle movement and respiratory effort forms the foundation of clinical assessment; electronic methods include the use of ventilator software allowing plethysmographic recording of pulmonary function to detect spontaneous ventilatory efforts and "twitch monitoring," i.e., the assessment of the muscular response by visual, tactile, or electronic means to a transcutaneous delivery of electric current meant to induce peripheral nerve stimulation (PNS).

Table 5.  
**Monitoring the Degree of Neuromuscular Blockade<sup>a</sup>**

Monitoring Method	Study Design	Reference	Level of Evidence
TOF vs. clinical assessment to guide dosing	Prospective, randomized, single-blind	14	2
TOF vs. clinical assessment to compare depth of neuromuscular blockade	Prospective, nonrandomized	43	4
Complications with various monitoring methods	Retrospective, nonrandomized cohort	44	4
Use of TOF in comparing NMBAs	Multicenter, double-blind, PRCT	12	2
Methods of monitoring NMBAs	Editorial	45	6
Methods of monitoring NMBAs	Review	46	6
Comparison of common NMBAs/pharmacology	Review	25	6
Frequency of NMBA monitoring methods	Nonrandomized, historic, descriptive	47	4
Comparison of NMBA monitoring methods	Editorial	48	6
Comparison of NMBA monitoring methods	Expert opinion	49	6
Comparison of NMBA monitoring methods	Expert opinion	50	6
Technical aspects and problems in NMBA monitoring	Review	51	6
Technical problems with NMBAs monitoring	Review	52	6
Technical problems with NMBA monitoring	Review	53	5
Methods of assessing depth of NMBA	Prospective, randomized, blinded	54	2
Patient assessment during NMBA use	Review	55	6

<sup>a</sup>TOF = train-of-four, NMBA = neuromuscular blocking agent, PRCT = prospective, randomized, controlled trial.

Since the last practice guidelines were published, only two studies have examined the best method of monitoring the depth of neuromuscular blockade, and none have compared the efficacy or accuracy of specific techniques. The first study was a prospective, randomized, single-blinded trial of 77 patients in a medical ICU who were administered vecuronium based on either clinical parameters (patient breathed above the preset ventilatory rate) or TOF monitoring, with a goal of one of four twitches.<sup>44</sup> PNS resulted in a significantly lower total dose and lower mean infusion rate of NMBA as well as a faster time to recovery of neuromuscular function and spontaneous ventilation.

A second study sought to compare the depth of blockade induced by atracurium either by “best clinical assessment” (i.e., maintenance of patient-ventilator synchrony and prevention of patient movement) or TOF monitoring (with a goal of three of four twitches). Analysis of the 36 medical ICU patients in this prospective, nonrandomized trial revealed no difference in the total dose, mean dose, or the mean time to clinical recovery.<sup>43</sup> This may have been due to sample size or study design.

An additional study examining the results of the implementation of a protocol using PNS to monitor the level of blockade in patients receiving a variety of NMBAs found a reduction in the incidence of persistent neuromuscular weakness.<sup>49</sup>

Other methods of electronic monitoring of the depth of blockade are fraught with difficulties; TOF monitoring of PNS remains the easiest and most reliable method available,<sup>43,44,46–50</sup> despite its shortcomings and technical pitfalls.<sup>51–53</sup> Currently, there is no universal standard for twitch monitoring. The choice of the number of twitches necessary for “optimal” blockade is influenced by the patient’s overall condition and level of sedation. The choice of the “best” nerve for monitoring may be influenced by site accessibility, risk of false positives, considerations for the effect of stimulation on patient visitors, and whether faint twitches should be included in the assessment of blockade.<sup>54–56</sup> Despite these gaps in research-generated knowledge, evidence-based practice appears to be influencing the increasing frequency with

which PNS is utilized.<sup>47</sup> The low correlation of blockade measured peripherally compared with that of the phrenic nerve and diaphragm underscores the importance of three issues: (1) more than one method of monitoring should be utilized, (2) poor technique in using any device will invariably produce inaccurate results, and (3) more clinical studies are necessary to determine the best techniques.

