Procedural Sedation Curriculum
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Module 3: Neuromuscular blocking agents

<u>Introduction</u>

In the Pediatric Intensive Care Unit (PICU) setting, there may be circumstances in which total prevention of movement is necessary thereby mandating the use of neuromuscular blocking agents (NMBA's)(table 1).[1]   Although these agents can be used as a single dose to facilitate endotracheal intubation, more prolonged administration may be needed in specific circumstances. A survey from the PICU setting suggests that the prolonged administration of these agents is used most commonly as an adjunct in the control of intracranial pressure (ICP).[2] With an improved understanding of the techniques for providing sedation and analgesia in the PICU setting and data demonstrating not only their adverse effect profile, but also their lack of efficacy in specific clinical scenarios, there has been a decrease in the prolonged administration of NMBA's.

Given their potential for adverse effects, it is recognized that NMBA's should be used only when absolutely indicated, only after appropriate training in their pharmacology, and only after obtaining the knowledge and skills needed to treat adverse effects related to their use. Furthermore, it may be appropriate to avoid the use of the terminology "muscle relaxant" as this seems to imply some implicit type of sedative property which of course they agents do not have. Rather, these agents should be thought of as NMBA's, thereby identifying in their name their mechanism of action and further emphasizing that they are devoid of sedative and analgesic properties. Given their action (blockade of skeletal muscle function), these agents will cause cessation of ventilatory function, mandating airway control and the institution of mechanical ventilation. The inability to manage the airway including the provision of bag-mask ventilation and endotracheal intubation will result in hypoxia and death. These agents should not be used if there is any question as to the normalcy of the airway and the ability to successfully accomplish

bag-mask ventilation and endotracheal intubation. In the absence of co-morbid disease processes which alter the sensorium, patients receiving NMBA's are unable to move and yet are totally aware. These agents provide no amnestic, analgesic, or sedative properties, and should not be used without the co-administration of an amnestic agent (i.e., benzodiazepine or barbiturate).

The Neuromuscular Junction

Normal neuromuscular transmission results from the release of acetylcholine from the nerve terminal, its movement across the synaptic cleft, and subsequent binding to the post-synaptic nicotinic receptor on the sarcolemma of the skeletal muscle. Acetylcholine is synthesized in the cytoplasm from acetyl coenzyme A and choline and stored in synaptic vesicles in the axonal terminals of the presynaptic membrane. Depolarization of the axonal membrane results in the opening of calcium channels (P channel) and the movement of calcium through channels in the presynaptic membrane resulting in the fusion of the synaptic vesicles with the axonal membrane and the release of acetylcholine into the synaptic cleft. The P-channel is blocked by divalent cations such as magnesium and lithium, but not by calcium channel antagonists. As such the concurrent administration of magnesium or lithium will potentiate the effect of NMBA's and the excessive administratrion of either divalent cation can have significant effects on normal neuromuscular function. After its release from the synaptic vesicles, acetylcholine diffuses across the synaptic cleft and binds to acetycholine receptors on the post-synaptic membrane (sacrolemma). The acetylcholine receptor (nicotinic receptor on the sarcolemma) is a pentameric protein composed of five subunits. There are 5 classes of subunits (alpha, beta, gamma, delta, and epsilon) each of which is coded for by a different gene. During various stages of development or in

pathologic disease states, the composition of the acetycholine receptor may change. The normal variant of the acetycholine receptors found in adults includes 2 alpha subunits combined with 1 each of the beta, delta, and epsilon subunits. Binding of an acetylcholine molecule to each of the two alpha subunits is necessary for opening of the channel and depolarization of the sarcolemma. Immature and denervated acetycholine receptors have a gamma subunit instead of the epsilon while a demyelinated neuromuscular junction contains acetycholine receptors composed of a pentamer of alpha$_7$ subunits. The importance of these variants is that their response (opening of the ion channel) is dramatically different than the normal adult variant of the acetylcholine receptor. These differences can result in devastating consequences following the administration of succinylcholine (see below). The acetycholine receptor occupies the space from the outside of the muscle through the cell membrane to the inside and thereby regulates the transmembrane movement of ions. It converts the chemical stimulus (acetylcholine) into an electrical impulse (depolarization of the sarcolemma). Stimulation of the acetylcholine receptors opens ion channels allowing the movement of small, positively charged cations such as sodium, potassium, and calcium. The sodium influx depolarizes the muscle membrane leading to excitation-contraction coupling with the release of calcium from the sarcoplasmic reticulum and muscle contraction. Cessation of muscle contraction and repolarization occurs when acetylcholine is metabolized by a specific enzyme, acetylcholinesterase, which is present in the synaptic cleft. This repolarization sets the muscle for the next round of depolarization and excitation-contraction coupling.

Neuromuscular blocking agents: Depolarizing agents

The two general classes of NMBA's (depolarizing and non-depolarizing agents) differ in

their basic mechanism of action. Depolarizing agents such as succinylcholine (suxamethonium in Europe and the United Kingdom) mimic acetylcholine, binding to the acetylcholine receptor at the neuromuscular junction, and activating it. As succinylcholine is resistant to degradation by acetylcholinesterase, there is sustained occupation of the receptor and thereby failure of repolarization resulting in a more prolonged duration of neuromuscular blockade. This action of succinylcholine accounts for the clinical effects that are seen including the initial muscle fasciculations followed by flaccid paralysis which generally lasts 5-10 minutes, the time necessary for the degradation of succinylcholine by pseudocholinesterase. The onset of action of succinylcholine is more rapid than any of the non-depolarizing agents with neuromuscular blockade occurring in 30-45 seconds thereby allowing for rapid control of the airway with endotracheal intubation. Succinylcholine undergoes rapid redistribution and metabolism by the plasma enzyme, pseudocholinesterase (plasma cholinesterase), which limits its clinical duration to 5-10 minutes.

In isolated cases, a congenital or acquired deficiency of pseudocholinesterase can lead to a prolonged duration of action. In general, there may be issues with the total amount of the enzyme (quantitative defect) or the efficacy of the enzyme (qualitative defect).[3] Quantitative problems are generally acquired while qualitative issues are inherited. The inherited form of pseudocholinesterase deficiency results in a qualitative defect in the enzyme. It is an autosomal recessive trait with an incidence of 1:2,500-3,500. Only homozygotes have a clinically significant prolongation of the effect of succinylcholine with neuromuscular blockade lasting up to 4-8 hours following a single normal intubating dose of succinylcholine (1-2 mg/kg). Disease states which lead to a quantitative decrease in pseudocholinesterase levels include severe liver disease,

myxedema, pregnancy, protein-calorie malnutrition, and certain malignancies. Drugs and medications can also affect pseudocholinesterase levels including chemotherapeutic agents such as cyclophosphamide and echothiopate ophthalmic drops. Deficinecy can also result from the recent use of plasmapheresis as the enzyme is removed with the plasma. Treatment is aimed at prompt identification by noting failure of the return of the train-of-four (TOF) with peripheral nerve stimulation (see below). The possibility of such an occurrence stresses the need to ensure return of neuromuscular function following the administration of succinylcholine prior to the administration of a non-depolarizing agent. If such a problem is suspected, primary therapy includes continuation of ventilatory support until the patient's muscle strength returns and the provision of amnesia with a benzodiazepine or some other anesthetic agent since. Although the patient cannot move, they will be aware and awake once the effects of the anesthetic induction agents have diminished. The enzyme, plasma cholinesterase is contained in fresh frozen plasma (FFP); however, due to the infectious disease risk with the use of blood products, reversal with the administration of FFP cannot be recommended.[4-6] More recently, purified human plasma cholinesterase has also been used in such circumstances; however, such a practice is expensive and generally not available in most centers.

Despite its rapid onset and rapid offset, the potential adverse effects associated with succinylcholine can be devastating and even fatal (table 2). Direct effects on cardiac rhythm have been described following the administration of succinylcholine including bradycardia, tachycardia, and atrial or ventricular ectopy.[7] Succinylcholine has a chemical structure similar to two molecules of acetylcholine and may result in bradycardia from activation of cardiac muscarinic receptors. This effect is especially common in infants and children, when patients are anesthetized with

halothane given its negative chronotropic effects, in the presence of hypoxemia, with intravenous as compared to intramuscular administration, when succinylcholine is given concurrently with other medications that have negative chronotropic effects (propofol, fentanyl), or with repeated doses. Therefore, in these populations or scenarios, succinylcholine should always be preceded by an anticholinergic agent such as atropine. The bradycardic effects of succinylcholine may also be accentuated in the presence of hypothermia and increased ICP. Arrhythmias may also be seen and although may be common, occurring in up to 50% of patients, they are generally short-lived and of no clinical significance. The use of an anticholinergic agent will decrease, but not eliminate the incidence of arrhythmias. As with the potential for bradycardia, arrhythmias tend to be more common with repeated doses of succinylcholine.

As succinylcholine activates the acetylcholine receptor prior to producing neuromuscular blockade, depolarization of the muscle end-plate occurs with contraction of the muscle fascicles or fasciculations. These fasciculations are responsible for the myalgias which may occur following succinylcholine.[8] Although not a significant issue when succinylcholine is used for emergently securing the airway, these fasciculations can result in severe muscle pain and therefore many advise against the use of succinylcholine for outpatient surgery when such issues may interfere with activities of daily living and return to work. The severity of the fasciculations can be prevented by the administration of a small dose of a non-depolarizing agent (curare 0.03-0.05 mg/kg, rocuronium 0.05 mg/kg, or pancuronium 0.01 mg/kg) prior to succinylcholine. The dose of the non-depolarizing agent is generally $1/10^{th}$ of the recommended dose for endotracheal intubation.[9] This is referred to as a "defasciculating dose". The technique is commonly used in the operating room when succinylcholine is administered to adults as a means of preventing or

attenuating the postoperative myalgias that may occur with succinylcholine. One advantage of fasciculations is that their cessation signals that neuromuscular blockade is complete and the patient's trachea can be intubated.

