Neuromuscular Blockade and Reversal: An Overview of Key Concepts

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Neuromuscular Blockade and Reversal: An Overview of Key Concepts

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- Satya Krishna Ramachandran, M.D.
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- Rachel C. Wolfe, Pharm.D., BCCCP
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Learning Objectives

At the conclusion of this activity, participants should be able to

- Explain the physiology, incidence, and complications of residual neuromuscular blockade (NMB)
- Compare the options for neuromuscular blockade reversal and monitoring with regard to efficacy, safety, and pharmacoeconomics
- Explore how attitudes and clinical behaviors related to dosing, monitoring, and reversal of neuromuscular blockade can affect practice and outcomes

Outcome Questions: Measuring Your Learning

- Several outcome questions will be repeated during this activity, first before the content then again after the content has been presented.

- Faculty will discuss the correct answers after the content has been presented.

On average, how many distinct surgical patients do you provide care for each week (either as part of the anesthesia/surgical team or as preoperative/postoperative care)?

a. None - Not my area of practice or not directly involved in patient care
b. 1-5 patients/week
c. 6-15 patients/week
d. 16-25 patients/week
e. More than 25 patients/week

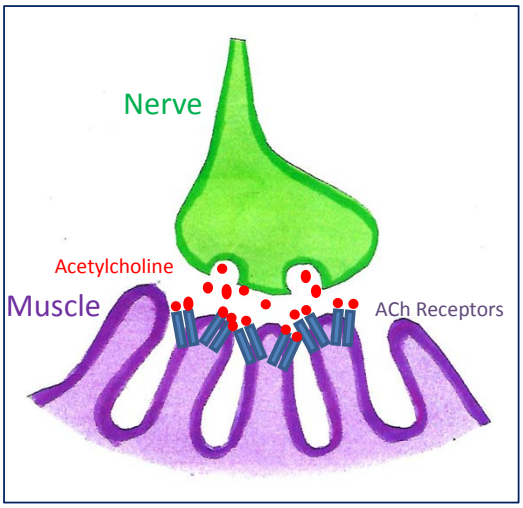
Physiology, Incidence, and Complications of Residual Neuromuscular Blockade

Overview

- Muscle relaxation is a major component of providing anesthesia in many surgical cases
  - *Analgesia, Amnesia, Muscle Relaxation*
  - Prevents patient from moving while surgeon operates
  - Relaxes muscle for surgeon, making it easier to operate
- If muscles are paralyzed, the paralysis must be completely reversed prior to awakening
- If not completely reversed, the patient may experience postoperative residual muscle weakness

Physiology of Neuromuscular Junction

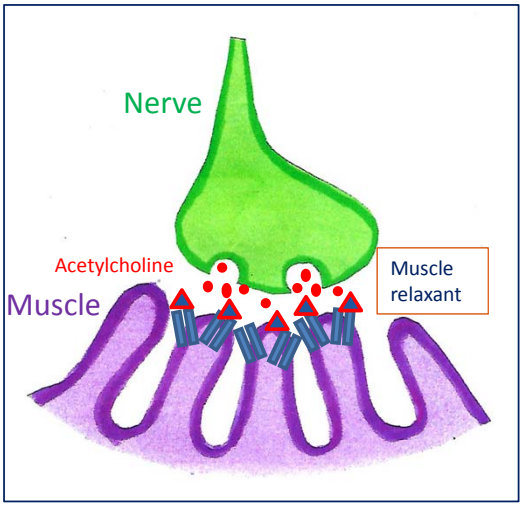
- Acetylcholine (ACh) is released from nerve and travels across synaptic cleft
- ACh then binds to ACh receptors on muscle membrane
- Channels open and the influx of ions (sodium, calcium) results in endplate depolarization and muscle contraction
- ACh is broken down by the enzyme acetylcholinesterase and recycled
- Channels close, the endplate repolarizes, and the muscle relaxes



Hemmings HC et al., eds. Pharmacology and physiology in anesthesia; 2013.