### Recommendations for Monitoring Degree of Blockade

Even though the patient may appear quiet and “comfortable,” experienced clinicians understand the indications and therapeutic limits of NMBAs. Despite multiple admonitions that NMBAs have no analgesic or amnestic effects, it is not uncommon to find a patient’s degree of sedation or comfort significantly overestimated or even ignored. It is difficult to assess pain and sedation in the patient receiving NMBAs, but patients must be medicated for pain and anxiety, despite the lack of obvious symptoms or signs. In common practice, sedative and analgesic drugs are adjusted until the patient does not appear to be conscious and then NMBAs are administered. There have been no studies of the use of electrophysiologic monitoring in assessing adequacy of sedation or analgesia.

In a phenomenological study of 11 critically ill adult trauma patients who required therapeutic NMBA, patients compared their feelings of vagueness to dreaming.<sup>56</sup> Few patients recalled pain or painful procedures. Family members understood the rationale for the use of the drugs and remembered being encouraged to touch and talk with patients. The use of effective pain and sedation protocols and a liberalized visiting policy may have affected the findings.

*Recommendations: Patients receiving NMBAs should be assessed both clinically and by TOF monitoring (Grade of recommendation = B), with a goal of adjusting the degree of neuromuscular blockade to achieve one or two twitches. (Grade of recommendation = C)*

*Before initiating neuromuscular blockade, patients should be medicated with sedative and analgesic drugs to provide adequate sedation and analgesia in accordance with the physician's clinical judgment to optimize therapy. (Grade of recommendation = C)*

## Complications

Skeletal muscle weakness in ICU patients is multifactorial, producing a confusing list of names and syndromes, including acute quadriplegic myopathy syndrome (AQMS), floppy man syndrome, critical illness polyneuropathy (CIP), acute myopathy of intensive care, rapidly evolving myopathy, acute myopathy with selective lysis of myosin filaments, acute steroid myopathy, and prolonged neurogenic weakness (Table 6).<sup>57,58</sup>

There are probably two adverse events related to prolonged paralysis following discontinuation of NMBAs. We define the first, "prolonged recovery from NMBAs," as an increase (after cessation of NMBA therapy) in the time to recovery of 50–100% longer than predicted by pharmacologic parameters. This is primarily due to the accumulation of NMBAs or metabolites. By comparison, the second, AQMS, presents with a clinical triad of acute paresis, myonecrosis with increased creatine phosphokinase (CPK) concentration, and abnormal electromyography (EMG). The latter is characterized by severely reduced compound motor action potential (CMAP) amplitudes and evidence of acute denervation. In the beginning, these syndromes are characterized by neuronal dysfunction; later (days or weeks), muscle atrophy and necrosis may develop.<sup>59</sup>

**Prolonged Recovery from NMBAs.** The steroid-based NMBAs are associated with reports of prolonged recovery and myopathy.<sup>57,60</sup> This association may reflect an increased risk inferred by these NMBAs or may reflect past practice patterns in which these drugs may have been more commonly used.<sup>61</sup> Steroid-based NMBAs undergo extensive hepatic metabolism, producing active drug metabolites. For instance, vecuronium produces three metabolites: 3-des-, 17-des-, and 3,17-desacetyl vecuronium.<sup>62</sup> The 3-desacetyl

metabolite is estimated to be 80% as potent as the parent compound. The 3-desacetyl vecuronium metabolite is poorly dialyzed, minimally ultrafiltrated, and accumulates in patients with renal failure because hepatic elimination is decreased in patients with uremia. Thus, the accumulation of both 3-desacetyl vecuronium and its parent compound, vecuronium, in patients with renal failure contributes to a prolonged recovery by this ICU subpopulation. Other explanations have been proposed. One suggests that the basement membrane of the neuromuscular junction acts as a reservoir of NMBAs, maintaining NMBAs at the nAChRs long after the drug has disappeared from the plasma.<sup>63</sup>