Defasciculation is not commonly used in the pediatric population for several reasons: 1) children less than 6 years of age do not fasciculate, 2) the use of the defasciculating dose delays the onset of paralysis and increases the dose requirements succinylcholine needed, 3) in patients with severe respiratory or hemodynamic compromise, the defasciculating dose can cause a significant degree of neuromuscular blockade leading to respiratory insufficiency or laryngeal incompetency with the risk of aspiration, and 4) full efficacy may require up to 2-3 minutes thereby making the technique less optimal when emergent securing of the airway is necessary. If a defasciculating dose is used in patients who are awake and coherent, they should be warned that they may feel the effects of the medication, generally resulting in diplopia related to the effects of the drug on the extraocular muscles. Additionally, some patients may feel the effects on the muscles of ventilation resulting in complaints of shortness of breath or dyspnea.

In addition to myalgias, the fasciculations caused by succinylcholine may result in a transient increase in plasma CPK (creatinine phosphokinase) and myoglobin levels. Myoglobinemia occurs most often (up to 40% of patients) when there is the concomitant administration of general anesthesia with halothane. In these patients, levels high enough to result in myoglobinuria have been reported in 8% of patients.[10] The rise in plasma CPK and myoglobin levels does not occur with intramuscular administration and may be attenuated by the administration of a defasciculating dose of a non-depolarizing agent (see above). These effects should be differentiated for the potentially level complications of rhabdomyolysis which may occur

in patients with specific disorders of the neuromuscular junction and malignant hyperthermia (see below). These latter disorders absolutely contraindicate the use of succinylcholine. The fasciculations may also lead to an increase in intragastric (IGP) and intraocular pressure (IOP). The transient and minimal rise in IGP is generally of limited clinical significance and does not increase the risk of vomiting or passive regurgitation during endotracheal intubation. In the emergency setting, when succinylcholine is chosen for endotracheal intubation, rapid sequence intubation will be used with the application of cricoid pressure to protect against acid aspiration. The contraction of extraocular muscles leads to an increase of IOP following the administration of succinylchoine. The increase is transient with a return of the IOP to baseline within 5-8 minutes. Given this effects, administration to patients with an open globe injury is generally contraindicated due to the theoretical risk of causing extrusion of the intraocular contents. Although succinylcholine has been safely administered to such patients[11], standard practice generally considers the presence of an open globe injury a contraindication to its use.

The effects of succinylcholine on ICP and its use in patients with altered intracranial compliance remain controversial. Succinylcholine increases ICP not only through the production of muscle fasciculations and increased venous tone, but also via a direct cholinergic mechanism due to activation of muscle spindles in the peripheral skeletal musculature.[12] The effects on ICP are generally mild and transient. Given its rapid onset (30-45 seconds), succinylcholine allows for rapid endotracheal intubation and control of arterial oxygenation and ventilation. As the latter are primary determinants of ICP, any mild increase due to the direct effects of succinylcholine are rapidly controlled. Succinylcholine's effects on muscle spindles have also been postulated as an explanation of the CNS activation and dreaming which has been reported during general anesthesia

in patients who received succinycholine.[13] The dreaming has not been associated with awareness or recall.

Succinylcholine has also been shown to occasionally result in a transient increase in the tone of the masseter muscles. This effect may be seen in all of the peripheral skeletal musculature, but may be accentuated in the masseter muscles resulting in what is clinically known as masseter spasm. The effect is generally mild and can be overcome by manual opening of the mouth.[14] A defasciculating dose of a non-depolarizing agent may abolish this phenomenon. In rare circumstances, the masseter spasm may be severe, preventing mouth opening and precluding standard oral endotracheal intubation. It has been suggested that patients who manifest masseter spasm to this degree are at risk for MH, a rare inherited disorder of muscle metabolism which, if untreated, is generally fatal (see below). The data regarding the relationship between masseter spasm and MH are conflicting. In a prospective evaluation with monitoring of masseter muscle tone, patients who developed significant increases in masseter muscle tone did not proceed to develop MH.[15] However, retrospective series have suggested that the development of masseter spasm may be a preclude to MH thereby clouding the issue as to how to deal with such patients.[16] In the emergency situation, should patients develop masseter spasm following the administration of succinylcholine, patients should be monitored for signs of MH including hypercarbia, hyperthermia tachycardia, and rhabdomyolysis with myoglobinuria. Treatment with dantrolene is suggested should there be a concern regarding the development of MH (see below).

The major concerns with succinylcholine are its potential to trigger MH and its ability to cause massive hyperkalemia if administered to patients with various co-morbid disease processes. MH is an inherited disorder (autosomal dominant) of muscle metabolism with abnormalities of the

ryanodine receptor (the calcium release channel of the sarcoplasmic reticulum of skeletal muscle). The point mutation of the ryanodine receptor leads to ongoing release of calcium and therefore sustained muscle contraction following exposure to succinylcholine or a potent inhalational anesthetic agent. During MH, ongoing muscle contraction and metabolism leads to hyperthermia, acidosis, tachycardia, hypercarbia, and rhabdomyolysis with secondary hyperkalemia. Treatment includes discontinuation of the triggering agent, treatment of hyperthermia and the biochemical derangements including acidosis and hyperkalemia, and administration of dantrolene which blocks ongoing calcium release from the sarcoplasmic reticulum. Therefore, in clinical scenarios where succinylcholine may be administered, ready access to dantrolene is recommended.

The other major concern with succinylcholine is the occurrence of lethal hyperkalemia in patients with certain underlying disorders or co-morbid diseases (table 3).[17] The reader is referred to reference 17 for a full discussion of the hyperkalemic response following succinylcholine. While many of the disorders listed in table 3 are readily apparent such as the muscular dystrophies, the occurrence of cardiac arrest following succinylcholine administration to apparently healthy children has led to a restructuring of the recommendations for the use of succinylcholine. The problem is that some children with muscular dystrophy may not manifest symptoms until they are 4-6 years of age. If succinylcholine is administered to these children during perioperative care or other clinical scenarios, lethal hyperkalemia can occur. Because of such problems, the current recommendations are that succinylcholine should only be used for emergency airway management when rapid endotracheal intubation is necessary, when there is a concern about the ability to provide endotracheal intubation (potentially or documented difficult airway), or when intramuscular administration is needed because an appropriate intravenous access cannot be

secured. Also of concern in the pediatric population are patients with relatively rare genetic, chromosolmal or metabolic defects in whom the effects of succinylcholine have not been evaluated. In such settings, the risk:benefit ratio of succinylcholine must be fully examined. In many of these patients, the use of a rapidly acting, non-depolarizing agent may be the best option. However, succinylcholine is generally an acceptable option in patients with cerebral palsy and related problems. Regardless of the clinical scenario, if problems occur following the administration of succinylcholine, hyperkalemia should be suspected and the resuscitation tailored to treat it.

In emergency situations when intravenous access cannot be readily obtained, succinylcholine can be administered intramuscularly in a dose of 4-5 mg/kg. Intramuscular administration will result in neuromuscular blockade sufficient to allow for endotracheal intubation in 2-3 minutes and will rapidly (less than 30 seconds) treat laryngospasm occurring during anesthetic induction when intravenous access is not available thereby allowing for effective bag-valve-mask ventilation. In this scenario, it is generally recommended that succinylcholine be administered into the deltoid muscle as the onset times are more rapid than with administration into the quadriceps. Alternatively, administration into the tongue or the submental space has been suggested as blood flow to this area is generally well maintained even when peripheral vasoconstriction has occurred. Unlike intravenous administration, there is limited risk of bradycardia with IM administration.[18] However, the IM route is not recommended in patients with conditions that decrease cardiac output or blood flow to the muscles such as shock or bradycardia. In the latter situation, the onset of action will be significantly delayed. Given these concerns, IM administration is generally not recommended in critically ill children and intraosseous

administration (1-2 mg/kg) should be considered when IV access is not available.[19]

Currently, the package insert and good clinical practice allows for the administration of succinylcholine when there may be a potentially difficult airway, in the emergency situation when rapid securing of the airway is necessary (full stomach when a rapid sequence intubation is performed), and when there is no intravenous access (IM administration), provided that there is no contraindication to its use (table 3 and reference 17). When dealing with the potentially difficult airway or unrecognized difficult airway, the major advantage of succinylcholine is that there should be return of normal neuromuscular function within 10 minutes as opposed to 60 minutes following a 1 mg/kg intubating dose of rocuronium (see below). Clinically used dosing for recommendations for succinylcholine vary from 1-2 mg/kg.[20] Larger doses are likely not to improve intubating conditions while slightly prolonging the duration of action.

Neuromuscular blocking agents: Non-depolarizing agents

The non-depolarizing NMBA's act as competitive antagonists at the neuromuscular junction, blocking the effects of acetylcholine at the receptor. Unlike succinylcholine, these agents do not activate the acetylcholine receptor and therefore do not result in fasciculations and the associated problems which may occur. Non-depolarizing NMBA's are used most commonly intraoperatively to facilitate endotracheal intubation and also to provide ongoing muscle relaxation for specific surgical procedures such as exploratory laparotomy. When used to provide ongoing neuromuscular blockade in the operating room or the intensive care unit, these agents can be administered by intermittent bolus dosing or continuous infusions. There are two basic chemical structures of the non-depolarizing NMBA's available for clinical use: aminosteroid and

benzylisoquinolinium compounds (table 4). The difference in their chemical structure has limited clinical significance. Of more importance are differences regarding: onset, duration of action, cardiovascular effects, metabolism, metabolic products, and cost. These principles will be reviewed in the remainder of this chapter.

The first non-depolarizing NMBA's (curare, gallamine, metocurine), which were introduced into clinical practice in the 1940's, are rarely if ever used in today's clinical practice. The past 20 years has seen a rapid growth in the development and introduction of non-depolarizing NMBA's for clinical use. As these agents have more favorable profiles (onset times, recovery times, metabolic fate), they have displaced the original group introduced in the 1940's. However, with the introduction of new agents comes the potential for unrecognized morbidity and even mortality related to adverse physiologic effects. This potential is highlighted by the introduction and subsequent withdrawal of one agent, rapacuronium (see below). With the heightened awareness of and the potential for problems with succinylcholine, the search continues for a non-depolarizing NMBA with a similar onset and offset of action.