How a Nondepolarizing Muscle Relaxant Works

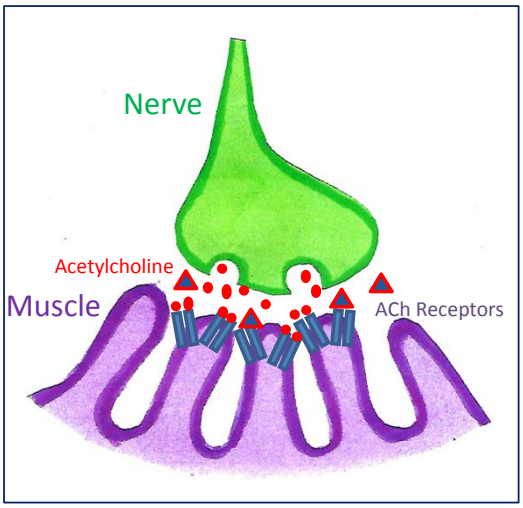
- ACh receptor can be activated to open the channel and cause the muscle to contract ONLY when both alpha subunits are occupied by ACh
- When a nondepolarizing muscle relaxant (e.g., rocuronium, vecuronium) is given, the muscle relaxant blocks ACh from occupying the receptors, preventing contraction and leading to muscle paralysis



Hemmings HC et al., eds. Pharmacology and physiology in anesthesia; 2013.

How Acetylcholinesterase Inhibitors Work

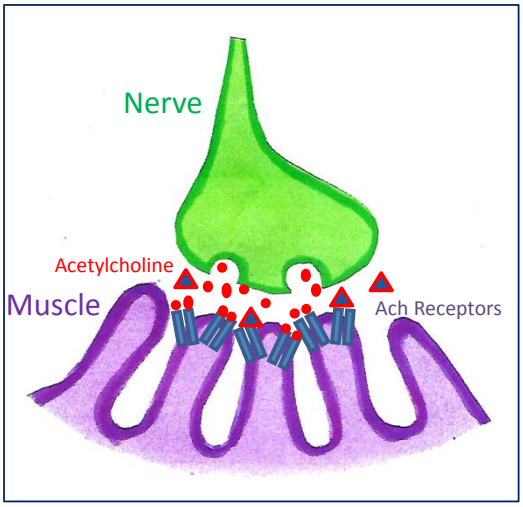
- An acetylcholinesterase inhibitor (e.g., neostigmine) may be given to reverse the effects of a muscle relaxant
- Acetylcholinesterase inhibitors prevent the breakdown of ACh
- This leads to more ACh at the neuromuscular junction, displacing the muscle relaxant
- The ACh then binds to the receptors, leading to muscle contraction



Hemmings HC et al., eds. Pharmacology and physiology in anesthesia; 2013.

Pathophysiology of Postoperative Residual NMB

- If **insufficient** reversal agent is given, partial paralysis will occur because some of the receptors remain occupied by the muscle relaxant
- Partial paralysis can also occur due to the slow onset of action of neostigmine
- If **too much** acetylcholinesterase inhibitor (reversal agent) is given , there will be increased ACh at the site, leading to weakness related to cholinergic symptoms



Incidence of Postoperative Residual NMB

- Postoperative residual NMB is a common occurrence
- Reported occurrence: 40%-60% of cases where muscle relaxation is given
- Associated with an increased risk of critical respiratory events in the post anesthesia care unit (PACU)
- Despite routine use of anticholinesterase reversal agents, 40-60% of patients arrive in the PACU with objective evidence of residual neuromuscular blockade

Sabo D et al. *J Anesthe Clinic Res*. 2011; 2:140.
Brull SJ et al. *Anesthesiology*. 2017; 126:173-90.
Fortier LP et al. *Anesth Analg*. 2015; 121:366-72.

Incidence of Postoperative Residual NMB

- Review of 15 studies by Murphy and Brull in 2010 revealed that, on average, approximately 40% of recovery room patients experienced postoperative residual NMB
- One study reported that only 12% of providers used qualitative monitoring and only 25% reversed the muscle relaxant
- Train of four (TOF) ratio < 0.9 (i.e., residual NMB) was more frequent in the inpatient group (47%) compared with outpatient group (38%)

Murphy GS et al. *Anesth Analg*. 2010; 111:120-8.

