

## Avoiding Pulmonary Complications Summarized Reference List

### Neuromuscular Blockade

1. Brull SJ, Murphy GS. Residual neuromuscular block: lessons unlearned. Part II: methods to reduce the risk of residual weakness. *Anesthesia and analgesia*. 2010;111(1):129-140.

Review article that examines optimal neuromuscular management strategies used by clinicians to reduce the risk of residual paralysis in the early postoperative period. Current evidence demonstrates that frequently utilized clinical tests of neuromuscular junction (head lift or hand grip) cannot reliably exclude presence of residual paralysis. Clinicians are often unable to detect fade when TOF ratios are between .6 and 1.0. Strong evidence that acceleromyography detects small degrees of residual blockade (TOF ratios > .6). Complete recovery of neuromuscular function is more likely when anticholinesterases are administered early (>15-20 mins before extubation) and at shallower depth of block (TOF count of 4). Selective neuromuscular reversal agents may provide clinicians with better tools for prevention of postoperative residual weakness.

2. Fortier LP, McKeen D, Turner K, et al. The RECITE Study: A Canadian Prospective, Multicenter Study of the Incidence and Severity of Residual Neuromuscular Blockade. *Anesthesia and analgesia*. 2015;121(2):366-372.

A prospective observational study within 8 Canadian hospitals investigating the incidence of residual NMB (neuromuscular blockade). Primary objective of the RECITE (Residual Curarization and its Incidence of Tracheal Extubation) study was to investigate the incidence of postoperative residual NMB, defined as TOF ratio <0.9, at tracheal extubation. Secondary objective was to determine incidence of residual NMB upon arrival in PACU. 302 adult patients undergoing open or laparoscopic abdominal surgery lasting <4 hours, with ASA 1-3, scheduled for general anesthesia with at least one dose of NMB agents for tracheal intubation or maintenance of NMB were enrolled. Data were available for 241 patients at tracheal extubation, and 207 patients at PACU arrival. Rocuronium was the NMB used in 99% percent of cases, with remaining participants receiving cisatracurium. Patients intubated with succinylcholine received at least 1 dose of nondepolarizing agent, with neostigmine used for reversal. The incidence of residual NMB without reversal (TOF ratio < 0.9) was 63.5% at extubation and 56.5% upon arrival at PACU. Among patients receiving NMB reversal with neostigmine, residual paralysis was present in 64.6% at tracheal extubation and 59.7% at PACU arrival. Exploratory analysis showed use of qualitative peripheral neuromuscular monitoring was associated with significantly lower NMB at PACU arrival. The incidence of residual NMB both at tracheal extubation and PACU arrival was positively associated with significantly higher doses of rocuronium per minute of surgery. This article concluded that residual paralysis was common with use of NMB agents, even when monitoring and reversal was used. Better use of these agents and monitoring tools is needed.

3. Bulka CM, Terekhov MA, Martin BJ, Dmochowski RR, Hayes RM, Ehrenfeld JM. Nondepolarizing Neuromuscular Blocking Agents, Reversal, and Risk of Postoperative Pneumonia. *Anesthesiology*. 2016;125(4):647-655.

An observational study including 13,290 surgical cases involving patients receiving general anesthesia between July 2005 and September 2013 were extracted from Vanderbilt University Medical Center's NSQIP database. Of the 13,100 eligible cases, 1,455 surgical cases receiving an intermediate-acting

depolarizing NMBA were compared to 1,455 propensity score-matched cases not receiving NMBA. Additionally, 1,320 cases with NMBA and reversal with neostigmine were compared to 1,320 propensity-score matched cases without reversal. Cases were followed 30 days postoperatively. Two propensity-score-matched analyses was performed. Postoperative pneumonia IRRs (incidence rate ratios) and bootstrapped 95% CIs were calculated. Of the 1,455 surgical cases in the cohort receiving NMBA intraoperatively, 38 developed pneumonia. Of the surgical cases who did not receive NMBA, 22 developed postoperative pneumonia. IRR was statistically significant. Of the 1,320 surgical cases who received an NMBA intraoperatively without reversal, 149 developed postoperative pneumonia. Of the surgical cases who received NMBA with neostigmine, 70 developed pneumonia within 30 days postop. Patients not reversed with acetylcholinesterase inhibitor were more than twice as likely to develop pneumonia postoperatively compared to those who received reversal with neostigmine. Intraoperative use of intermediate nondepolarizing NMBAs is associated with postoperative pneumonia. Among patients receiving NMBAs, non-reversal is associated with increased risk of postoperative pneumonia.

