Protocol #: 18-2707
Project Title: A double-blind, randomized, parallel study to compare the efficacy of sugammadex versus neostigmine for reversal of neuromuscular blockade at the end of kidney transplantation surgery in patients with severe kidney dysfunction.
Principal Investigator: Ana Fernandez-Bustamante M.D., Ph.D.
Version # and Date: #3 – 09/18/2020

Hypotheses and Specific Aims

Clinical Hypotheses

Sugammadex, compared to neostigmine, reduces inadequate neuromuscular blockade reversal (NMBR) and its related hypoventilation, as measured by reducing the frequency of patients with one or more episodes of hypoventilation, by at least 50% during the first 3h after the end of kidney transplantation surgery (or until meeting discharge criteria from the PACU if sooner than 3h) after adjusting for quantitative train-of-four (qTOF) T4/T1 monitoring and morphine equivalents received. Hypoventilation events are defined by the presence of ≥1 minute-long events of minute ventilation (MV) <40% of the expected MV for each patient (expMV).

Sugammadex, compared to neostigmine, reduces inadequate NMBR and its related hypoventilation, as measured by reducing the frequency of patients with one or more episodes of hypoventilation, by at least 50% for up to 3 days after kidney transplantation surgery after adjusting for qTOF T4/T1 monitoring and morphine equivalents received.

Our overall hypothesis is that sugammadex will provide improved NMBR and postoperative ventilation than neostigmine. Prevention of hypoventilation with sugammadex may contribute to reduce patient's reported dyspnea scores (PROMIS® Dyspnea Functional Limitation questionnaire scores), decrease PPCs possibly related to inadequate NMBR after kidney transplantation surgery (i.e. respiratory insufficiency, gastric aspiration, pneumonia), improve kidney graft outcomes, reduce hospital resources utilization and estimated healthcare costs. A study powered to test these as a hypothesis would require a substantially larger sample size and it may be pursued in the future.

Objectives

Primary objective: To test the efficacy of NMBR with sugammadex, compared to neostigmine, to reduce inadequate NMBR and its related hypoventilation during the immediate postoperative period after kidney transplantation surgery, after adjusting for qTOF recovery and morphine equivalents received. We define hypoventilation as the incidence of ≥1 minute-long events of MV <40% of expMV. Minute ventilation will be measured continuously with a noninvasive respiratory volume monitor for the first 3h after the end of surgery or until meeting discharge criteria from the post-anesthesia care unit (PACU) (if sooner than 3h).

Secondary objective: To test the efficacy of NMBR with sugammadex, compared to neostigmine, to reduce inadequate NMBR and its related hypoventilation during the first 3 postoperative days in patients after kidney transplantation surgery, after adjusting for qTOF recovery and morphine equivalents received. We define hypoventilation as the incidence of ≥1 minute-long events of MV <40% of expMV. Minute ventilation will be measured continuously with a noninvasive respiratory volume monitor for up to 3d after surgery or until meeting end of monitoring criteria (if sooner than 3d)

Additional secondary objectives: To test if NMBR with sugammadex, compared to neostigmine, reduces patient's reported dyspnea scores (with the validated Patient-Reported Outcomes Measurement Information System, PROMIS®, assessment), decreases postoperative pulmonary complications (PPCs)

possibly related to inadequate NMBR after kidney transplantation surgery (i.e. respiratory insufficiency, gastric aspiration, pneumonia), improves kidney graft outcomes and reduces hospital resources utilization (i.e. hospital length of stay, ICU admission) and estimated healthcare costs.