Incidence of Postoperative Residual NMB

- Analysis of studies using intermediate-acting nondepolarizing muscle relaxants (e.g., atracurium, cisatracurium, rocuronium, vecuronium)
  - Incidence of TOF ratio < 0.7 was 12%
  - Incidence of TOF ratio < 0.9 was 41%
- Conclusions
  - There was a "continued high incidence of postoperative residual curarization reported from multiple academic centers"
  - The incidence of postoperative residual NMB after surgery did not seem to be decreasing over time

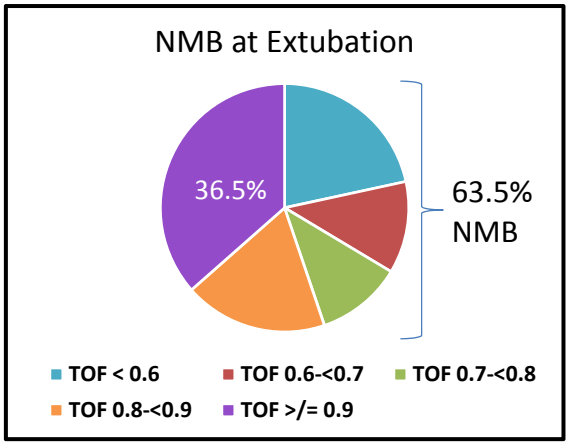
Murphy GS et al. *Anesth Analg*. 2010; 111:120-8.

Incidence of Postoperative Residual NMB

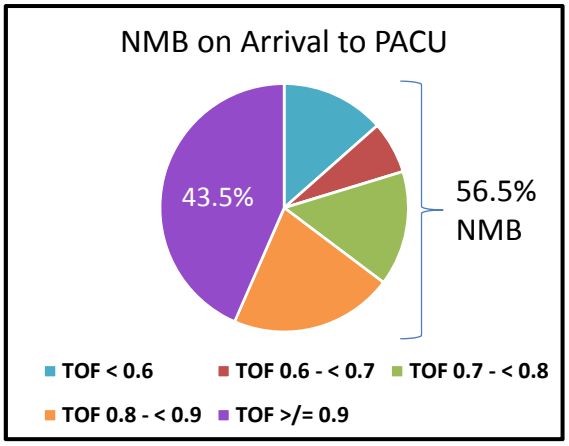
- RECITE (Residual Curarization and its Incidence at Tracheal Extubation) studied incidence of residual NMB
- It has been proposed that the minimally acceptable level of recovery is a TOF ratio ≥0.9 because even mild residual NMB (TOF ratio 0.7–0.9) is associated with postoperative complications

Fortier LP et al. *Anesth Analg*. 2015; 121:366-72.

RECITE Study: Incidence of Postoperative Residual NMB



Only 36.5% had TOF ratio ≥ 0.9



Only 43.5% had TOF ratio ≥ 0.9

Fortier L et al. *Anesth Analg*. 2015; 121:366-72.

Complications of Postoperative Residual NMB

- Obstruction of upper airway
- Pharyngeal and esophageal dysfunction
- Hypoxemia, impaired hypoxic ventilatory response
- Patient discomfort
- Postoperative pulmonary atelectasis
- Pulmonary edema
- Reintubation
- Unexpected admission to the ICU

Carron M et al. *J Clin Anesth*. 2016; 35:1-12.
Dunworth BA et al. *AANA J*. 2018; 86:269-77. Sabo D et al. *J Anesthe Clinic Res*. 2011; 2:140.

Complications of Postoperative Residual NMB

- Aspiration pneumonitis
- Pneumonia
- Generalized muscle weakness
- Significant morbidity and perioperative mortality
- Prolonged stay in the recovery room
- Upper airway obstruction and respiratory failure when neostigmine unnecessarily given after full recovery