PANCURONIUM: Pancuronium is an aminosteroid compound. It is generally available in a solution containing 1 mg/mL of pancuronium although, depending on the manufacturer, other concentrations are available. The common clinically used dose of 0.1-0.15 mg/kg provide adequate conditions for endotracheal intubation in approximately 90-120 seconds. Although the higher end of the dosing range may speed the onset time for acceptable conditions for endotracheal intubation, the clinical duration is prolonged from 40-60 minutes to 70-80 minutes. Given its duration of action, pancuronium is considered a long-acting NMBA (table 5). The ED_{95} in children is 52 µg/kg during halothane anesthesia and 81-93 µg/kg during a opioid-based anesthesia. The latter

being more applicable to the PICU setting.[21] Further study has shown that the ED_{95} in children is slightly higher than that of adolescents (77 µg/kg).[22] Following a dose of 70 µg/kg, the onset of neuromuscular blockade occurs more quickly in children when compared to adults with 90% twitch ablation occurring at an average of 2.4 minutes in children and 4.3 minutes in adults.[23] The time to return of the twitch height to 10% of baseline was 25 minutes in children and 46 minutes in adults.

Vagal blockade and release of norepinephrine from adrenergic nerve endings results in an increase in heart rate and blood pressure. Intraoperatively, this effect can be used to balance the negative chronotropic effects of certain anesthetic agents such as fentanyl and halothane. However, there may be a slight pro-arrhythmogenic effect for atrial tachycarrhythmias in patients with co-morbid diseases or when used when other agents that increase heart rate. Elimination is primarily renal (80%), resulting in a significantly prolonged effect with renal insufficiency or failure. Hepatic metabolism is primarily hydroxylation with production of an active 3-OH metabolite which retains approximately half of the neuromuscular blocking effects of the parent compound. The 3-OH metabolite is also dependent on renal excretion thereby further prolonging the effect in the setting of renal insufficiency or failure.

Given its longer half-live, pancuromium is generally used by intermittent dosing to provide ongoing neuromuscular in the PICU setting. One prospective study has evaluated dosing requirements in the PICU population.[24] The study cohort included 25 patients, ranging in age from 3 months to 17 years and in weight from 3.2 to 68 kilograms. Pancuronium was administered as an initial bolus dose of 0.1 mg/kg followed by an infusion starting at 0.05 mg/kg/hr. The infusion was titrated up and down to maintain one to two twitches of the TOF(see below). Pancuronium

infusion requirements varied from 0.3 to 0.22 mg/kg/hr with an average infusion rate of 0.07 ± 0.03 mg/kg/hr for the 1,798 hours of the infusion. Approximately 70% of the time, the infusion requirements were within the range of 0.05 to 0.08 mg/kg/hr. Seven patients were receiving anticonvulsant agents including pentobarbital, carbamazepine, felbamate, valproic acid, phenytoin, and phenobarbital. Increased infusion requirements were noted in these patients (0.14 ± 0.06 versus 0.056 ± 0.03 mg/kg/hr) and in patients that received pancuronium for more than 5 days. The requirements on day 1 were 0.059 mg/kg/hr versus 0.083 mg/kg/hr on day 5. Upon discontinuation of the infusion, time to spontaneous recovery of neuromuscular function (return of the TOF to baseline and sustained tetanus to 50 Hz) varied from 35 to 75 minutes. No adverse effects directly related to pancuronium were noted. The authors concluded that pancuronium could be effectively administered by continuous infusion to provide neuromuscular blockade in the PICU setting and that it provided a cost-effective alternative to other available agents.

VECURONIUM: Like pancuronium, vecuronium is an aminosteroid compound. It was released for clinical use in the 1980's. Despite minor differences in pharmacologic structure from pancuronium, its plasma clearance is 2-3 times as rapid. Vecuronium is available as a powder (10 mg) which in common clinical practice is diluted to a concentration of 1 mg/mL. Given the added step of mixing the solution and thereby introducing another step during which a mistake may occur, some practitioners have voiced preference for other agents which are premixed.

In the usual clinically used doses of 0.1-0.15 mg/kg, acceptable intubating conditions are provided in 90 seconds with a clinical duration of action of 30-40 minutes, making it an intermediate-acting agent.[25] Increasing the dose to 0.3 mg/kg speeds the onset time for acceptable conditions for endotracheal intubation to 60-75 seconds, but also prolongs the duration of

neuromuscular blockade to 60-90 minutes. Even with higher doses, vecuronium is devoid of cardiovascular effects. Metabolism is primarily hepatic (70-80%); however, hepatic metabolism results in the production of pharmacologically active metabolites which are water soluble and therefore dependent on renal excretion. These metabolites possess roughly half of the neuromuscular blocking effects of the parent compound. This combined with the 20-30% renal excretion of the parent compound results in a prolonged clinical duration in patients with renal insufficiency. Given its 70-80% dependency on hepatic metabolism, the duration of action is also prolonged with hepatic insufficiency. Additionally, due to immaturity of the hepatic microsomal enzymes, a prolonged duration can also be expected in neonates. Vecuronium in doses of 0.1 and 0.15 mg/kg maintained neuromuscular blockade at ≥ 90% of baseline for 59 and 110 minutes in neonates and infants, 18 and 38 minutes in children, and 37 and 68 minutes respectively in adolescents.[26] The opposite effect occurs with the chronic administration of anticonvulsant agents with resistance to the neuromuscular blocking effects and increased dose requirements in patients receiving phenytoin.[27] A similar effect has been reported with other anticonvulsant agents and NMBA's of the aminosteroid group. Given its lack of hemodynamic effects and current availability in generic form thereby providing a cost effective agent for neuromuscular blockade, veucronium remains a commonly used agent when administered by continuous infusion for ongoing neuromuscular blockade in the Pediatric ICU setting.

ROCURONIUM: Rocuronium is one of newer aminosteroid NMBA's having been released for clinical use in the early to mid 1990's. It is available in a solution containing 10 mg/mL of rocuronium in 5 or 10 mL vials. Following the commonly used dose for endotracheal intubation of 0.6 mg/kg, the duration of action is 20 to 40 minutes making it an intermediate acting agent;

however, larger doses (1-1.2 mg/kg) are frequently used during rapid sequence intubation as the onset time with these doses has been shown to approximately parallel those of succinylcholine (see below). As with other agents, the duration of action increases when larger doses are administered so that 60-90 minutes of neuromuscular blockade occurs following a dose of 1.0 mg/kg. A mild vagolytic effect, less in intensity than that seen with pancuronium, may increase heart rate in the range of 10-20 beats per minute and mean arterial pressure following bolus dosing.

Rocuronium undergoes primarily hepatic metabolism without the production of active metabolites. Its clinical duration is prolonged and its clearance decreased in patients with hepatic insufficiency or failure. Despite its primary dependence on hepatic elimination, there are mixed results in both adults and children regarding the duration of its effects in patients with renal insufficiency or failure. When comparing adults with and without renal failure, Robertson et al. reported that there was prolongation of the clinical duration (time to recovery of the first twitch of the TOF to 25% of baseline) from 32 to 49 minutes following a dose of 0.6 mg/kg in patients with renal failure.[28] The same investigators reported no difference in the pharmacodynamics in adults with and without renal failure with the use of a smaller dose (0.3 mg/kg).[29] With the smaller dose of 0.3 mg/kg, the onset time was 4 minutes and neuromuscular blockade was reversible at 20 minutes. When comparing adults with renal failure and those with normal renal function, Cooper et al. reported that following rocuronium (0.6 mg/kg), onset time (65 ± 16 versus 61 ± 25 seconds), clinical duration (55 ± 26.9 versus 42 ± 9.3 minutes), and spontaneous recovery (time for return of the final twitch of the TOF to 70% of baseline) were all prolonged (99 ± 41 versus 73 ± 24 minutes).[30] Following an initial dose of 0.3 mg/kg, pediatric patients with renal failure had a longer onset time (139 ± 71 versus 87 ± 43 seconds); however, there was no difference in the clinical

duration.[31]   More specific pharmacokinetic data and an explanation for the apparent prolonged elimination half-life of rocuronium in renal failure patients are provided by Szenohradszky et al. in their evaluation of rocuronium in cohort of 10 adult patients undergoing renal transplantation.[32] Following a dose of 0.6 mg/kg, although the total plasma clearance and the volume of the central compartment did not differ between renal failure and control patients, the volume of distribution at steady state was larger in patients with renal failure and this resulted in a longer elimination half-life with renal failure (97.2 ± 17.3 versus 70.9 ± 4.7 minutes).   A summary of these studies demonstrate a slightly prolonged onset time with rocuronium and a prolonged elimination half-life (and therefore a prolonged clinical effect) in the presence of renal failure. The current data suggest that these findings result from alterations in the volume of distribution rather than primary alterations in clearance due to renal effects.   The prolonged duration of action may be clinically significant with doses ≥ 0.6 mg/kg and can be minimized with doses of 0.3 mg/kg.   However, with the smaller doses, onset times for successful endotracheal intubation will be prolonged to 2-3 minutes.

Given its dependence on hepatic metabolism, alterations in clearance are likely not only in patients with primary hepatic diseases, but also in neonates and infants due to the immaturity of the hepatic microsomal enzymes. When comparing infants (0.1-0.8 years) and children (2.3-8 years), plasma clearance is decreased (4.2 ± 0.7 versus 6.7 ± 1.1 mL/kg/min), the volume of distribution is increased (231 ± 32 versus 165 ± 44 mL/kg), and the mean residence time is increased (56 ± 10 versus 26 ± 9 minutes).[33]   Also of note, the plasma concentration required to exert a 50% neuromuscular blocking effect is decreased in neonates and infants compared to older children (1.2 ± 0.4 versus 1.7 ± 0.4 mg/mL). The latter effect, which indicates that the neuromuscular junction

of neonates and infants is more sensitive to the effects of NMBA's, is not specific for rocuronium and is seen with all NMBA's. Similar results were reported by Rapp et al as they reported progressive increases in the clinical duration with a decrease from 5-12 months to 2-4 months to 0-1 months of age.[34] The effect was further magnified when increasing the dose from 0.45 to 0.6 mg/kg. The authors also reported excellent or good intubating conditions in all infants with doses of 0.45 mg/kg and ablation of the twitch response at 15-30 seconds in neonates thereby demonstrating a rapid onset even with the use of lower doses (0.45 mg/kg). As with other medications that undergo primary hepatic metabolism, the clinical effects of rocuronium are prolonged in neonates and infants. Metabolism and clinical effects approach those of the adult population by 6-12 months of age. In the neonate or younger infant, acceptable conditions for endotracheal intubation can be achieved at 45-60 seconds with doses of 0.3-0.45 mg/kg.