II. Background and Significance/Preliminary Studies:

Inadequate neuromuscular blockade reversal (NMBR) leads to different degrees of residual muscle weakness at extubation and during the post-anesthesia care unit (PACU) in up to 70% of patients[1-3]. Estimates of inadequate NMBR depends on the methods of diagnosis and definitions used (i.e. quantitative vs. qualitative TOF, T4/T1 threshold), surgery type, and patient comorbidities. Even mild incomplete NMBR (e.g. T4/T1 0.7-0.8) impairs ventilatory compensation to hypoxia and coordination of the upper airway muscles[4-6]. Therefore it increases the risk for postoperative atelectasis, aspiration, and pneumonia[7-9]. The use of any NMB agent, lack of TOF monitoring or NMBR administered, and NMBR with neostigmine, as opposed to NMBR with sugammadex, are strongly associated with PPCs. These PPCs include mild (e.g. atelectasis, lung edema, hypoxemia requiring oxygen supplementation) and major complications (e.g. pneumonia, re-intubation)[7, 10-12]. Mild PPCs (e.g. atelectasis) are often underestimated, but we have recently shown their association with worse clinical outcomes[13]. In this multicenter study in American Society of Anesthesiologists (ASA) class 3 patients undergoing non-cardiothoracic surgery, mild PPCs (including atelectasis) were associated with increased early postoperative mortality, ICU admission and hospital stay[13]. However, the existing data on the association between inadequate NMBR and quantitative assessment of ventilation is scarce. Only one study[14] analyzed respiratory muscle weakness after either sugammadex or placebo with pulmonary function tests (maximum inspiratory and expiratory pressures, forced vital capacity and forced expiratory volume in 1 second). Pulmonary function tests are certainly quantitative but depict the pulmonary function at only one time point[14]. Respiratory function during the first hours after general anesthesia is influenced by a series of factors, from residual NMB to sedation by residual anesthetics and opioid analgesics, pain-induced hypoventilation, respiratory obstruction due to sleep apnea, and others. In fact, patients with severe kidney dysfunction present an increased risk to the respiratory depression induced by opioids due to their reduced pharmacokinetic elimination[15]. The diagnosis of respiratory depression in the PACU routinely depends on the development of hypoxemia, even though this is a well-known late sign of hypoventilation. There is increasing evidence suggesting the value of continuous noninvasive quantitative expiratory volume monitoring in patients at increased risk for multifactorial hypoventilation[16-20]. Investigators have reported up to 76% of patients after general anesthesia present at least one hypoventilation event, defined as a $\geq$1 minute-long episode of minute ventilation (MV) <40% of expected (expMV) for the patient's age, gender, height and weight or body surface area[21]. The effect of sugammadex on the quantitative assessment of hypoventilation in postoperative patients adjusted for TOF monitoring or opioid consumption has not been evaluated.

There is insufficient information on the use of sugammadex for NMBR in patients with kidney dysfunction. The clearance of sugammadex is proportional to creatinine clearance (ClCr), and thus delayed with kidney dysfunction[22-25]. However, no safety adverse events related to inadequate NMBR or delayed recurrence of NMB have been observed in patients with kidney dysfunction receiving sugammadex[26]. Nonetheless, patients with kidney impairment often receive the cholinesterase inhibitor neostigmine for NMBR. Neostigmine provides a slower and less effective NMBR than that achieved with sugammadex in the overall population, and its overdose is itself associated with increased muscle weakness[3, 10, 27-31] and postoperative pulmonary morbidity[1, 12]. It is critical to investigate the effect of sugammadex as NMBR in patients with kidney dysfunction.
Thus, we are proposing to randomize patients with severe kidney dysfunction (ClCr <30 mL/min) undergoing kidney transplantation surgery to receive either NMBR with sugammadex (intervention) or neostigmine (control) following qTOF monitoring-guided and FDA-approved doses. Despite their severe kidney disease these patients are receiving a kidney transplantation surgery. The exact kidney function during the first hours after reperfusion of the graft kidney in the receiving patient is unknown. Thus the clearance and duration of effect of sugammadex in kidney transplant recipients during the early postoperative period is unknown but relevant. Their kidney function is expected to improve over the following days to months after transplant, and considered stable 6-12 months after transplant.

III. Research Methods

A. Outcome Measure(s)

The **primary outcome** will be the frequency of patients with one or more ≥1 minute-long episodes of hypoventilation within 3 hours after the end of surgery or until meeting discharge criteria from the PACU (if sooner than 3h), assessed with a continuous noninvasive respiratory volume monitor that will be blinded to care providers.