Drug–drug interactions that potentiate the depth of motor blockade (Table 7) may also prolong recovery. The specific interaction of NMBAs and exogenous corticosteroids is discussed later.<sup>57,62–65</sup>

Physiologic changes of the nAChRs are enhanced when patients are immobilized or denervated secondary to spinal cord injury, and perhaps during prolonged NMBA drug-induced paralysis. The nAChRs may be triggered to revert to a fetal–variant structure (Figure 3), characterized by an increase in total number, frequent extrajunctional proliferation, and resistance to nondepolarizing NMBAs. The proliferation and distribution of these altered receptors across the myomembrane may account for tachyphylaxis and the neuromuscular blocking effects of these drugs.

**AQMS.** AQMS, also referred to as postparalytic quadriplegia, is one of the most devastating complications of NMBA therapy and one of the reasons that indiscriminate use of NMBAs is discouraged (Table 8).<sup>65,66</sup> This entity must be differentiated from other neuromuscular pathologies (Table 6) seen in an ICU and requires extensive testing. Reports of AQMS in patients receiving NMBAs alone are quite limited; no experimental model has been able to produce the histopathology of this syndrome by administering NMBAs. Afflicted patients demonstrate diffuse weakness that persists long after the NMBA is discontinued and the drug and its active metabolites are eliminated. Neurologic examination reveals a global motor deficit affecting muscles in both the upper and lower extremities and decreased motor reflexes. However, extraocular muscle function is usually preserved. This myopathy is characterized by low-amplitude CMAPs, and muscle fibrillations but normal (or nearly normal) sensory nerve conduction studies.<sup>63,67</sup> Muscle biopsy shows prominent vacuolization of muscle fibers without inflammatory infiltrate, patchy type 2 muscle fiber atrophy, and sporadic myofiber necrosis.<sup>64</sup> Modest CPK increases (0 to 15-fold above normal range) are noted in approximately 50% of patients and are probably dependent on the timing of enzyme measurements and the initiation of the myopathic process. Thus, there may be some justification in screening patients with serial CPK determinations during infusion of NMBAs, particularly if the patients are concurrently treated with corticosteroids. Also, since AQMS develops after prolonged exposure to NMBAs, there may be some rationale to daily "drug holidays" (i.e., stopping the drugs for a few to several hours and restarting them only when necessary). However, no one has demonstrated that drug holidays decrease the frequency of AQMS. Other factors that may contribute to the development of the syndrome include nutritional deficiencies, concurrent drug administration with aminoglycosides or cyclosporine, hyperglycemia, renal and hepatic dysfunction, fever, and severe metabolic or electrolyte disorders.

Evidence supports, but occasionally refutes,<sup>14</sup> the association of concurrent administration of NMBAs and corti-

Table 6.

### Weakness in ICU Patients: Etiologies and Syndromes<sup>a</sup>

1. Prolonged recovery from NMBAs (secondary to parent drug, drug metabolite, or drug–drug interaction)
2. Myasthenia gravis
3. Lambert-Eaton syndrome
4. Muscular dystrophy
5. Guillain-Barré syndrome
6. Central nervous system injury or lesion
7. Spinal cord injury
8. Steroid myopathy
9. Mitochondrial myopathy
10. HIV-related myopathy
11. Acute myopathy of intensive care
12. Disuse atrophy
13. Critical illness polyneuropathy
14. Severe electrolyte toxicity (e.g., hypermagnesemia)
15. Severe electrolyte deficiency (e.g., hypophosphatemia)