Rocuronium's welcome in the clinical arena has been expedited by its majority clinical advantage over other non-depolarizing NMBA's, a rapid onset. Clinical studies have demonstrated acceptable conditions for endotracheal intubation in the majority of older children and adolescents within 60 seconds following a dose of 1.0 mg/kg. Of the currently available non-depolarizing NMBAs, only rocuronium has an onset of action which approaches that of succinylcholine. The remainder of the NMBAs require 90-120 seconds to provide conditions acceptable for endotracheal intubation even when larger doses are used. In both the pediatric and adult populations, various studies have demonstrated that rocuronium in a dose of 1 mg/kg provides acceptable intubating conditions within 60 seconds in the majority of patients.[35-37] Mazurek et al. prospectively compared the onset times of rocuronium (1.2 mg/kg) and succinylcholine (1.5 mg/kg) in a cohort of 26 children.[36] Anesthesia was induced with thiopental (5 mg/kg). Endotracheal intubation

attempts were started 30 seconds after the administration of the agent. Time to endotracheal intubation was comparable between the two groups being 41.8 ± 2.9 seconds (range: 36-45 seconds) with succinylcholine and 40.2 ± 4.0 seconds (range: 33-48 seconds) with rocuronium. However, the conditions for endotracheal intubation were slightly less favorable with rocuronium as 7 were excellent, 5 good, and 1 fair versus 10 excellent, 2 good, and 1 fair with succinylcholine. Schreibner et al. compared conditions for endotracheal intubation provided by 3 of the commonly used NMBA's (rocuronium 0.6 mg/kg, vecuronium 0.1 mg/kg, and atracurium 0.5 mg/kg).[37] Endotracheal intubation was attempted every 30 seconds. Conditions for all of the endotracheal intubations were graded as excellent or good, 60 seconds after rocuronium, 120 seconds after vecuronium, and 180 seconds after atracurium. Although a larger dose of rocuronium speeds the onset time to acceptable conditions for endotracheal intubation, there is also a prolonged duration of action (60-80 minutes) unlike that of succinylcholine (5-10 minutes). The longer duration of action may be problematic should difficulties arise with the performance of endotracheal intubation resulting in a "cannot intubate/cannot ventilate" scenario. Additionally, in patients with traumatic brain injury or other conditions resulting in alteration of mental status, the neurologic examination will be lost for 60-80 minutes following rocuronium in doses of 1 mg/kg. Despite these issues, because of its rapid onset, rocuronium remains the drug of choice for rapid sequence intubation when there are concerns regarding the use of succinylcholine (see above).

Various investigators have evaluated potential techniques to increase the onset of rocuronium without the need to increase the dose. Although there was no difference noted in the time to 50% blockade (42 ± 14 versus 45 ± 10 seconds) or onset time when comparing rocuronium 0.6 mg/kg administered with either ketamine 1.5 mg/kg or thiopental 4 mg/kg in parturients,

tracheal intubation at 50% blockade was easily performed in all patients in the ketamine group while it was difficult in 75% of patients who received thiopental.[38] Munoz et al. demonstrated a significant decrease in the onset time of rocuronium (0.6 mg/kg) in patients who received ephedrine (70 μg/kg), 30 seconds prior to the start of rapid-sequence induction compared to patients receiving placebo (72 ± 19 versus 98 ± 31 seconds).[39] Ephedrine indirectly increases cardiac output through the release of endogenous catecholamines. The increase in cardiac output increases blood flow and therefore drug delivery to the skeletal muscle thereby accelerating the onset time.

As with other NMBA's such as vecuronium, priming may accelerate the onset times of rocuronium.[40] In a cohort of 84 children randomized into one of 4 groups: saline-rocuronium 0.45 mg/kg, rocuronium 0.045 mg/kg-rocuronium 0.405 mg/kg, saline, rocuronium 0.6 mg/kg or rocuronium 0.06-rocuronium 0.054 mg/kg, the median onset times and 95% confidence in the 4 groups were 122.5 (8-186), 92.5 68-116), 85 (60-142), and 55 (48-72) seconds respectively thereby demonstrating a clinical advantage of priming regardless of whether the total dose was 0.45 or 0.6 mg/kg. However, as noted previously, there may be issues with priming including the potential to induce upper airway or respiratory muscle weakness with the potential for aspiration, airway obstruction or hypoventilation especially in critically ill patients even with the small priming dose as well as the need to wait 60 seconds for the full effect of the priming dose.

Given its rapid onset and lack of adverse effects, most notably rhabdomyolysis and hyperkalemia with underlying neuromuscular disorders, the use of rocuronium via the IM route instead of succinylcholine in the treatment of emergencies such as laryngospasm during anesthetic induction when IV access is lacking would be clinically applicable. However, when evaluating

onset and recovery times following IM rocuronium, adequate or good-excellent intubating conditions took an average of 2.5 minutes in infants following a dose of 1 mg/kg and 3 minutes in children following a dose of 1.8 mg/kg.[41] The clinical duration was 57 ± 13 minutes in infants and 70 ± 23 minutes in children. The authors also demonstrated a more rapid and predictable onset with IM administration into the deltoid as compared to the quadriceps muscle, an effect similar to that noted with succinylcholine (see above). Given these onset times, the authors cautioned that IM rocuronium was not an alternative to IM succinylcholine for the emergent treatment of laryngospasm.

An additional issue with rocuronium in clinical practice includes pain on injection through a peripheral IV cannula.[42] Although the issue may be of limited significance in the Pediatric ICU setting given the clinical scenarios in which this agent is administered, pretreatment (defasciculation etc) is occasionally used when rocuronium is administered. Additionally, the practitioner should be aware of this problem as even when rocuronium is administered immediately after the induction agent for endotracheal intubation, limb withdrawal and grimacing may be seen. The incidence of pain on injection with rocuronium has been reported to be as high as 50-80% with a higher incidence in women that men. As with propofol, various techniques have been suggested to prevent or lessen this problem including diluting the rocuronium solution to 0.5 mg/mL instead of the commercially available 10 mg/mL or the pre or co-administration of various pharmacologic agents including lidocaine, ketamine, dexmedetomidine, thiopental, magnesium, alfentanil, and ondansetron. All of these have met with varying degrees of success. When rocuronium is co-administered with thiopental into the same IV site, a precipitate may form and occlude the IV cannula or tubing. This problem can be prevented by thoroughly flushing the IV site between the

thiopental and the rocuronium. As with the other aminosteroid NMBA's, chronic anticonvulsant therapy causes resistance to the neuromuscular blocking effects of rocuronium.[43]

Although used most commonly by bolus injection for rapid-sequence endotracheal intubation, there has been one publication addressing the use of rocuronium infusions in the PICU setting.[44] In a cohort of 20 PICU patients, rocuronium was administered by continuous infusion to maintain 1-2 twitches of the TOF. The duration of the rocuronium infusion varied from 26 to 172 hours with a total of 1492 hours of administration. Following the initial bolus dose of 0.6 mg/kg, there was an increase in heart rate of 24 beats/minute and a modest increase in blood pressure (maximum increase in systolic blood pressure of 24 mmHg). The infusion requirements on day 1 varied from 0.3 to 0.8 mg/kg/hr (0.76 ± 0.3 mg/kg/hr). When evaluating all patient days, the infusion requirements varied from 0.3 to 2.2 mg/kg/hr (0.95 ± 0.4 mg/kg/hr). The infusion requirements were 0.5 to 0.8 mg/kg/hr in 45 of the 64 patient days (70%) and 0.3 to 1.0 mg/kg/hr in 58 of the 64 patient days (90%). As with other agents, there was an increase in infusion requirements over time. In 14 patients who received rocuronium for 3 days or more, infusion requirements increased from 0.65 mg/kg/hr on day 1 to 0.84 mg/kg/hr on day 3 and in 5 patients that received rocuronium for 5 days, the infusion requirements increased from 0.67 mg/kg/hr on day 1 to 1.2 mg/kg/hr on day 5. When the infusion was discontinued, spontaneous return of neuromuscular function occurred in 24 to 44 minutes (31 ± 12 minutes). No adverse effects related to the use of rocuronium were noted.

PIPECURONIUM: Pipecuronium is structurally related the other aminosteroids including pancuronium and vecuronium. Like vecuronium, it is devoid of cardiovascular effects. Following the clinically recommended dose for endotracheal intubation of 0.07 mg/kg, onset times vary from

2 to 3 minutes with a longer duration of action (70 to 80 minutes) than pancuronium. Pipecuronium is eliminated primarily by the kidneys (80%) with the remainder of the elimination dependent on hepatic metabolism. Unlike the other previously mentioned aminosteroid NMBAs, there is little enthusiasm for or clinical information concerning the use of pipecuronium in the pediatric population.

RAPACURONIUM: As mentioned previously, there remains a clinical need for a non-depolarizing NMBA whose onset and offset parallel that of rocuronium. In an effort to meet this need, rapacuronium was introduced into the clinical arena in 1998. The initial clinical experience demonstrated a rapid onset, paralleling that of succinylcholine or larger doses of rocuronium, with a recovery time of less than 10 minutes thereby offering a significant clinical advantage over rocuronium. Hemodynamic effects included a mild tachycardia like other aminosteroid NMBA's related to a vagolytic effect. Metabolism was hepatic with the presence of active metabolites that were dependent on renal excretion although did not appear to result in a clinically significant duration of action in the presence of renal failure or insufficiency.