Additional outcomes will include: intraoperative minutes from NMBR administration to qTOF T4/T1 >0.9, to extubation, and total in operating room time; incidence of residual NMB in PACU based on qTOF; number of events and accumulated minutes of hypoventilation in PACU; frequency of patients with ≥1 events of delayed postoperative hypoventilation (daily for up to 3 postoperative days) and accumulated minutes of hypoventilation; delayed recurrence of NMB based on qTOF; presence of pre-defined postoperative pulmonary complications during hospital stay and by the postoperative day 14±3; standardized Patient-Reported Outcomes Measurement Information System (PROMIS®) dyspnea functional limitations questionnaire score compared to patient's baseline; pre-defined kidney graft outcomes; hospital resources utilization (e.g. hospital length of stay, ICU admission) and their cost estimates.

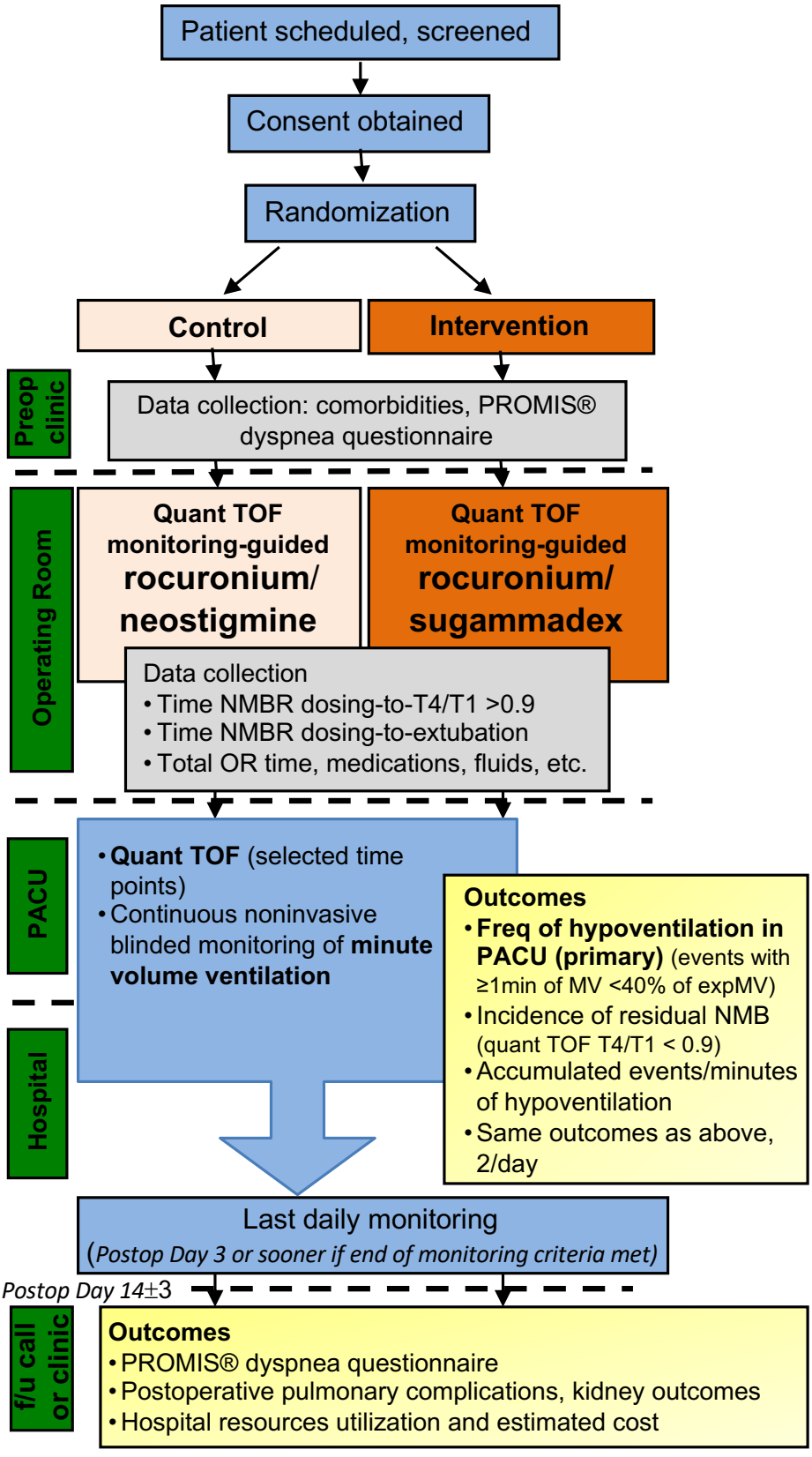
B. Description of Population to be Enrolled