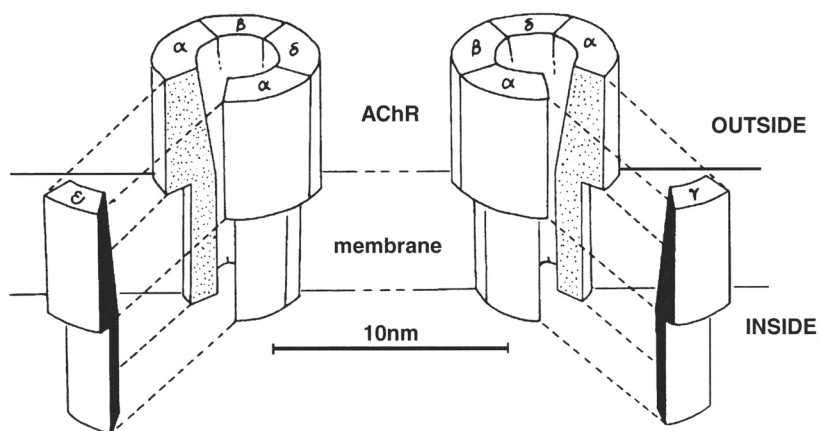
<sup>a</sup>ICU = intensive care unit, NMBAs = neuromuscular blocking agents, HIV = human immunodeficiency virus.

Table 7.

**Drug-Drug Interactions of Neuromuscular Blocking Agents (NMBAs)**

Drugs that potentiate the action of nondepolarizing NMBAs	Drugs that antagonize the actions of nondepolarizing NMBAs
Local anesthetics	Phenytoin
Lidocaine	Carbamazepine
Antimicrobials (aminoglycosides, polymyxin B, clindamycin, tetracycline)	Theophylline
Antiarrhythmics (procainamide, quinidine)	Ranitidine
Magnesium	
Calcium channel blockers	
$\beta$ -Adrenergic blockers	
Immunosuppressive agents (cyclophosphamide, cyclosporine)	
Dantrolene	
Diuretics	
Lithium carbonate	

**Figure 3.** Acetylcholine Receptor. The mature nicotinic acetylcholine receptor (AChR) (left) with its glycoprotein subunits arranged around the central cation core. Two molecules of acetylcholine bind simultaneously to the two alpha subunits to convert the channel to an open state. The immature, or fetal-variant, receptor is shown on the right, with a single subunit substitution which follows major stress such as burns or denervation. These immature receptors are characterized by 10-fold greater ionic activity, rapid metabolic turnover, and extrajunctional proliferation. (Reprinted, with permission, from Martyn JAJ, White DA, Gronert GA et al. Up-and-down regulation of skeletal muscle acetylcholine receptors. *Anesthesiology*. 1992; 76:825.)



corticosteroids with AQMS.<sup>59,63,68,69</sup> The incidence of myopathy may be as high as 30% in patients who receive corticosteroids and NMBAs. While no period of paralysis is risk free, NMBA administration beyond one or two days increases the risk of myopathy in this setting.<sup>63</sup> Similarly, there is an inconsistent correlation with the dose of corticosteroids, but total doses in excess of 1 g of methylprednisolone (or equivalent) probably increase the risk. Afflicted patients manifest an acute, diffuse, flaccid weakness and an inability to wean from mechanical ventilation. Sensory function is generally preserved.<sup>63</sup> Muscle biopsy shows extensive type 2 fiber atrophy, myonecrosis, disarray of sarcomere architecture, and an extensive, selective loss of myosin. Experimental evidence in animals shows that denervation for  $\geq 24$  hours induces profound negative nitrogen balance and increases expression of steroid receptors in muscle. Such denervation sensitizes muscle to even normal corticosteroid concentrations, and evidence suggests that the combination of denervation and high-dose corticosteroids precipitates myosinolysis.

Acute myopathy in ICU patients is also reported after administration of the benzyloquinolinium NMBAs (i.e., atracurium, cisatracurium, doxacurium).<sup>24,34,69</sup> Common to all these reports is the coadministration of benzyloquinolinium NMBAs and large doses of corticosteroids, aminoglycosides, or other drugs that affect neuromuscular transmission.