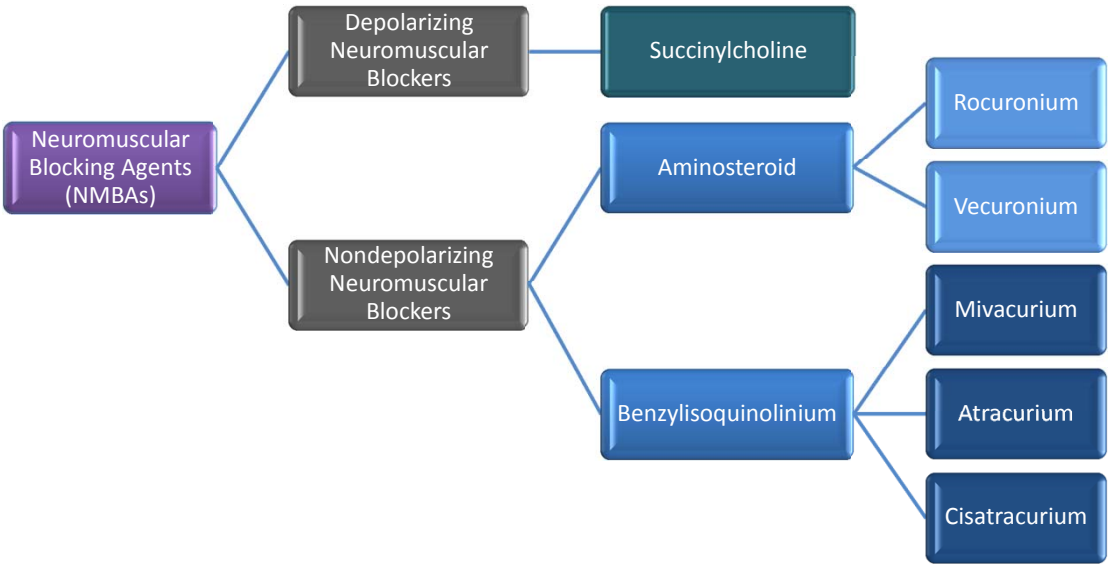
Carron M et al. *J Clin Anesth*. 2016; 35:1-12.
Dunworth BA et al. *AANA J*. 2018; 86:269-77. Sabo D et al. *J Anesthe Clinic Res*. 2011; 2:140.

Key Takeaways

- Postoperative residual NMB is a serious complication that may occur after giving muscle relaxants when the effects are not fully reversed
- Postoperative residual NMB can lead to respiratory complications, including airway obstruction, aspiration, and pneumonia
- This can lead to prolonged length of stay in the PACU and increased morbidity and mortality

Therapeutic Options for Reversal of Neuromuscular Blockade

Classification of Neuromuscular Blockers



Neuromuscular Blocker Monitoring

Depth of Block	Post-tetanic count (PTC)	Qualitative TOF	Quantitative TOF Ratio	TOF Depiction
Profound	0	0	0	Tetany
Deep	≥ 1	0	0	Tetany
Moderate	NA	1-3	0	
Light	NA	4, with fade	0.1 to 0.4	
Minimal	NA	4, no fade	0.4 to < 0.9	
Full recovery	NA	4, no fade	≥ 0.9 to 1	

Brull SJ. *Anesthesiology*. 2017; 126:173-90.

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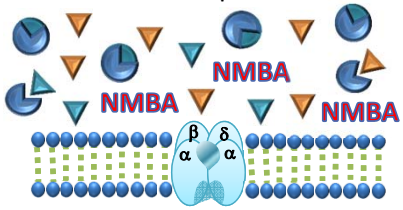
Residual NMB

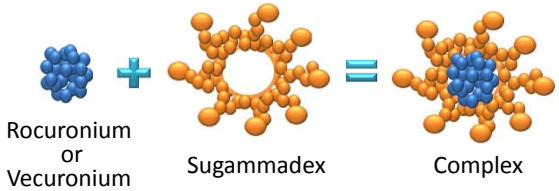
Brull SJ. *Anesthesiology*. 2017; 126:173-90.