We will include adults (≥ 18 years and ≤ 90) diagnosed with severe kidney dysfunction (defined by plasma creatinine clearance <30 mL/min) and planning on kidney transplantation surgery at the University of Colorado Hospital. Exclusion criteria: patients unable to sign the informed consent, pregnant women, Body Mass Index (BMI) > 40, pre-existing oxygen or ventilatory dependency (24h use of oxygen or other noninvasive or invasive ventilatory support), or patients with any pulmonary, neuromuscular or other disease that severely limits their respiratory functional status (e.g. unable to achieve 4 Metabolic Equivalent of Tasks, METs, such as climbing up 1 flight of stairs[32]), or any contraindication for any of the study-related medications or interventions.

C. Study Design and Research Methods

We have designed a prospective randomized double-blind single center study on 100 patients with severe kidney failure undergoing kidney transplantation surgery. Patients will be randomized to receive either NMB with rocuronium and sugammadex for NMBR (intervention group) or NMB with rocuronium and neostigmine for NMBR (control group). Respiratory function will be objectively monitored starting in PACU and during the first 3 postoperative days or until end of monitoring criteria are met. A blinded assessor will record the frequency of hypoventilation events as well as the accumulated minutes of hypoventilation. Quantitative TOF monitoring will be evaluated by a blinded investigator. Additional data related to patient's comorbidities, morphine equivalents (mg/kg) received, validated dyspnea patient-reported scores, pulmonary complications, kidney graft relevant data and outcomes, and hospital resource utilization and estimated costs will also be collected.

After signing informed consent, patients will be randomized to receive, during kidney transplant surgery, NMB with rocuronium and NMBR with either sugammadex (intervention group) or neostigmine (control group). Both groups will receive intraoperative NMB agents and reversal medications as guided by qTOF monitoring and following FDA-approved doses (see details below). In the PACU, we will perform continuous monitoring of their MV during their PACU stay and assess qTOF at selected time points in all patients. Institutional discharge criteria from PACU is based on an Aldrete's score[33] ≥8 assuming there are no discharge concerns by the patient's healthcare providers (PACU nurse, anesthesiologist and/or surgeon). After discharge from PACU and during the first 3 postoperative days (or until end of monitoring criteria if sooner) we will maintain the continuous MV monitoring and daily quantitative TOF assessment, collect opioids received and data relevant to pulmonary complications, kidney graft outcomes and estimated healthcare costs. At the postoperative surgery clinic visit or by phone interview we will collect patient's subjective dyspnea scores and compare to their baseline (with a validated questionnaire), as well as updated PPCs, kidney graft outcomes, hospital resources utilization and estimated healthcare costs.


Patient scheduled, screened
Consent obtained
Randomization
Control
Intervention
Preop clinic
Data collection: comorbidities, PROMIS® dyspnea questionnaire
Operating Room
Quant TOF monitoring-guided rocuronium/ neostigmine
Quant TOF monitoring-guided rocuronium/ sugammadex
Data collection
• Time NMBR dosing-to-T4/T1 >0.9
• Time NMBR dosing-to-extubation
• Total OR time, medications, fluids, etc.
PACU
Hospital
• Quant TOF (selected time points)
• Continuous noninvasive blinded monitoring of minute volume ventilation
Outcomes
• Freq of hypoventilation in PACU (primary) (events with ≥1min of MV <40% of expMV)
• Incidence of residual NMB (quant TOF T4/T1 < 0.9)
• Accumulated events/minutes of hypoventilation
• Same outcomes as above, 2/day
Last daily monitoring
(Postop Day 3 or sooner if end of monitoring criteria met)
Postop Day 14±3
f/u call or clinic
Outcomes
• PROMIS® dyspnea questionnaire
• Postoperative pulmonary complications, kidney outcomes
• Hospital resources utilization and estimated cost

Preoperative phase

Screening for eligibility and consenting will take place once the patient has been accepted for kidney transplantation at the University of Colorado Hospital by the Transplant Surgery team. Randomization will occur after patients consent for the study. Only the PI will remain unblinded to the group allocation (see below).
Preoperative data will be collected by the blinded investigator (study coordinator), including baseline vital signs (including room air SpO_2), comorbidities, medications, and kidney graft relevant factors. The baseline dyspnea scores will be assessed by asking patients to complete the PROMIS® v1.0 Dyspnea Functional Limitations Short Form 10a_9-2-2016 questionnaire (available at http://www.healthmeasures.net/administrator/components/com_instruments/uploads/PROMIS%20SF%20v1.0-Dyspnea%20Functional%20Limitations%2010a_9-2-2016.pdf). This is a validated and standardized short questionnaire to quantitate if sugammadex used for NMBR reduces the subjective dyspnea scores relative to baseline.