Unfortunately, with increased clinical use came the recognition that profound and even potentially fatal bronchospasm were associated with its administration. Although initially postulated to be the result of an inadequate depth of anesthesia, subsequent studies suggested a direct effect on the cholinergic receptors of the airway. In a retrospective review of their clinical data base, Rajchert et al. reported that bronchospasm occurred in 12 of 287 (4.2%) of patients receiving rapacuronium.[45] Five of the episodes with rapacuronium resulted in an inability to move the chest with no exhaled end-tidal CO_2 following endotracheal intubation. The risk of bronchospasm was 10.1 times greater with rapacuronium compared to other NMBA's. Additional

clinical data demonstrating the potential for alterations in respiratory compliance and resistance were reported in a prospective trial in 20 adults randomized to receive either cis-atracurium or rapacuronium.[46] Rapacuronium was administered following endotracheal intubation and the provision of general anesthesia by the continuous infusion of propofol and remifentanil. No changes in compliance or resistance of the respiratory system were noted with cis-atracurium; however following rapacuronium administration, peak inflating pressure increased from 22 ± 6 to 28 ± 9 cmH$_2$0, compliance decreased from 108 ± 43 to 77 ± 41 mL/cmH$_2$0, peak inspiratory flow rate decreased from 0.43 ± 0.11 to 0.39 ± 0.09 liters per second, peak expiratory flow rate decreased from 0.67 ± 0.10 to 0.59 ± 0.09 liters per second, and tidal volume decreased from 744 ± 152 to 647 ± 135 mL. Mechanisms for rapacuronium's effects on airways have focused on alterations in cholinergic function with antagonism of the M$_2$ muscarinic receptor, augmentation of acetylcholine effects at the M$_3$ muscarinic receptor, and potentiation of vagal nerve and acetylcholine induced bronchoconstriction.[47-49] The M$_2$ muscarinic mechanism may be of particular interest as various NMBA's have been shown to have differing degrees of activity at this receptor. These effects have been reported with pipecuronium, but not with rocurnium.[50] During normal function at the neuromuscular junction of smooth muscle including the airway, some of the acetycholine that is released diffuses back to the pre-junctional (M$_2$) receptor and shuts off ongoing acetycholine release. Thus the M$_2$ receptor is a negative feedback receptor which regulates acetycholine release. With blockade of the M$_2$ receptor, there may be exaggerated release of acetycholine and hence exaggerated muscle contraction or bronchospasm. Although rapacuronium was removed from the market in 2001, there may be other NMBA in the clinical development process and their potential activity at the M$_2$ receptor warrants investigation.

   MIVACURIUM: Although it has currently disappeared from the US market, mivacurium may still be available outside of the United States. Mivacurium is a benzylisoquinolinium NMBA which is the shortest acting of the non-depolarizing NMBA's. It is available in a premixed solution containing 2 mg/mL of mivacurium. Following a dose of 0.2 mg/kg, onset times vary from 2-3 minutes with a duration of action of approximately 10 minutes. In a cohort of 62 children anesthetized with nitrous oxide and fentanyl, mivacurium infusion rates to maintain neuromuscular blockade were 375 ± 19 µg/m^2/min with a spontaneous recovery time ($T_4/T_1 \geq 0.75$) of 9.8 ± 0.4 minutes.[51] There was no evidence of accumulation during prolonged infusions. Mivacurium is metabolized by plasma cholinesterases. Prolonged blockade can occur in the same clinical situations described with succinylcholine (see above) including congenital and acquired deficiencies of this enzyme system.[52,53] The metabolites of mivacurium, which are renally excreted, have limited neuromuscular blocking properties. Like all of the benzylisoquinoliniums, mivacurium can produce histamine release. In children, the histamine release may be associated with flushing and erythema of the skin; however, the hemodynamic effects are generally of limited clinical significance.[54]

   Mivacurium's role in clinical practice has been when neuromuscular blockade is required for brief procedures (less than 10 minutes) either in the operating room or in the PICU. Mivacurium can be a useful agent to provide a brief duration of neuromuscular blockade for direct laryngoscopy in the PICU patient to follow the progression of epiglottitis or some other airway problem and then provide spontaneous return of neuromuscular function without the use of reversal agents. In the intraoperative setting, the avoidance of the need to reverse residual neuromuscular blockade with neostigmine (see below) may be beneficial as a means of limiting postoperative

nausea and vomiting.

A second potential use for mivacurium has been in combination with other non-depolarizing NMBA to provide a rapid onset of neuromuscular blockade and yet avoid the prolonged duration seen when large doses of vecuronium (0.3 mg/kg) or rocuronium (1-1.2 mg/kg) are administered.[55,56] Onset times to 90% neuromuscular blockade was 39 ± 2.3 seconds with 1 mg/kg succinylcholine and 48 ± 3.5 seconds with vecuronium 0.16 mg/kg and mivacurium 0.2 mg/kg.[55] Conditions for endotracheal intubation were graded as excellent in 10 of 10 patients in both groups. Despite the rapid onset, recovery times were prolonged with the combination of vecuronium and mivacurium. Similar results were reported with a combination of mivacurium 0.2 mg/kg and rocuronium 0.6 mg/kg.[56] Although the onset times paralleled that of succinylcholine, the recovery times (49.0 ± 9.6 minutes) were prolonged.

Mivacurium may also been potentially advantageous in patients with underlying neuromuscular disorders (i.e., muscular dystrophy). In such patients, prolonged neuromuscular blockade may occur even following a single dose of intermediate acting agents such as vecuronium, atracurium or cis-atracurium. Therefore, the use of an agent with the shortest clinical duration may be beneficial.[57-59] When compared with healthy control subjects, although there was no difference noted in the onset times, patients with Duchenne muscular dystrophy demonstrated only a modest prolongation of the clinical effect of mivacurium.[57] The median times for recovery of the first twitch of the TOF to 10%, 25% and 90% of baseline in controls and patients with muscular dystrophy were 8.4 versus 12.0 minutes, 10.5 and 14.1 minutes, and 15.9 and 26.9 minutes. Similar results were demonstrated by Tobias and Atwood in their cohort of 7 children with Duchenne muscular dystrophy. Following a dose of 0.2 mg/kg, time to recovery of the first

twitch varied from 12 to 18 minutes. They also noted significant interpatient variability with infusion requirements varying from 3 to 20 μg/kg/min. Five of the 7 patients required ≤ 10 μg/kg/min further demonstrating increased sensitivity to this agent in patients with muscular dystrophy. Of note, there was no correlation with infusion requirements and the patient's preoperative motor function.

ATRACURIUM: Atracurium is a non-depolarizing NMBA of the benzylisoquinolinium class, which was released for clinical use in the 1980's. It is supplied in a 10 mg/mL solution. Following a dose of 0.6 mg/kg, acceptable conditions for endotracheal intubation are achieved in 2-3 minutes with complete twitch suppression for 15-20 minutes followed by another 10-15 minutes with a variable degree of blockade (twitch height 5-25%). Spontaneous recovery ($T_4/T_1 \geq 0.7$) occurs in 40-60 minutes. As with all of the NMBA's, the use of a smaller dose (0.3-0.4 mg/kg) is feasible, but will prolong the time to the onset of acceptable conditions for endotracheal intubation as well shortening the recovery time. Atracurium's recovery profile makes it an intermediate acting agent. When compared with vecuronium, approximately 5 times as much atracurium is required to provide the same degree of neuromuscular blockade. As with other NMBA's of the benzylisoquinolinium class, atracurium can lead to histamine release. Although facial, cutaneous flushing, and erythema may occur as with mivacurium, effects on heart rate and blood pressure are generally minimal following doses up to 0.6 mg/kg.[60] With larger doses, hypotension may occur. In the pediatric-aged patient, histamine release is less frequent and less profound than in adults and even when histamine release occurred, no hemodynamic changes were noted.[61] Following its introduction into clinical practice, ongoing safety surveillance demonstrated no difference in the adverse effect profile of atracurium related to histamine release when compared with other

NMBA's.[62] Extremely rare, anecdotal case reports exist regarding anaphylactoid reactions with severe bronchospasm temporally related to its administration; however, a true causal relationship cannot be proven as the patients also received thiopental during anesthetic induction.[63]

Atracurium undergoes spontaneous degradation via a process known as Hofmann elimination as well as ester hydrolysis. Therefore, its duration of action is unchanged by either renal or hepatic insufficiency. Because of these properties, it rapidly gained favor for providing neuromuscular blockade in intensive care unit patients. For this purpose, it is most commonly used by continuous infusion (see below). The metabolites of atracurium do not possess significant neuromuscular blocking properties. However, one of the metabolic byproducts of Hofmann degradation, laudanosine, has been shown to be epileptogenic in animals. The actual concentrations required to cause seizures in humans is unknown and no formal study has ever documented problems from high laudanosine levels. Laudanosine is renally excreted and its accumulation in patients with renal insufficiency is at least a theoretical concern.

Infusion requirements to maintain clinical neuromuscular blockade, defined as a single twitch height of 1-10% of baseline, averaged 9 µg/kg/min during a nitrous oxide-opioid based anesthetic.[64] Recovery remains predictable and stable regardless of the duration of the infusion. Within 30 minutes of discontinuation of the infusion, twitch height had spontaneously recovered to $T_4/T_1 \geq 0.7$.[65] Reversal with neostigmine (see below) is generally available within 10-15 minutes of discontinuing an infusion or following the administration of a single dose of 0.6 mg/kg. When compared to a longer acting agent such as pancuronium, spontaneous recovery following a continuous infusion occurred at an average time of 15 minutes (range 6 to 34 minutes) with atracurium compared to 25 minutes (10.5 to 37 minutes) with pancuronium.[66] Given its

intermediate duration of action and stable recovery profile , atracurium has been used safely and effectively in patients with neuromuscular disorders including myasthenia gravis, myotonic dystrophy, and muscular dystrophy[67,68]; however, prolonged neuromuscular blockade of 3-4 hours has also been reported following a single dose of 0.6 mg/kg. In the PICU, similar recovery profiles have been reported. In a cohort of 20 infants and children requiring neuromuscular blockade for 10 to 163 hours during mechanical ventilation, the mean dose of atracurium was 1.4 mg/kg/hr (range: 0.44 to 2.4 mg/kg/hr).[69] When there was no TOF which could be elicited, the time required for the first twitch to become evident with discontinuation of the infusion was 13.8 minutes (range: 1 to 38 minutes). The authors reported that there was no correlation between the recovery time and the dose that was being administered; however, they did note a faster recovery time when the infusion had been administered for more than 48 hours. Given its non-organ dependent elimination, atracurium has also been used in pediatric patients following orthotopic liver transplantation.[70] Recovery time ($T_4/T_1 \geq 0.7$) when the infusion was discontinued averaged 23.6 minutes (range: 12 to 27 minutes) and was not prolonged compared to the general pediatric population.

As with rocuronium, administration with thiopental may result in precipitation and occlusion of the intravenous cannula necessitating flushing the line with normal saline between these two agents. Given its dependence on Hofmann elimination, a temperature dependent process, elimination will be prolonged during induced or inadvertent hypothermia.[71] During induced hypothermia ($32^{o}C$) in a cohort of children, atracurium infusion requirements were 784 µg/kg/hour or 56% of that in normothermic children (1411 µg/kg/hour). Recovery times were also prolonged to 2.86 times that seen in normothermic patients. A similar effect has been reported with the use of cis-atracurium during hypothermia (see below).