*Recommendations:* For patients receiving NMBAs and corticosteroids, every effort should be made to discontinue NMBAs as soon as possible. (Grade of recommendation = C)

*Drug holidays* (i.e., stopping NMBAs daily until forced to restart them based on the patient's condition) may decrease the incidence of AQMS. (Grade of recommendation = C)

Other nerve and muscle disorders have been recognized in the last decade in ICU patients (Table 6). For instance, CIP is a sensory and motor polyneuropathy identified in elderly, septic patients or those with MODS.<sup>58,66,70</sup> EMG testing reveals decreased CMAP, fibrillation potentials, and positive sharp waves.<sup>60,63,64</sup> CIP is primarily an axonopathy and may be related to microvascular ischemia of the nerve but is not directly related to the use of NMBAs. Recovery from ICU myopathy requires a protracted (weeks or months) hospitalization. One economic analysis of 10 patients who developed AQMS showed the median additional hospital charge to be \$66,000 per patient.<sup>65</sup> As for any critically ill patient, particularly immobilized patients, deep venous thrombosis (DVT) prophylaxis and physical therapy to maintain joint mobility are important.

Patients receiving NMBAs are also at risk of developing keratitis and corneal abrasion. Prophylactic eye care is highly variable and recommendations may include methylcellulose drops, ophthalmic ointment, taping the eyelids shut to ensure complete closure, or eye patches. In a study of 69 paralyzed or heavily sedated patients by Lenart and Garrity,<sup>71</sup> there was strong evidence that the use of an artificial tear ointment prevented corneal exposure. In this randomized study, patients served as their own controls.

**Myositis Ossificans (Heterotopic Ossification).** Myositis ossificans can develop in patients who are paralyzed for long periods of time, but inflammation is not characteristic of the ailment. The name is misleading because the process involves connective tissue (not muscle). The name originates from the ossification that occurs within the connective tissue of muscle but may also be seen in ligaments, tendons, fascia, aponeuroses,

Table 8.

**Potential Complications of Neuromuscular Blockade Use in the ICU<sup>a</sup>**

Complications and contraindications of succinylcholine in the ICU	General complications associated with NMBAs in the ICU
Loss of airway	Awake, paralyzed patient—anxiety and panic
Hyperkalemia	Risk of ventilator disconnect or airway mishap
Plasma pseudocholinesterase deficiency	Autonomic and cardiovascular effects (i.e., vagolytic) Decreased lymphatic flow Risk of generalized deconditioning Skin breakdown Peripheral nerve injury Corneal abrasion, conjunctivitis Myositis ossificans Risk of prolonged muscle weakness, AQMS Potential central nervous system toxicity

<sup>a</sup>NMBA = neuromuscular blocking agent, AQMS = acute quadriplegic myopathy syndrome.

and joint capsules. The acquired form of the disease may occur at any age in either sex, especially around the elbows, thighs, and buttocks. The basic defect is the inappropriate differentiation of fibroblasts into osteoblasts and is usually triggered by trauma and muscle injury, paraplegia or quadriplegia, tetanus, and burns. Treatment consists of promoting an active range of motion around the affected joint and surgery when necessary.

**Tachyphylaxis.** For reasons mentioned earlier, tachyphylaxis to NMBAs can and does develop.

Coursin and colleagues<sup>31</sup> administered doxacurium to four patients who developed tolerance to atracurium infusions (range, 16 to 40 µg/kg/min). Patients were successfully blocked with infusion rates of doxacurium 0.25–0.75 µg/kg/min.

Tschida et al.<sup>72</sup> described a patient whose atracurium requirement escalated from 5 to 30 µg/kg/min over 10 days. The patient was successfully blocked with a pancuronium infusion of 10–50 µg/kg/min for a period of five days.