Intraoperative phase

We will perform a prospective parallel randomized study of rocuronium/sugammadex (intervention) vs. rocuronium/neostigmine (control) for NMB and NMBR at the end of kidney transplantation surgery. This will be performed by the unblinded investigator, following the following protocol(s):

- A quantitative TOF (qTOF) monitor (the Stimpod NMS450®, Xavant Technology Ltd., South Africa, the acceleromyography-based monitor available at UCH, and/or the TwitchView™, Blink Device Company, Seattle, WA, an electromyography-based monitor) will guide the NMB and NMBR management in all study patients. Quantitative NMB monitoring are considered superior to the more routinely-used but subjective qualitative TOF monitors[34, 35]. The qTOF monitor will be placed in the ulnar nerve territory to stimulate the adductor pollicis muscle[36] immediately after loss of consciousness during induction of anesthesia. The exact location of monitoring will be marked and used for qTOF measurements in the postoperative period.
- NMB brief protocol: Rocuronium will be the NMB agent used in both groups as guided by the qTOF and following standard dosing protocols in order to achieve adequate NMB to allow the intubation and surgical procedure (routinely T4/T1 <T3 until closure of surgical incision). Rocuronium dosing: 0.6-1.2 mg/kg for intubation, 0.08-0.2 mg/kg bolus for maintenance with recovery of second twitch (T2) in qTOF.
- NMBR brief protocol: The sugammadex (intervention) or neostigmine (control) will be administered at the end of the surgery. The goal will be to administer the appropriate NMBR medication when ≥2 twitches are objectivized with the qTOF monitor. NMBR drugs and dosing for each group will follow standard of care FDA-approved doses, as follows: Sugammadex 2 mg/kg will be administered when spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation.

	Sugammadex dosing (mg/kg)	Neostigmine dosing (mg/kg)
T4 recovered	2	0.03-0.05 (max 5 mg)
T2/T3 recovered	2	0.05-0.07 (max 5 mg)
T0/T4 with 1-2 post-tetanic twitches present or T1 recovered	4 or wait	Wait

Overdosing of neostigmine will be avoided to prevent neostigmine-induced muscle weakness. Neostigmine will be administered simultaneously with the appropriate glycopyrrolate dose (0.2 mg per 1.0 mg of neostigmine).

Extubation will be performed following the usual standard of care criteria of adequate level of consciousness, presence of airway protection reflexes and spontaneous ventilation parameters in addition to quantitative TOF T4/T1 >0.9. The following times (minutes) will be recorded: NMBR administration-to-T4/T1 >0.9, NMBR administration-to-extubation, total operating room time.

Postoperative in-hospital phase

The blinded investigator will collect the following study-related information:

- Continuous respiratory volume monitoring: From the moment of arrival to the PACU, the patient will be continuously monitored with the FDA-approved noninvasive respiratory volume monitor ExSpiron® (Respiratory Motion, Inc.) available at UCH. This electrical impedance-based monitor uses a sensor that is applied to the chest's skin at three pre-determined locations: sternal notch, xyphoid and right mid-axillary line at the level of the xyphoid. By monitoring the thoracic impedance to a high frequency current it continuously assesses the estimated volume between three thoracic points of reference. It provides 5-second updates of average respiratory rate, tidal volume and MV volume (= respiratory rate * tidal volume). Calibration is no longer required, but it requires the user to enter some patient's information (gender, and height + weight, or body surface area) for the mathematical calculation of tidal volume and minute volume for that particular patient. By calculating the expected minute volume (expMV = tidal volume times respiratory rate) based on patient's characteristics it provides the option to compare the observed estimated MV and detect hypoventilation events. The settings of hypoventilation events are customizable by duration and the percent of expected MV below which the MV is observed. This monitor will be blinded to healthcare providers to avoid biasing routine standard of care. Continuous data from this monitor (respiratory rate, tidal volume and MV volume) are automatically stored and will be exported at the end of PACU and daily for up to 3 days or sooner if the patient fulfills the following end of monitoring criteria: is discharged from the hospital; or is freely ambulating (defined as patient walking outside of the hospital room $\geq$2 times a day) and shows no signs or symptoms of respiratory complications, swallowing problems or muscle weakness. While attached to the monitor, this will be secured to a wheeled pole to facilitate the process for patient mobilization and ambulation. Once the respiratory volume data is exported, we will measure the incidence of hypoventilation as defined below (primary outcome) during PACU and daily for up to 3 postoperative days, as well as characterize the distribution of respiratory volume parameters (average, median, percentiles) during PACU and daily for up to 3 postoperative days.
- The blinded investigator will assess the presence of residual NMB with the quantitative TOF monitor by calculating the average of 3 measurements of qTOF T4/T1 (40mA or adequate to achieve TOF response while comfortable for the patient) within 15min of PACU arrival and hourly until up to 3h after the end of surgery or sooner if the patient meets PACU discharge criteria. We will record the initial PACU TOF and calculate the PACU average TOF. After transfer to the postoperative floor, the blinded investigator will assess residual or recurrent NMB with the qTOF monitor twice a day, with 3 repetitions each time, and each assessment separated by $\geq$6h. This will be maintained for up to 3 days after the end of surgery or until end of monitoring criteria are met.
- The individual doses of administered opioids received by the patient during the study (PACU and daily for up to 3 postoperative days or until the end of monitoring criteria are met) will be recorded and converted to morphine equivalents[21] to statistically evaluate the effect of opioid administration on hypoventilation events.
- Nursing-charted episodes of respiratory depression during the PACU stay will also be recorded. Postoperative pulmonary complications (as defined elsewhere[13]) during PACU and up to 3 postoperative days will be collected.

Postoperative end of study follow-up

At postoperative day 14$\pm$3 during the patient's visit to the transplant surgery clinic or via a phone call, the PROMIS® Dyspnea Functional Limitations Short Form questionnaire will be repeated

and normalized to the patient's baseline. Any postoperative pulmonary complications[13] and hospital resources utilization occurring from the hospital discharge until this end of study follow-up will be collected from the patient and the medical record, and the estimated costs based on average hospital daily stay depending on type of care unit or reported cost of complications calculated.

Any signs and symptoms of hypersensitivity (e.g. rash, anaphylaxis) detected during PACU and up to 3 postoperative days will be collected from the patient and patient's providers. The relationship of these signs and symptoms to sugammadex will be assessed by the patient's providers and also by the study safety officer. Their confirmatory diagnostic testing and management will be performed at the discretion of the patient's providers.

We **hypothesize** that the intervention group will present a ≥50% reduction in the incidence of hypoventilation for the first 3h after the end of kidney transplantation surgery or until meeting discharge criteria from the PACU (if sooner than 3h), as defined by the incidence of ≥1 minute-long events of observed MV of <40% of expMV detected with a noninvasive respiratory volume monitor after adjusting for qTOF T4/T1 and morphine equivalents received.

Tele-communication for screening, e-consenting and any eligible study-related visits

In line with current efforts to minimize face-to-face contact with potential candidates and/or study participants in response to the COVID-19 pandemic, we will maximize when possible HIPPA-compliant methods of tele-communication for any study-related tasks. HIPPA-compliant applications (i.e. REDCap, Qualtrics, MS Office, Zoom, Skype, or Vidyo) will be used for prospective study participants for electronic screening, consenting and any eligible study-related visits. The first goal of tele-communication with eligible candidates is to provide a detailed overview of the study protocol and consent form to be signed by study participant and PI (or research study staff).

a. After subject screening, a phone call will be made to introduce the purpose of the study and to request prospective study participation, upon verbal consent, a personal e-mail address will be requested.

b. After phone call, consent study forms in .pdf format will be sent via e-mail to prospective study participant with a follow up 30-minute video meeting request.

c. During 30-minute video meeting, detailed e-consent guidance will be provided to prospective study participant.

d. Participant will document and sign informed consent electronically or by printing the consent form, signing with pen, and then scanning and emailing back to study team.