CIS-ATRACURIUM: Cis-atracurium is one of the 10 stereoisomers that comprise atracurium. It is 6-8 times as potent as atracurium, but devoid of clinically significant histamine release and hemodynamic effects.[72] Cis-atracurium is available as a 2 mg/mL solution. Like atracurium, cis-atracurium is an intermediate acting neuromuscular blocking agent with a duration of action of 20-30 minutes following a bolus dose of 0.2 mg/kg. Acceptable conditions for endotracheal intubation are provided in approximately 2 minutes. In a cohort of 80 adult patients, cis-atracurium in doses of 0.1, 0.15, and 0.2 mg/kg provided acceptable conditions for endotracheal intubation in 4.6, 3.4, and 2.8 minutes with a clinically effective duration of 45, 55, and 61 minutes.[73] In a cohort of 27 infants (1-23 months of age) and 24 children (2-12.5 years of age), the onset time to achieve maximal blockade following a dose of 0.15 mg/kg was more rapid in infants (2.0 ± 0.8 versus 3.0 ± 1.2 minutes, p=0.0011).[72] The clinical duration (recovery to 25% of baseline) was longer in infants (43.3 ± 6.2 versus 36.0 ± 5.4 minutes, p<0.0001). Once neuromuscular started to recovery, the rate of recovery was similar between the two groups. However, de Ruiter et al. reported no difference in the ED_{50}, ED_{95} or the infusion rate required to maintain 90-99% block when comparing 32 infants (0.3-1 year of age) and 32 children (3.1-9.6 years of age).[74] The ED_{50} in the two groups was 29 ± 3 versus 29 ± 2 µg/kg, the ED95 was 43 ± 9 versus 47 ± 7 µg/kg, and the infusion rate required to maintain 90-99% blockade in the two groups was 1.9 ± 4 versus 2.0 ± 0.5 µg/kg/min.

A prospective study evaluated cis-atracurium dosing requirements in 15 PICU patients ranging in age from 10 months to 11 years and in weight from 4 to 28 kgs.[75] The cis-atracurium infusion was adjusted to maintain one twitch of the TOF. Infusion requirements varied from 2.1 to 3.8 µg/kg/min (average of 3.1 ± 0.6 µg/kg/min) on day 1, from 2.9 to 8.1 µg/kg/min (average of 4.5 ± 1.6 µg/kg/min, p<0.01 compared to day 1) on day 3, and from 1.4 to 22.7 µg/kg/min during all

patient days. The highest infusion requirements were noted following the administration of the drug for prolonged periods of time (150 and 224 hours). When the infusion was discontinued, spontaneous return of neuromuscular function was noted in 14 to 33 minutes. Effective neuromuscular blockade was provided and no adverse effects related to cis-atracurium were noted. In particular, no hemodynamic changes were noted with bolus dosing. Odetola et al. evaluated the dosing requirements of cis-atracurium in a cohort of 11 PICU patients, ranging in age from 0 to 2 years.[76] The duration of the infusions varied from 14 to 122 hours (64.5 ± 36 hours). The infusion requirements to maintain 90-95% neuromuscular blockade were 5.36 ± 3.0 µg/kg/min. Laudanosine concentrations during the infusion were 163.3 ± 116 ng/mL. As in the previous study, there was an increase in dose requirements over time and no hemodynamic effects were noted with cis-atracurium.

Reich et al. compared vecuronium and cis-atracurium, administered by continuous infusion, to provide neuromuscular blockade following surgery for congenital heart disease in a cohort of 19 patients, less than 2 years of age.[77] The NMBA was administered to maintain one twitch of the TOF. Median infusion times were 64.5 hours for cis-atracurium and 46 hours for vecuronium (p=NS). Median recovery time, defined as a normal TOF without fade, was shorter with cis-atracurium than with vecuronium (30 minutes versus 180 minutes, p<0.05). Recovery time was more than 4 hours in 3 of 9 patients who received vecuronium. Two of these patients had high vecuronium plasma concentrations while the other had an elevated 3-OH vecuronium level. There was no difference in time to tracheal extubation, intensive care unit stay, or hospital stay.

As with other NMBA's, resistance to the effects of cis-atracurium may be seen in patients treated with anticonvulsant agents.[78] Time to recovery of T_1 to 25% of baseline was 69 ± 13

minutes in patients not receiving anticonvulsant medications, 64 ± 19 minutes in those receiving acute therapy with anticonvulsants, and 59 ± 19 minutes in those receiving chronic anticonvulsant therapy. As with atracurium, altered clearance and decreased infusion requirements occur with hypothermia.[79] During induced hypothermia ($34^{\circ}C$) to control increased ICP, cis-atracurium infusion requirements were 1.7 µg/kg/min and increased to 3.4 µg/kg/min with return to normothermia.

DOXACURIUM: Doxacurium is the benzylisoquinolinium derivative with the longest duration of clinical activity. It is the most potent of the clinically available NMBA's with approximately twice the potency of pancuronium or pipecuronium. Following a dose of 0.05 mg/kg, its duration of action is 80 to 90 minutes. The ED_{95} in children is 30 µg/kg, approximately 1.5 times that reported for the adult population.[80] Elimination is primarily renal with a small percentage dependent on hepatic excretion. The duration of action is prolonged in patients with either hepatic or renal insufficiency. Despite it being a benzylisoquinolinium derivative, it is primarily devoid of histamine releasing properties and cardiovascular or hemodynamic effects. To date, there has been limited use of this agent in the Pediatric ICU population.

Reversal of neuromuscular blockade

Although neuromuscular blockade is necessary for many surgical procedures or used for various indications in the PICU setting, even a small residual amount of blockade may compromise ventilation or upper airway patency in the critically ill patient or during the immediate postoperative period. In the operating room setting, residual neuromuscular blockade is frequently reversed at the completion of the procedure to ensure adequate strength to maintain airway patency

and ventilatory function following extubation of the trachea. In the PICU setting, reversal of neuromuscular blockade is less common. In most clinical scenarios, when there is no longer a need for neuromuscular blockade, the agent is discontinued and spontaneous recovery is allowed. The latter is generally appropriate in the PICU setting, as ongoing tracheal intubation and mechanical ventilation will likely be provided for some period of time following the discontinuation of the NMBA. However, in a smaller percentage of patients, tracheal extubation coincides with discontinuation of the NMBA thereby mandating the use of a reversal agent.[81]

Reversal of neuromuscular blockade is possible only with non-depolarizing NMBA's. Additionally, some degree of residual neuromuscular function is necessary to allow for effective reversal of neuromuscular blockade. In general clinical practice, this means that there should be 1-2 twitches in the TOF or that the T_1 has recovered to 25% of its baseline height. Therefore, reversal with a drug that inhibits acetycholinesterdase is not feasible immediately after the administration of an NMBA. Rather, depending on the dose, some time, generally 15-30 minutes with intermediate acting agents, is necessary.

The drugs used to reverse neuromuscular blockade inhibit the enzyme, acetylcholinesterase. This, in turn, provides more acetylcholine to compete with the NMBA at the nicotinic receptor of the neuromuscular junction. The commonly used acetylcholinesterase inhibitors or "reversal agents" include neostigmine, pyridostigmine, and edrophonium. Despite a similar mechanism of action, the clinical effects (onset, duration, etc.) of these agents differ. Neostigmine and pyridostigmine are hydrolyzed by acetylcholinesterase. During this process, the enzyme is carbamylated and inactivated. Edrophonium does not breakdown the enzyme, acetycholinesterase, rather it competitively and reversibly inhibits its function. The difference in the molecular

mechanism of these agents has little impact on clinical use or practice. With these 3 agents, the peak plasma concentration is achieved at 5-10 minutes following bolus administration followed by an elimination half-life of 60-120 minutes. Clearance is markedly reduced in the setting of renal failure or insufficiency. There is a marked difference in the onset times of the 3 reversal agents. The onset of peak effect is 1-2 minutes with edrophonium, 7-11 minutes with neostigmine, and 16 minutes with pyridostigmine.[82,83] An additional difference is the efficacy of these agents when reversing intense blockade (≥ 90%), in that neostigmine is more effective than either edrophonium or neostigmine.

Adverse effects related to the use of reversal agents generally relates to their inhibition of acetycholinesterase at sites away from the neuromuscular junction. These agents should always be preceded by an anticholinergic agent such as atropine or glycopyrrolate since the inhibition of acetylcholinesterase occurs not only at nicotinic receptors (neuromuscular junction), but also at muscarinic receptors. Therefore, unless preceded by an anticholinergic (anti-muscarinic) agent, bradycardia and asystole can occur. The time course of the bradycardic effects varies based on the onset time of the agents (see above). As such, if edrophonium is used, glycopyrrolate should be administered first and followed in 1-2 minutes by edrophonium given that the onset time of glycopyrrolate is longer than that of edrophonium. The onset time of glycopyrrolate correlates well with that of neostigmine and pyridostigmine and therefore these agents may be administered at the same time. Given that the onset of atropine is rapid, it may be administered with any of the 3 reversal agents. Other adverse effects related to the reversal agents included augmentation of cholinergic function in the gastrointestinal tract (salivation, diarrhea, nausea and vomiting) and the respiratory tract (bronchospasm). Although the anticholinergic agents may block salivation and

alterations in airway tone, their efficacy in blocking the increased gastrointestinal motility are somewhat limited.

More recently, there has been development of a novel agent for reversal of neuromuscular blocking agents. However, this drug has not as of the end of 2009 achieved approval from the United State's Food and Drug Administration. The agent, suggamadex, is a cyclodextrin and instead of inhibiting the enzyme, acetylcholinesterase, it forms a tight 1:1 complex with the steroidal neuromuscular blocking agents. It has been show to rapidly and effectively reverse rocuronium and vecuronium and perhaps even pancuronium.[84,85] There is a limited dissociation rate so that the reversal is maintained. Unlike the use of acetycholinesterase inhibitors, reversal using suggamadex is feasible even with intense blockade thereby providing the potential for the rapid reversal of neuromuscular blockade in the "cannot intubate – cannot ventilate" scenario. Future studies are needed to fully evaluate this medication in the pediatric population.