4. Lien CA, Kopman AF. Current recommendations for monitoring depth of neuromuscular blockade. *Current opinion in anaesthesiology*. 2014;27(6):616-622.

Literature review of neuromuscular monitoring and minimum specifications for the purpose of improving patient management. Adequate recovery of neuromuscular function has been defined as TOF of at least 0.9 measured at the adductor pollicis, monitoring with qualitative nerve stimulator facilitates actual TOF ratio. Peripheral nerve stimulators are not routinely used in clinical practice, suggesting dosing of NMBAs and anticholinesterases is inappropriate when recovery of neuromuscular function upon extubation cannot be guaranteed. Routine use of peripheral nerve stimulators allows rational administration of NMBAs.

5. Abad-Gurumeta A, Ripolles-Melchor J, Casans-Frances R, et al. A systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade. *Anaesthesia*. 2015;70(12):1441-1452.

Systematic review of Sugammadex versus Neostigmine for reversing neuromuscular blockade. 14 RCTs included 1,553 participants. Sugammadex reduced all signs of residual postoperative paralysis compared to neostigmine, confirming reliable relative risk reduction of at least 50%. Residual paralysis after administration of Neostigmine was 8.4 per 100 participants, whereas Sugammadex reduced by 4.5 per 100 to 3.9 per 100. Sugammadex reduced minor postoperative paralysis compared to neostigmine with a relative risk of at least 75%. Pooled rate of weakness post neostigmine was 9.4 per 100, compared to 4.7 out of 100 with Sugammadex. Sugammadex reduced drug-related side effects compared with Neostigmine, while rates of PONV were similar for Sugammadex and Neostigmine. Sugammadex reduced the number of patients with clinical signs of postoperative residual paralysis caused by Rocuronium as compared to Neostigmine.

## Protective Ventilation Strategies

6. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *The New England journal of medicine*. 2000;342(18):1301-1308.

A multicenter randomized trial performed in the United States with 861 ICU patients with Acute Lung Injury or Acute Respiratory Distress Syndrome. 387 patients received lower tidal volumes 6 mL/kg for predicted body weight and 405 patients received traditional tidal volumes of 12mL/kg for predicted body weight. Patients were monitored for 28 days for pulmonary and non-pulmonary complications. The mortality rate in the group with lower tidal volumes was significantly lower as compared to the traditional tidal volume group (31 percent vs. 39.8 percent). In addition, ventilator-free days were significantly lower in the group with lower tidal volumes with ventilator days at 8 as compared to those in the traditional tidal volume group with ventilator days totaling 10.5. The incidence of barotrauma was the same in both groups.

7. Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *The New England journal of medicine*. 2013;369(5):428-437.

A multicenter, double-blind, parallel-group trial with 400 patients randomly assigned to receive either protective mechanical ventilation or non-protective mechanical ventilation intraoperatively. All patients were at least 40 years old and scheduled to undergo elective abdominal surgery lasting 2 or more hours. Participating patients were assessed preoperatively for risk of pulmonary complications. Those with a score greater than 2 on a 5 point index were included in the trial. Patients in the protective ventilation group received tidal volumes of 6-8 mL/kg of predicted body weight, PEEP of 6-8 cm of water, and recruitment maneuvers every 30 minutes after tracheal intubation. Patients in the non-protective ventilation group received tidal volumes of 10-12 mL/kg of predicted body weight, no PEEP, and no recruitment maneuvers. The patients who did not receive protective ventilation had a higher incidence of atelectasis (17%) and pneumonia (8%) within 7 days as compared to the protective ventilation group with rates of 6.5% of atelectasis and 1.5% experiencing pneumonia. In addition, non-protective ventilation strategies resulted in 3% of patients in that group having acute lung injury or ARDS within 7 days postoperatively compared to only 0.5% in the protective ventilation group. The median length of stay for the protective ventilation patients was shorter than the non-protective ventilation group (adjusted difference of 2.45 days shorter). There was no difference in ICU admissions or mortality between the two groups.