After signed informed consent, all study-related visits will be evaluated for possible use of tele-communication. The study intervention during surgery and those postoperative in-hospital visits to assess respiratory function and residual NMB are not eligible for tele-communication, but all other visits for data collection from the participant (e.g. PROMIS questionnaires, end-of-study follow-up) will be attempted via tele-communication as described above.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

- **Insufficient neuromuscular blockade reversal (NMBR):** Insufficient neuromuscular blockade reversal at the end of surgery can lead to postoperative complications related to neuromuscular weakness. Complications due to insufficient NMBR range from mild subjective sensation of muscle weakness and up to respiratory failure requiring reintubation and mechanical ventilation, including problems with swallowing, speech or vision, airway aspiration of gastric contents, hypoventilation and increased requirement of oxygen supplementation and pneumonia. The use of sugammadex in this population with severe

kidney disease has not been sufficiently studied but previous small studies have not observed early or delayed events of insufficient NMBR in patients with severe kidney disease. The long-term goal of this study is to reduce insufficient NMBR after kidney transplant surgery, and its contribution to hypoventilation and other complications.

- **Adverse effects related to NMBR agents, including sugammadex (intervention patients) and neostigmine (control patients):** The most common adverse effects to sugammadex include: nausea, vomiting, pain, hypotension and headache. The most common adverse effects for neostigmine include: salivation, fasciculation, bowel cramps and diarrhea. A recent Cochrane systematic review with meta-analysis and trial sequential analysis found that the overall risk of adverse effects, including residual NMBR, nausea/vomiting and bradycardia is lower for sugammadex than for neostigmine, and the risk of severe adverse reactions is similar after sugammadex and neostigmine[30].
- **Local skin irritation to respiratory volume sensor.** The ExSpiron sensor has three electrode pads to be placed against the patient's skin at the sternal notch, xiphoid and right mid-axillary line at the level of the xiphoid. The risk of this bio-impedance-based monitor is minimum, with some possible irritation of the skin in susceptible patients. This monitor has been used with no adverse events[16-21, 37, 38].
- **Discomfort during neuromuscular blockade monitoring:** Monitoring of NMB with a Train-Of-Four (TOF) monitor consists of provoking muscle twitches that can be uncomfortable in awake patients, proportionally to the amplitude of the electrical signal used. In awake the TOF monitoring is usually well tolerated at 30-40 mA, which is the amperage we are planning on using. This has been used without problems by us and others[3, 29, 39], but we will reduce the amperage if uncomfortable for a study patient.
- **Risk to privacy**: There is a small risk of loss of privacy of confidential data collected from study participants. We will collect the minimum patient information required for the study and use RedCap for data collection and storage. The paper copies of study data and the electronic master file will be stored behind locked doors in the PI's office and protected by the security measures established by the University of Colorado network.

E. Potential Scientific Problems:

This study has been designed to detect differences in the incidence of hypoventilation (primary outcome) but the sample size may be insufficient to detect differences in clinically relevant complications secondary to hypoventilation. Such a study would require a larger study sample.

F. Data Analysis Plan:

The investigator and statistician will be responsible for analyzing the study data. The PI will be unblinded in order to follow the intraoperative study protocol. The study coordinator will be blinded to the randomization allocation, and will be responsible for performing the preoperative (baseline) and postoperative assessments. The official clinical database will not be unblinded until the data is clean and complete and the last independent safety review has been performed, and the study database is locked. The groups will be blindly labeled in the study website and only the PI and the safety review monitor will have access to the group codes.

Variables/Time Points of Interest

Frequency of patients with one or more episodes of hypoventilation events in PACU (primary outcome). This will be obtained from the noninvasive respiratory monitor that provides a continuous assessment of the patient's respiratory rate, tidal volume and minute volume. This continuous monitoring will be performed continuously during the PACU stay. When meeting PACU discharge criteria based on institutional standard of care (based on an Aldrete's score[33] $\geq$8 with patient's nurse and anesthesiologist agreement and no surgical concerns), the every 5-second information will be exported, and the periods with MV <40% of expMV for that patient that last $\geq$1 minute will

be identified and counted. For the primary outcome patients will be classified as presenting or not at least one event of hypoventilation, summarized per group and compared.