Monitoring neuromuscular blockade

In the operating room, NMBAs may be used as a single dose at the start of the case to facilitate endotracheal intubation or by repeated doses or a continuous infusion to provide ongoing neuromuscular blockade. Some means of monitoring neuromuscular blockade is necessary since administration of excessive doses may mandate the use of postoperative mechanical ventilation until neuromuscular blockade has worn off or can be reversed. Additionally, given concerns regarding prolonged paralysis, monitoring neuromuscular function may also be considered in the PICU setting.

Monitoring may include some combination of visual, tactile or electronic means of

measuring the residual neuromuscular function following electrical stimulation. The technique, most commonly used by anesthesiologists in the operating room to monitor the degree of neuromuscular blockade, is peripheral nerve stimulation or train-of-four (TOF) monitoring. TOF monitoring involves placement of standard electrocardiographic electrodes over a peripheral nerve. The nerves most commonly used are the facial, ulnar, or common peroneal which result in corresponding movement in the muscles of the hand, face or leg. In some circumstances, direct stimulation of the muscle may occur giving the false impression that an appropriate amount of neuromuscular blockade has not been achieved. To avoid such problems, it may be appropriate, to place the TOF monitor and assess the twitch response prior to the administration of the initial dose of the NMBA. The electrodes of the TOF monitor are connected to a hand held peripheral nerve stimulator which delivers two stimuli per second at 50 mA for two seconds. A total of 4 stimuli are administered over two seconds hence the term train-of-four. As this is painful, it should only be performed in patients that are anesthetized or sedated. Depending on the number of acetylcholine receptors that are occupied by the non-depolarizing NMBA, there will be anywhere from 0 to 4 responses or twitches. Despite the availability of other more sophisticated machines to monitor the degree of neuromuscular blockade in the operating room and ICU setting, these monitors are generally used only for clinical research purposes and in clinical practice in either the operating room or the PICU, TOF monitoring remains the technique that provides the most useful information with limited requirements for training and equipment.

In clinical practice, the TOF monitoring is combined with clinical assessment at the end of the case to ensure that the patient is strong enough for extubation. Following reversal of neuromuscular blockade, clinical assessment of strength is combined with neuromuscular

monitoring. These latter measures become necessary as residual weakness may be present despite apparent reversal using TOF monitoring. Techniques of clinical assessment to evaluate the presence of residual neuromuscular blockade include measurement of negative inspiratory force (NIF) or maximum inspiratory pressure (MIP), hand grip, or head lift. Although head-lift and hand grip require the ability to follow a simple command, the measurement of NIF does not. The technique involves measuring the inspiratory force that the patient can generate against an occluded airway. The test can be completed with a simple manometer attached to the 15 mm adaptor of the ETT. Initial studies suggested that a NIF of at least -20 cmH$_2$O indicated sufficient muscle strength to maintain an adequate minute ventilation.[86] Subsequently, a value of -25 to -30 cmH$_2$O became the generally accepted value for use in clinical practice. However, subsequent work suggested that although strength was adequate to maintain minute ventilation, it may not be adequate to maintain upper airway patency and therefore, the use of voluntary responses (head life for 5 seconds or hand grip) were suggested as adjuncts to ensure adequate reversal of neuromuscular blockade.[81] In infants, reflex leg lift (both legs lifted off of the operating room table) was shown to correlate with a mean NIF or MIP of -51 cmH$_2$O and therefore, the authors concluded that this was a sign of adequate reversal of neuromuscular blockade in infants.[87] Given the variability of these responses and their correlation with reversal of neuromuscular blockade, the best clinical approach may be the use of several clinical maneuvers if TOF monitoring is not available. The literature suggests that the ability to maintain a sustained head life for 5 seconds is the most sensitive clinical tool.[81]

In the ICU setting, given the degree of neuromuscular blockade that is induced, voluntary measures of muscle strength are not adequate and therefore, titration of NMBA's should be guided by the use of TOF monitoring. The technique may allow the use of the lowest possible dose of

agents and theoretically avoid complications such as prolonged blockade (see below). In a prospective randomized trail in 77 adults, TOF monitoring (maintaining one twitch of the TOF) was compared with clinical parameters (patient breathing over the preset ventilator rate) as a means of titrating NMBA's.[88] TOF monitoring resulted in a lower total dose and lower average infusion rate of vecuronium as well as a more rapid recovery once the infusion was discontinued. A subsequent study in adults revealed a decreased incidence of persistent neuromuscular weakness when using TOF monitoring.[89]

Although data are lacking to clearly demonstrate the superiority of TOF monitoring in the PICU setting, its use is suggested as a means of titrating the administration of NMBA agents. Of note, is the significant interpatient variability that has been reported in the PICU setting and the inability to therefore ensure an appropriate dose without some monitoring modality. The choice of the number of twitches to maintain has not been prospectively study. The majority of the clinical evidence suggests that maintaining one twitch of the TOF ensures an adequate degree of neuromuscular blockade while potentially limiting the incidence of persistent neuromuscular weakness. However, the least amount of blockade that can be clinically tolerated is suggested. In some patients, maintaining two twitches may be acceptable especially with the use of an appropriate degree of sedation and analgesia.

No study has evaluated the best nerve (facial, ulnar, common peroneal) to monitor. In clinical practice, any accessible nerve can be used. However, several patient and technical factors may affect the response. As such, whenever feasible, placement of the monitor prior to the institution of neuromuscular blockade is suggested to ensure that a TOF can be obtained prior to the administration of the NMBA. If no response is obtained, the technique should be evaluated by

first evaluating the monitor (faculty monitor, electrodes, or batteries). Is the electrode too far from the nerve (improper placement, edema, obesity)? If these technical problems are ruled out, the infusion can be decreased by 10-15% and the TOF measured again in 2 hours. When two or more twitches are noted, if the patient is stable and a more profound degree of blockade is not required, ongoing observation is suggested. If a deeper level of blockade is required, a bolus equivalent to the hourly infusion rate should be administered and the infusion increased by 10-15%.

Adverse Effects of Neuromuscular Blockade

As with any medication used in the PICU patient with co-morbid diseases, adverse effects may occur with NMBA's. Perhaps the most devastating of these adverse effects is the inability to provide adequate ventilation following the administration of a medication that induces apnea. Therefore, these medications should never be used if there is any suspicion that the airway cannot be controlled. In rare circumstances, endotracheal intubation using direct laryngoscopy may be impossible and in even rarer circumstances, adequate bag-mask ventilation cannot be provided. In such scenarios, death or permanent CNS morbidity will result with the administration of NMBA's. Measures to avoid such problems include an assessment of the airway prior to the administration of these agents and a knowledge of the "cannot intubate – cannot ventilate" algorithm as outlined by the American Society of Anesthesiologists.

Various physical characteristics may suggest that direct laryngoscopy and intubation will be difficult including micrognathia, a short neck, limited neck mobility (flexion/extension), limited mouth opening, a large tongue, and a small mouth. An additional tool is the Mallampati grade

which describes the ability to visualize the tip of uvula and the tonsillar pillars. If there is a suspicion that endotracheal intubation using direct laryngoscopy will not be possible and there is time, other techniques to control the airway are suggested. Some of the more commonly used approaches to the difficult airway in infants and children are outlined in reference 90.[90] More importantly, the techniques needed for the "cannot intubate – cannot ventilate" scenario should be understood and available in any situation in which NMBA's are being administered. Aside from repositioning the patient or using a direct type of laryngoscope, physicians using NMBA's should have a working knowledge of the laryngeal mask airway as it can be used to rescue patients when direct laryngoscopy, endotracheal intubation, and bas-mask ventilation fail.[91]

Other adverse effects from NMBA's relate to the elimination of routine physiologic functions. Eye care with the use of artificial tears or lacrilube at fixed intervals during the administration of NMBA's is necessary to avoid drying of or damage to the cornea. Additionally, repositioning of the patient at frequent intervals is needed to avoid pressure sores. For prolonged immobility, the use of special mattresses may be considered as an adjunct to frequent patient moving. Passive range of motion may also be implicated with splinting to prevent forearm and ankle contractures while sequential compression devices may be indicated to prevent deep vein thrombosis. Ineffective coughing and clearance of secretions mandates the implication of suctioning protocols to limit the risk of nosocomial pneumonias. Alterations in functional residual capacity, deadspace, and ventilation-perfusion ratios may result in ventilatory issues including hypoxemia or hypercarbia and the need to adjust ventilatory parameters.

As noted previously, although these agents prevent movement, they provide no degree of sedation or analgesia. As such, the most important monitor of the depth of sedation, the clinical

score, is eliminated. Therefore, some other measure of the depth of sedation may be required. In the majority of clinical situations, physiologic parameters such as heart rate or blood pressure are used as a means of titrating sedative and analgesic agents. However, issues arise in critically ill patients in whom alterations in heart or blood pressure may not occur in response to stress or pain. In this patient population, exogenous vasopressors may be in use and thereby eliminate the reliability of physiologic parameters. In the operating room setting, the availability of depth of anesthesia monitors is recommended and it is suggested that their use be considered in patients at high risk for awareness. Despite the rare occurrence of such events, means for their prevention of awareness during the use of neuromuscular blocking agents in the Pediatric ICU appear indicated given the consequences of such problems.

In the operating room setting, various depth of sedation or anesthesia monitors are currently available. To date, there are no data in the PICU to demonstrate their efficacy in preventing recall during the use of neuromuscular blocking agents.   The bispectral index is a processed electroencephalographic parameter expressed as a numeric value ranging from 0 (isoelectric EEG) to 100 (awake, eyes open, no sedative agent). In the pediatric population, its intraoperative use has been suggested to decrease the incidence of awarness.[92] In the PICU population, the BIS value has been shown to correlate with the depth of sedation assessed using various clinical scoring systems.[93,94] BIS monitoring has been used to evaluate the depth of sedation in a cohort of 12 PICU patients receiving NMBA's.[95] BIS monitoring was used for a total of 476 hours in the patients and revealed that the desired depth of sedation (BIS number 50 to 70) was achieved 57% of the time. The BIS number demonstrated a deeper than desired depth of sedation (BIS number $\leq$ 49) 35% of the time and an inadequate depth of sedation in patients receiving neuromuscular

blockade (BIS number ≥ 71) 8% of the time. At the time that additional sedation was administered by the bedside nurse who was not allowed to view the monitor, but administered supplemental medication based on clinical judgment, the BIS number was ≥ 71, 64% of the time; 50 to 70, 31% of the time, and ≤ 49, 5% of the time. Although no long term follow-up or assessment of awareness was pursued, the authors concluded that physiologic parameters are not a viable means of assessing the depth of sedation during the use of NMBA's.