Options for NMB Reversal

- Neostigmine
  - Acetylcholinesterase (AChE) inhibitor
    - Prevents breakdown of acetylcholine (ACh)
    - Increased competition at the nicotinic receptor



- Sugammadex
  - Selective relaxant binding agent
  - Forms a complex with selected aminosteroid NMBAs
    - Sugammadex affinity
      - Rocuronium > vecuronium
      - No affinity for other NMBAs



Efficacy of NMB Reversal Options

Neostigmine

- Reverses ALL nondepolarizing NMBA
- Requires co-administration of an anticholinergic agent (e.g., glycopyrrolate) to prevent bradycardia
- Cannot reverse induction doses of rocuronium
- Does not adequately reverse profound or deep NMB; most effective for light to minimal NMB
- Residual NMB is prevalent due to competitive nature and ceiling effect

Sugammadex

- Reverses only rocuronium and vecuronium; has no affinity for other NMBAs
- Co-administration of medication not needed to prevent adverse drug events (ADEs)
- Effectively reverses induction doses of rocuronium (but not vecuronium)
- Reverses all depths of NMB within approximately 3 minutes
- Residual NMB rarely observed

Bridion (sugammadex) prescribing information. Merck and Co., Inc. 2017 Jun.
Bloxoverz (neostigmine) prescribing information. Avadel Legacy Pharmaceuticals, LLC. 2017 Jan.

Reversal Efficacy: Moderate to Deep Block

Study	Groups	Intervention	Primary Endpoint	Results
Jones RK et al. *Anesthesiology.* 2008; 109:816-24.	Neostigmine (n=37) Sugammadex (n=37)	Rocuronium-induced NMB, sevoflurane Reversal at PTC 1-2 1) Neostigmine 0.07 mg/kg 2) Sugammadex 4 mg/kg	Time to recovery to TOF ratio of 0.9	Neostigmine • 49 (13-146 [35.7-65.6]) min* Sugammadex • 2.7 (2.1-16.1 [2.1-4.1]) min*
Lemmens H et al. *BMC Anesthesiol.* 2010; 10:15.	Neostigmine (n=36) Sugammadex (n=47)	Vecuronium-induced NMB, sevoflurane Reversal at PTC 1-2 1) Neostigmine 0.07 mg/kg 2) Sugammadex 4 mg/kg	Time to recovery to TOF ratio of 0.9	Neostigmine • 50 (46-312.7 [46-96.6]) min* Sugammadex • 3.3 (1.4-68.4 [2.3-6.6]) min*
Kim KS et al. *Anesth Analg.* 2004; 99:1080-5.	Group 1 (n=20) Group 2 (n=20) Group 3 (n=20) Group 4 (n=20)	Rocuronium-induced blockade, sevoflurane Neostigmine 0.07 mg/kg at varying depths of blockade 1) TOF 1 2) TOF 2 3) TOF 3 4) TOF 4	Time to recovery to TOF ratio of 0.9	Neostigmine with TOF 1 • 28.6 (8.8 – 75.8) min† Neostigmine with TOF 2 • 22.6 (8.3 – 57.4) min† Neostigmine with TOF 3 • 15.6 (7.3-43.9) min† Neostigmine with TOF 4 • 9.7 (5.1-26.4) min†

*Median (range [interquartile range]), †median (range)

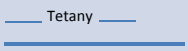
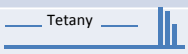
Reversal Efficacy: Light to Minimal Block

TOF of 4, with or without fade or a TOF ratio between 0.1 to < 0.9

- Neostigmine
  - Speed of reversal is increased
    - TOF ratio of ≥ 0.9 in less than 10 min for most patients
    - Some outliers require 25-30 min
  - Lower doses (0.02-0.03 mg/kg) are recommended
  - Excessive dosing (e.g., full reversal dose of 0.07 mg/kg)
    - Neostigmine-induced neuromuscular weakness
- Sugammadex
  - Predictably reverses within 2-3 min
  - 2 mg/kg is the approved dose for TOF ≥ 2
  - Doses of 0.25-2 mg/kg have been reported in the literature
    - Time to full recovery from NMB can be delayed with doses < 2 mg/kg
    - Efficacy dependent on NMBA and type of general anesthesia
    - Doses < 2 mg/kg have risk of residual NMB and re-paralysis

Brull SJ. *Anesthesiology*. 2017; 126:173-90. Schaller SJ. *Anesthesiology*. 2010; 113:1054-60.