Fish and Singletary<sup>33</sup> describe a patient who was inadequately blocked with a 60-µg/kg/min infusion of atracurium but adequately paralyzed for seven days with 2.3-mg/kg/hr infusion of vecuronium. Tachyphylaxis then developed to vecuronium which prompted discontinuation of NMBAs. Two days later, 50-µg/kg/min atracurium infusions were required with high-dose midazolam and fentanyl infusions to achieve adequate oxygenation and acceptable airway pressures.

*Recommendations: Patients receiving NMBAs should have prophylactic eye care (Grade of recommendation = B), physical therapy (Grade of recommendation = C), and DVT prophylaxis. (Grade of recommendation = C)*

*Patients who develop tachyphylaxis to one NMBA should try another drug if neuromuscular blockade is still required. (Grade of recommendation = C)*

## Economics

There have been few formal pharmacoeconomic evaluations of NMBAs. In one of these economic evaluations,

medication-related cost savings were found when voluntary prescribing guidelines for NMBAs were initiated in the operating room of a university hospital.<sup>73</sup> In another study that involved randomization to one of three NMBAs, there were no significant cost differences between atracurium, vecuronium, and rocuronium for surgeries lasting two hours or less, but vecuronium and rocuronium were economically advantageous if the duration of surgery was two to four hours.<sup>74</sup> In a third retrospective study, long-acting NMBAs (e.g., D-tubocurarine and pancuronium) were associated with prolonged postoperative recovery compared with shorter-acting agents (e.g., atracurium, mivacurium, and

vecuronium). The authors noted in the discussion section of the paper that based on intrainstitutional recovery room costs, delays in recovery times seen with the longer-acting agents offset the expected savings in drug costs.<sup>75</sup> For patients transferred to the ICU, this may not be a major problem.

Two pharmacoeconomic investigations involving NMBAs in the ICU evaluated the costs associated with prolonged recovery following discontinuation of nondepolarizing NMBAs. In one study, overall costs were lower when TOF monitoring was employed.<sup>76</sup> In another study, patients who had prolonged motor weakness after discontinuing NMBAs were compared with a control group<sup>77</sup>; ICU and hospital costs were substantially higher in the patients with prolonged weakness.

A study involving 40 academic medical centers with patients undergoing coronary artery bypass graft surgery found no significant differences in duration of intubation or duration of ICU or hospital stay among patients who received pancuronium ( $n = 732$ ), vecuronium ( $n = 130$ ), or both ( $n = 242$ ) agents.<sup>78</sup> It is unknown if these results pertain to subgroups of patients, such as those with renal or hepatic dysfunction. If the results of this study are confirmed, the choice of agent could be based solely on cost minimization using medication purchase cost information and equipotent dosage regimens.

A prospective, randomized trial comparing TOF to standard clinical assessment showed decreased NMBA usage and faster return of spontaneous ventilation with TOF monitoring.<sup>14</sup> TOF has the potential to decrease costs associated with NMBA use in ICUs.

Appendix B describes the basic steps involved in conducting a cost-effectiveness analysis of the NMBAs. Consequently, intrainstitutional data and assumptions can be used to perform the analysis along with local value judgments involved in selecting the appropriate agent(s).

*Recommendation: Institutions should perform an economic analysis using their own data when choosing NMBAs for use in an ICU. (Grade of recommendation = C)*

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### Appendix A—Summary of Recommendations