8. Guldner A, Kiss T, Serpa Neto A, et al. Intraoperative protective mechanical ventilation for prevention of postoperative pulmonary complications: a comprehensive review of the role of tidal volume, positive end-expiratory pressure, and lung recruitment maneuvers. *Anesthesiology*. 2015;123(3):692-713.

A comprehensive review article that explains the pathophysiology associated with postoperative pulmonary complications and further compares the literature regarding protective ventilation strategies. Guldner et al categorize patients as either having either non-injured or injured lungs preoperatively. Both groups are recommended to receive low tidal volumes: 6-8 mL/kg for predicted body weight for non-injured lung patients and 6 mL/kg predicted body weight for injured lung patients.

Low tidal volumes were determined to be the most important protective ventilation strategy. There is less evidence for a specific PEEP value or recruitment maneuvers.

9. Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet* (London, England). 2014;384(9942):495-503.

In this randomized controlled trial involving 30 centers across Europe and North and South America, patients undergoing open abdominal surgery were divided into two groups. Both groups received low tidal volumes (7 mL/kg PBW). However, 445 patients were assigned to a group with high PEEP settings (12 cm of water) & recruitment maneuvers while 449 patients were assigned to a second group receiving low PEEP (2cm of water) and no recruitment maneuvers. Postoperative pulmonary complications were identified in 174 (39%) of the 445 patients receiving high PEEP and recruitment maneuvers as compared to 172 (38%) of the 449 patients in the low PEEP group. The study concluded that in patients undergoing open abdominal surgery, the incidence of postoperative pulmonary complications was comparable in the first 5 days after surgery. However, patients in the high PEEP group experienced hypotension (46%) and required more vasoactive drugs (62%) intraoperatively as compared to the low PEEP group (hypotension: 36%; vasoactive drugs: 51%).

10. Sato H, Nakamura K, Baba Y, Terada S, Goto T, Kurahashi K. Low tidal volume ventilation with low PEEP during surgery may induce lung inflammation. *BMC anesthesiology*. 2016;16(1):47.

Twenty-eight patients were enrolled in a prospective, randomized controlled study examining the effects of low tidal volume ventilation paired with low PEEP for hepatectomy surgery. Half of the patients (14) received traditional tidal volumes of 12 mL/kg for predicted body weight and the other half of patients (14) received reduced tidal volumes of 6 mL/kg for predicted body weight. Both groups received PEEP of 3 cm of water. After six hours of ventilation, interleukin-8 levels were found to be elevated in the epithelial lining of the airway for the low tidal volume group. In addition, the P/F ratio was higher in the PACU for the traditional tidal volume patients (12mL/kg) when compared to the lower tidal volume group. The study concluded that low tidal volume with low PEEP may lead to pulmonary inflammation in hepatectomy surgery.

11. Serpa Neto A, Hemmes SN, Barbas CS, et al. Protective versus Conventional Ventilation for Surgery: A Systematic Review and Individual Patient Data Meta-analysis. *Anesthesiology*. 2015;123(1):66-78.

In this meta-analysis of fifteen randomized controlled trials, there was a decreased incidence of postoperative pulmonary complications (PPCs) in patients receiving low tidal volumes ( $\leq 8$  mL/kg for predicted body weight (PBW)) as compared to patients receiving conventional ventilation ( $> 8$  mL/kg PBW). The use of PEEP and/or recruitment maneuvers was not included in the definitions for protective or conventional ventilation. The reviewers did not determine a difference in PPC incidence with patients receiving high or low levels of PEEP when low tidal volumes were applied. However, there was a higher incidence of PPCs in patients who received tidal volumes  $> 10$  mL/kg PBW and PEEP  $\geq 5$  cm of water.