Depth of Blockade and NMB Reversal

Depth of Block	PTC	Qualitative TOF	Quantitative TOF Ratio	TOF Visual	Neuromuscular Blockade Reversal Agents	
Profound	0	0	0		Sugammadex 16 mg/kg (emergent reversal of rocuronium 1.2 mg/kg)	
Deep	≥ 1	0	0		Sugammadex 4 mg/kg	
Moderate	NA	1-3	0		Sugammadex 2-4 mg/kg	Neostigmine 0.07 mg/kg (TOF ≥ 2)
Light	NA	4, with fade	0.1 to 0.4		Sugammadex 2mg/kg	Neostigmine 0.03 mg/kg
Minimal	NA	4, no fade	0.4 to < 0.9		Sugammadex 2 mg/kg	Neostigmine 0.03 mg/kg
Full recovery	NA	4, no fade	≥ 0.9 to 1		No reversal agent required	

Brull SJ. *Anesthesiology*. 2017; 126:173-90.
Bridion (sugammadex) prescribing information. Merck and Co., Inc. 2017 Jun.
Bloxoverz (neostigmine) prescribing information. Avadel Legacy Pharmaceuticals, LLC. 2017 Jan.

Safety of NMB Reversal Options

Neostigmine

- Higher incidence of residual NMB
- Higher incidence of postoperative nausea and vomiting (PONV)
- Higher incidence of bradycardia (despite anticholinergic administration)
- Lower incidence of hypersensitivity and anaphylaxis
- No relevant drug–drug interactions

Sugammadex

- Lower incidence of residual NMB
- Lower incidence of PONV
- Severe bradycardia can occur (rare; unknown mechanism of action)
- Higher incidence of hypersensitivity and anaphylaxis
- Drug interactions: hormonal contraceptives and ondansetron

Min KC et al. *Br J Anaesth*. 2018; 121:749-57. De Kam P-J et al. *Br J Anaesth*. 2018; 121:758-67. Hristovska AM et al. *Cochrane Database Syst Rev*. 2017; 8:CD012763.

Summarizing what we know…

Neostigmine

- Should not be used to reverse profound or deep block
- May effectively reverse moderate block, but it takes time
- Effectively reverses minimal to light block within 10-15 minutes in most patients
- Glycopyrrolate coadministration required to prevent bradycardia
- ADEs, such as bradycardia, PONV, and residual NMB, are more prevalent than with sugammadex

Sugammadex

- Predictable, highly effective reversal agent for rocuronium and vecuronium NMB
- Niche is in its ability to reverse moderate to deep, and even profound block
- Emergent reversal (~3 min from induction) is only approved for rocuronium-induced blockade
- Associated with hypersensitivity reactions
- Drug cost is higher than the combination of neostigmine + glycopyrrolate

Cost Considerations

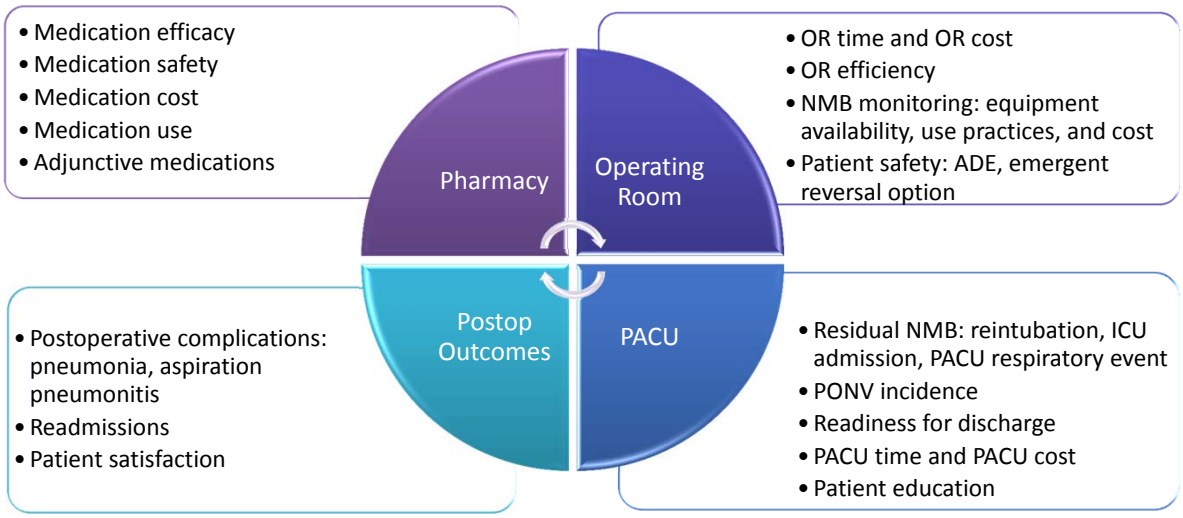
	Neostigmine 1 mg/mL 10 mL + Glycopyrrolate 0.2 mg/mL 5 mL	Neostigmine 1 mg/mL 3 mL + Glycopyrrolate 0.2 mg/mL 3 mL	Sugammadex 100 mg/mL 2 mL vial†	Sugammadex 100 mg/mL 5 mL vial†
Cost per vial or syringe*	$18 + $12	$33+$32	$90	$165
Reversal				
Deep	n/a	n/a	$180 (4 mg/kg)	$165 (4 mg/kg)
Moderate	$30	$130	$180 (4 mg/kg)	$165 (4 mg/kg)
Light	$30	$65	$90 (2 mg/kg)	----