1. NMBAs should be used for an adult patient in an ICU to manage ventilation, manage increased ICP, treat muscle spasms, and decrease oxygen consumption only when all other means have been tried without success.<sup>1</sup> (Grade of recommendation = C)
2. The majority of patients in an ICU who are prescribed an NMBA can be managed effectively with pancuronium. (Grade of recommendation = B)
3. For patients for whom vagolysis is contraindicated (e.g., those with cardiovascular disease), NMBAs other than pancuronium may be used. (Grade of recommendation = C)
4. Because of their unique metabolism, cisatracurium or atracurium is recommended for patients with significant hepatic or renal disease. (Grade of recommendation = B)
5. Patients receiving NMBAs should be assessed both clinically and by TOF monitoring (Grade of recommendation = B), with a goal of adjusting the degree of neuromuscular blockade to achieve one or two twitches. (Grade of recommendation = C)
6. Before initiating neuromuscular blockade, patients should be medicated with sedative and analgesic drugs to provide adequate sedation and analgesia in accordance with the physician's clinical judgment to optimize therapy. (Grade of recommendation = C)
7. For patients receiving NMBAs and corticosteroids, every effort should be made to discontinue NMBAs as soon as possible. (Grade of recommendation = C)
8. Drug holidays (i.e., stopping NMBAs daily until forced to restart them based on the patient's condition) may decrease the incidence of AQMS. (Grade of recommendation = C)
9. Patients receiving NMBAs should have prophylactic eye care (Grade of recommendation = B), physical therapy (Grade of recommendation = C), and DVT prophylaxis. (Grade of recommendation = C)
10. Patients who develop tachyphylaxis to one NMBA should try another drug if neuromuscular blockade is still required. (Grade of recommendation = C)

11. Institutions should perform an economic analysis using their own data when choosing NMBAs for use in an ICU. (Grade of recommendation = C)

### Appendix B—Determination of Cost Effectiveness Using Intra-institutional Data<sup>a</sup>

1. For each adverse effect (e.g., prolonged recovery) of any given neuromuscular blocking agent (NMBA), add all associated costs together and multiply this figure by the probability of the occurrence of the adverse effect. If adverse effects A, B, and C are associated with an NMBA, then

(Drug cost + cost A1) (probability of occurrence expressed as a decimal) = \$U

(Drug cost + cost B1) (probability of occurrence expressed as a decimal) = \$V

(Drug cost + cost C1) (probability of occurrence expressed as a decimal) = \$W

2. Calculate the product of the drug cost multiplied by the probability of occurrence of no adverse effects expressed as a decimal; add this product to the cost multiplied by the probability factor for each adverse effect calculated in step 1.

(Drug cost) (probability of occurrence of no adverse effects) + \$U + \$V + \$W = average cost of all pathways for agent

Note: The probabilities of all adverse effects plus the probability of no adverse effects associated with the NMBA must add up to 1.

3. Determine the cost effectiveness of the agent by dividing the total costs associated with the agent by the probability of occurrence of no adverse effects expressed as a decimal.

*Example using pancuronium:*

a. [\$224 (drug cost for 4 days of therapy) + \$1000 (estimated cost of 1 extra day of ICU stay due to prolonged paralysis

resulting from renal dysfunction)] [0.07 (estimated probability of renal dysfunction)] = \$85.68

[\$224 (drug cost for 4 days of therapy) + \$1000 (estimated cost of 1 extra day of ICU (intensive care unit) stay due to prolonged paralysis

resulting from hepatic dysfunction)] [0.04 (estimated probability of hepatic dysfunction)] = \$48.96

b. [\$224 (drug cost for 4 days of therapy, assuming no adverse effects) × 0.89 (estimated probability of no adverse effects)]

+ \$85.68 + \$48.96 = \$334.00

c. Cost effectiveness of pancuronium = 334.00/0.89 (probability of no adverse effects) = \$375.28

<sup>a</sup>Note that the term "adverse effects" includes problems such as prolonged paralysis resulting from decreased medication elimination due to impaired organ function. If a neuromuscular blocking agent is eliminated by more than one organ (e.g., kidney and liver), prolonged paralysis may result from impaired elimination due to a combination of organ problems. For example, one adverse effect

may be prolonged paralysis associated with renal dysfunction, while another adverse effect may be prolonged paralysis associated with hepatic dysfunction, while a third adverse effect may be prolonged paralysis associated with combined renal and hepatic dysfunction.

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The recommendations in this document do not indicate an exclusive course of treatment to be followed. Variations, taking into account individual circumstances, may be appropriate.

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