The adverse effect that has received the most attention in the adult population with the administration of NMBA's is residual neuromuscular paralysis. In clinical practice, it appears that there are two distinct entities that may account for prolonged neuromuscular paralysis including (1) prolonged recovery from neuromuscular blockade related to excessive dosing or delayed clearance of the parent compound or metabolites due to renal or hepatic issues and (2) what is now termed the acute quadriplegic myopathy syndrome (AQMS).[95,96] The former generally resolves spontaneously over time with the eventual clearance of the parent compound or its metabolites. In clinical practice, it is defined as a prolonged recovery time of more than 100% of the predicted parameter. In distinction, AQMS presents with acute paresis, myonecrosis with increased plasma markers demonstrating muscle breakdown such as creatinine phosphokinase (CPK), and abnormal electromyography (EMG) with the demonstration of reduced compound motor action potential amplitude, decreased motor nerve conduction, and evidence of acute denervation. Clinical findings include flaccid paralysis, relative preservation of extraocular movements, decreased deep tendon reflexes, respiratory insufficiency, intact sensory function, and normal findings in the cerebrospinal fluid. Recovery may require weeks to months, with the need for prolonged rehabilitation care, and tracheostomy with chronic ventilatory support. Although initially reported only with aminosteroid

compounds, it has been subsequently also reported with the benzylisoquinolinium derivatives. It remains to be determined if the relative majority of reports with the use of the aminosteroid compounds relates to the current clinical practice which favors the use of these agents or some particular vulnerability related to these agents.

Given that CPK values are elevated in up to 50% of patients with AQMS, periodic screening of patients receiving ongoing neuromuscular blockade may be indicated. Additionally, given that the syndrome is reported following the prolonged, continuous infusion of NMBA's, it has also been suggested that drug holidays or periodic interruption of the infusion be considered. However, there are no data to demonstrate that such practice will alter the incidence of AQMS and the withdrawal of neuromuscular blockade must be considered on a risk-benefit ratio. Obviously, termination of the use of NMBA's is suggested whenever it is clinically feasible given their adverse effect profile. Other factors and co-morbid processes that may contribute to the development of AQMS include nutritional deficiencies, coadministration of other medications (cyclosporine, corticosteroids, aminoglycosides), hyperglycemia, hepatic or renal insufficiency, and electrolyte disturbances. The association is most profound with the co-administration of NMBA's and corticosteroids thereby suggesting a heightened awareness in such patients.[97] In addition to AQMS, other conditions to consider in the differential diagnosis of patients with prolonged weakness following the use of NMBA's include neuromuscular conditions (myasthenia gravis, Eaton-Lambert syndrome, Guillain-Barre syndrome), acquired or primary myopathic conditions (mitochondrial myopathy, steroid myopathy), central nervous system injury, spinal cord injury, critical illness polyneuropathy, disuse atrophy, and electrolyte or metabolic disturbances. Critical illness polyneuropathy may be confused with AQMS. It is a combined motor and sensory

neuropathy that results from ischemia of the microvasculature of the nerves, which is seen most commonly in patients with multi-system organ failure. The EMG demonstrates a pattern different from that seen in AQMS.

Summary: Neuromuscular blocking agents in the PICU

In addition to their use in the operating room, specific situations may arise which mandate the use of neuromuscular blocking agents in the Pediatric ICU (table 1). Although these agents are generally administered as intermittent bolus doses in the operating room, in the PICU, a more stable baseline level of neuromuscular blockade may be desired and therefore, a continuous infusion may be used. When choosing an agent for use in the PICU population, the major issues include cardiovascular effects, metabolism, and cost. Since many of the patients in the PICU have some degree of hemodynamic instability, agents that cause excessive histamine release should be avoided. Additionally, the presence of hepatic or renal insufficiency may affect metabolism or elimination or the parent compound as well as its metabolites. In the absence of end-organ dysfunction, pancuronium offers an inexpensive means of achieving neuromuscular blockade. Its vagolytic effect will result in tachycardia with an increase in heart rate of 10-20 beats per minute above baseline. Given its duration of action, intermittent dosing is feasible. With its availability in generic form, vecuronium provides another cost effective option in the PICU setting while eliminating the tachycardia that is seen with pancuronium. Although vecuronium and pancuronium are generally effective and inexpensive in patients without end-organ dysfunction, significant alterations in infusion requirements occur in patients with renal insufficiency/failure (pancuronium and vecuronium) or hepatic insufficiency/failure (vecuronium). Atracurium or cis-atracurium may

be a more appropriate choice in patients with hepatic or renal failure since such problems do not alter dosing requirements of either agent.[99]

In the PICU setting like the operating room, adjustment of the dose based on monitoring with a peripheral nerve stimulator is recommended. Regardless of the agent used, significant interpatient variability with up to 10-fold variations in infusion requirements may be noted. The variability results not only from inter-patient variability, but also from various associated conditions which may increase or decrease the sensitivity to NMBA's (tables 6 & 7). Based on this knowledge, the recommended doses (table 8) for the various NMBAs are starting guidelines and the infusion should be increased or decreased as needed to maintain one twitch of the TOF or provide the required depth of neuromuscular blockade. An additional problem which occurs in the ICU patient who receives NMBAs for a prolonged period of time is the development of tachyphylaxis or an increased dose requirement over time. The primary cause is an upregulation of acetylcholine receptors in patients who are chronically exposed to NMBAs. Dodson et al demonstrated an increased density of acetylcholine receptors in muscle from patients who had received prolonged infusions of NMBA's.[100] Prolonged neuromuscular blockade like partial or complete deafferentation, leads to proliferation of acetylcholine receptors at the neuromuscular junction. This problem requires that the dose of the NMBA be increased over time to maintain the same amount of neuromuscular blockade.

Given their adverse effect profile, it is recommended that NMBA's be administered only when aggressive attempts at sedation have failed to provide the desired level of patient immobilization. An ongoing assessment regarding the need for continuing such therapy is suggested with discontinuation of the medication as early as is feasible. Specific protocols should

be in place to ensure appropriate care of the patient who is receiving neuromuscular blockade with attention toward the provision of adequate sedation and analgesia, eye care, prevention of pressure sores, and pulmonary toilet. Given the variability in requirement which are present in the PICU setting, monitoring with the TOF is recommended.

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Table 1: Reported indications for neuromuscular blockade in the Pediatric ICU

Facilitation of procedures or diagnostic studies:
     endotracheal intubation
     central line placement
     radiological imaging (MRI, CT scanning)
Immobilization during inter-hospital or intra-hospital transport
Intensive care indications:
     facilitate mechanical ventilation
     control increased intracranial pressure
     eliminate shivering (especially during therapeutic hypothermia)
     decrease peripheral oxygen utilization
     control severe agitation unresponsive to adequate sedation
     maintain immobilization after surgical procedures
     decrease the risk of pulmonary vasospasm in patients with pulmonary hypertension
     manage patients with tetanus

Table 2: Adverse effects of succinylcholine

arrhythmias:
       bradycardia
       tachycardia
       asystole
       atrial and ventricular ectopy
hypertension
increased intraocular pressure
increased intragastric pressure
increased intracranial pressure
diffuse myalgias
myoglobinuria
malignant hyperthermia
prolonged paralysis with pseudocholinesterase deficiency
hyperkalemia (see table 3)

Table 3: Conditions associated with hyperkalemia after succinylcholine administration

pre-existing hyperkalemia
muscular dystrophy
burns
metabolic acidosis
paraplegia/quadriplegia
denervation injury
metastatic rhabdomyosarcoma
Parkinson's disease
disuse atrophy/prolonged bedrest
polyneuropathy
degenerative CNS disorders
purpura fulminans
tetanus
Guillain-Barre
myotonia dystrophy
prolonged administration of non-depolarizing NMBA

Table 4: Classification of non-depolarizing NMBAs

Aminosteroid compounds:
      pancuronium
      rocuronium
      vecuronium
      pipecuronium
      rapacuronium (no longer available)

Benzylisoquinolinium compounds:
      mivacurium
      atracurium
      cis-atracurium
      doxacurium

Table 5: Duration of action of NMBA's

Short-acting (10 minutes):
        succinylcholine
        mivacurium
        rapacurium

Intermediate-acting (20 to 40 minutes):
        atracurium
        vecuronium
        cis-atracurium
        rocuronium

Long-acting (60 to 90 minutes):
        pancuronium
        pipecuronium
        doxacurium

Table 6: Factors which increase sensitivity to NMBAs

Medications:
        inhalational anesthetic agents
        local anesthetic agents
        antibiotics (aminoglycosides)
        anti-arrhythmic agents (quinidine, procainamide)
        calcium channel blockers
        beta adrenergic antagonists
        chemotherapeutic agents (cyclophosphamide)
        diuretics (furosemide)
        dantrolene
        lithium, magnesium
        cyclosporin
Underlying disorders:
        electrolyte disturbances (hypokalemia, hypermagnesemia, hypocalcemia)
        hypothermia
        respiratory acidosis
        metabolic alkalosis
        myasthenia gravis
        Eaton-Lambert syndrome
        muscular dystrophy
        multiple sclerosis
        amyotrophic lateral sclerosis
        poliomyelitis

Table 7: Factors which decrease the sensitivity to NMBAs

Medications:
      anticonvulsant agents (phenytoin, carbamazepine)
      aminophylline
Underlying conditions:
      hypercalcemia
      burns
      prolonged administration of NMBAs

Table 8: Suggested starting guidelines for the continuous infusion of neuromuscular blocking agents

Agent	Dose	Comments
pancuronium	0.06-0.08 mg/kg/hr	vagolytic effect, primary renal excretion
vecuronium	0.1-0.15 mg/kg/hr	no cardiovascular effects, hepatic metabolism to active metabolites which are renally excreted
rocuronium	0.6-0.8 mg/kg/hr	mild vagolytic effect, hepatic metabolism
atracurium	1-1.5 mg/kg/hr	mild histamine release, non-organ dependent elimination
cis-atracurium	0.2 mg/kg/hr	no cardiovascular effects, non-organ dependent elimination