*Based on average health-system purchase price for a single-dose or single-use vial.
†Based on 85-kg patient.

At what acquisition price does sugammadex's greater efficacy translate into added clinical value?

Added institutional value?

Pharmacoeconomic Considerations



Key Components

- Interprofessional collaboration
- Literature review (efficacy, safety, risk factors, outcomes)
- Data collection and/or data pull
- Data analysis
- Relationship building and trust establishment
- Open-mindedness
- Workflow analysis
- Institutional guideline development and revisions
- Guideline implementation
- Post-implementation oversight

Key Takeaways

- Neuromuscular blockade should be monitored quantitatively (preferably) or qualitatively whenever neuromuscular blockers are used
- To prevent postoperative complications, strategies to minimize residual NMB should be implemented
- Medications should be reviewed in collaboration with the requesting department to ensure a thorough pharmacoeconomic assessment is conducted and all data supporting clinical and institutional value are included

Changing Attitudes and Clinical Behaviors

Section Content

- Clinical behaviors
  - Dosing, monitoring, and reversal
  - Special populations – situational awareness
- Process measures and relevant outcomes
  - Stratification, attribution
- Changing attitudes and clinical behaviors
  - Implementation science – relevant constructs
  - Learning environments vs. incentives

Clinician Behaviors - NMB and Reversal

- Patient factors
- Surgical factors
- Outcomes
  - Randomized controlled trial (RCT) vs. big data
  - Measured vs. unmeasured factors
  - Are specific clinical behaviors related to outcomes?

Evidence for Dosing and Monitoring

- Use of NMB independently associated with postoperative respiratory complications (PRC)
- Higher doses of intermediate-acting NMB associated with dose-dependent increases in incidence of PRC
- Appropriate reversal may limit risk of PRC associated with high dose NMB
- Use of quantitative monitoring may be associated with lower risk of PRC

Kirmeier E et al. *Lancet Respir Med*. 2018 Sept 14. Epub ahead of print.
McLean DJ et al. *Anesthesiology*. 2015; 122:1201-13.

Appropriate Reversal Can Be a Target

	Appropriate Reversal		Inappropriate Reversal	
NMBA Dose Quintiles (x ED95 dose)	PRC rate	Effect Size	PRC rate	Effect Size
I (Lowest)	0.39%	n/a	0.43%	n/a
II	0.45%	1.04 (0.7-1.6)	0.56%	1.03 (0.8-1.3)
III	0.60%	1.16 (0.8-1.7)	0.65%	1.06 (0.8-1.3)
IV	0.63%	0.95 (0.6-1.4)	0.89%	1.20 (1-1.5)
V (Highest)	0.91%	0.98 (0.6-1.5)	1.49%	1.41 (1.1-1.8)

Appropriate reversal (neostigmine ≤0.06 mg/kg at TOF count of at least 2)

Inappropriate reversal (no neostigmine administration, neostigmine administration not guided by TOF count or doses >0.06 mg/kg)

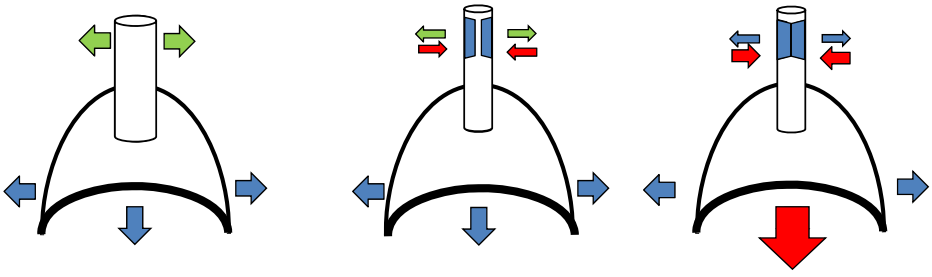
ED95 = effective dose to produce 95% depression in twitch height

McLean DJ et al. *Anesthesiology*. 2015; 122:1201-13.

Clinical Management Adaptability

- Special populations (two examples)
  - Obstructive sleep apnea (OSA)
  - Obesity
- Disease mechanisms for adverse outcomes
- Pharmacokinetic implications

Airway Failure in OSA



Normal Airway Respiratory Pump Coupling

OSA Airway Respiratory Pump Uncoupling

OSA with Residual NMB

Eckert DJ et al. *Prog Cardiovasc Dis*. 2009; 51:313-23.

Obesity – NMB and Reversal Dosing

- Standard aliquot sizes are inadequate for effect
  - Tendency to dose NMBA to effect
  - High risk of inadequate reversal
  - Avoidance of reversal is a fairly prevalent practice
- OSA is more prevalent in obese patients

Brull SJ et al. *Anesthesiology*. 2017; 26:173-90.
Ramachandran SK et al. *Anesth Analg*. 2017; 125:272-9.

Process Measures and Outcomes

- What is the goal?
  - Is it to reduce variation in NMB management?
  - Or is it to reduce PRC rates?
- What is the optimal strategy?
- How do we maximize our chances of success?

Kirmeier E et al. *Lancet Respir Med*. 2018 Sept 14. Epub ahead of print.

Process Measures and Outcomes

- Importance of process measures
  - Meaningless variation = costs vs. art of anesthesia?
  - Meaningless compliance = risk of complications
- Stratification
  - Apples are not oranges
- Attribution: Case-for-change 101 = sniff test
  - Learning environments vs. incentives

Stratification and Adjustment

- Over 30 factors in POPULAR
- Patient complexity
- Procedural complexity
- Workflow/scheduling/nontechnical complexity

Kirmeier E et al. *Lancet Respir Med*. 2018 Sept 14. Epub ahead of print.

Changing Clinician Behaviors

- Who is the customer?
- Who is the change agent?

Changing Clinician Behaviors

- Who is the customer?
- Who is the change agent?
- How do you get clinicians to adhere to best practices and learn about outcome change?
  - Not a one-time intervention
  - Requires multiple interventions over time, and clinical responses titrated to effect

Effective Outcome Change Management

- The intervention
  - Source, strength of evidence, adaptability, feasibility, value
- Inner setting
  - Tension for change, organizational culture
- Outer setting
  - External pressures

Damschroder LJ et al. *Implement Sci*. 2009, 4:50.

Effective Outcome Change Management

- The individuals involved = buy-in
  - Biases, self-efficacy, individual stage of change, alignment with organization
- The implementation process
  - Planning, engaging, executing, reflecting

Damschroder LJ et al. *Implement Sci*. 2009, 4:50.

Which of these practice changes will you consider making?

- Discuss the incidence of residual NMB with colleagues
- Consider depth of NMB when selecting reversal agent
- Evaluate methods of neuromuscular monitoring within the institution
- Consider factors beyond drug cost when making formulary decisions
- Quantify complications associated with residual NMB, focusing on patient outcomes
- Develop shared goals as a step in changing practice behaviors related to NMB and reversal

Selected Resources

- Damschroder LJ et al. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci*. 2009, 4:50.
- Hemmings HC, Egan TD, eds. Pharmacology and physiology in anesthesia. Philadelphia: Elsevier-Saunders; 2013.
- Brull SJ et al. Current status of neuromuscular reversal and monitoring: challenges and opportunities. *Anesthesiology*. 2017; 126:173-90.