Frequency of patients with one or more episodes of hypoventilation events daily for 3 first postoperative days or sooner if patient meets end of monitoring criteria. Similar as before, hypoventilation will be assessed once daily for up to 3 days, or less if the patient is discharged from the hospital or is freely ambulating (ambulates outside of the hospital room ≥2 times a day) with no signs or symptoms of respiratory complications.

Additional assessments of hypoventilation (e.g. accumulated minutes of hypoventilation) will be performed during PACU and daily for up to 3 postoperative days.

Incidence of residual or recurrent NMB in PACU. This will be determined from the quantitative TOF measurements and calculated as the average qTOF T4/T1 at 40 mA from 3 repetitions at selected time points: 15min after arrival to PACU, hourly and before transfer to floor. A patient will be classified as presenting an episode of residual NMB if the average T4/T1 at any time point during PACU is <0.9. In addition, a percentage of timepoints with an average T4/T1 <0.9 will be analyzed as an accumulated time with residual or recurrent NMB. This variable will be used as covariate in the logistic regression analysis (see below). An average TOF of 3 repetitions <0.4 will be considered a severe residual or recurrent NMB. Patient's safety will be prioritized and thus an average TOF of 3 repetitions <0.9 will be immediately reported to the patient's care team in addition to following the appropriate study regulatory safety communications of adverse events.

Incidence of residual or recurrent NMB in the postoperative floor. This will be calculated as described before (T4/T1 <0.9, considered severe if T4/T1 <0.4), as an average of 3 repetitions obtained on two occasions separated by ≥6h daily on postoperative days 1-3 or until the end of monitoring criteria have been met.

Morphine equivalents will be calculated from individual opioid doses administered to each patient following standard conversion formulas[21, 40]. This morphine equivalent dose will be calculated for the PACU period and daily for 3 first postoperative days or until the end of monitoring criteria have been met, and used as covariate in the logistic regression analysis.

Time from NMBR administration to quantitative TOF T4/T1 >0.9 (minutes, one decimal). The quantitative TOF will be repeated at 80 mA every 30 seconds from the moment the NMBR medication (sugammadex or neostigmine) has been completely administered intravenously.

Time from NMBR administration to extubation (minutes, once decimal).

Time of total operating room time (minutes), counting from in-room time stamp to out-of-room time stamp.

The PROMIS® v1.0 Dyspnea Functional Limitations Short Form 10a_9-2-2016 questionnaire is a validated and standardized short questionnaire to quantitate if sugammadex used for NMBR reduces the subjective dyspnea scores relative to baseline. It will be completed by the patient in the preoperative phase and during the postoperative follow up. It is available at http://www.healthmeasures.net/administrator/components/com_instruments/uploads/PROMIS%20SF%20v1.0-Dyspnea%20Functional%20Limitations%2010a_9-2-2016.pdf).

Postoperative Pulmonary Complications (PPCs) following previous definitions[13, 41, 42], including:

> Respiratory Failure, defined as[41]: "When postoperative PaO_2 <60mmHg on room air, a ratio of PaO_2 to inspired oxygen fraction <300 or arterial oxyhemoglobin saturation measured with pulse oximetry (SpO_2) <90% and requiring oxygen therapy".

Unplanned intubation with postoperative mechanical ventilation (POMV), defined as placement of a breathing tube that was not intended or planned, excluding instances of intubation during an unplanned return to the operating room. Also excluded those patients that were transferred intubated and ventilated to the intensive care unit (ICU) from the operating room.

ARDS, based on the Berlin definition[43] 3 mutually exclusive categories of ARDS based on degree of hypoxemia: mild (200 mmHg < PaO_2/FIO_2 ≤ 300 mmHg), moderate (100 mmHg < PaO_2/FIO_2 ≤ 200 mmHg), and severe (PaO_2/FIO_2 ≤ 100 mmHg) and 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance (≤40 mL/cm H_2O), positive end-expiratory pressure (≥10 cm H_2O), and corrected expired volume per minute (≥10 L/min).

Pneumonia – or "Respiratory infection" as defined per NSQIP criteria[42]: "having at least 1 definitive chest radiologic examination and at least 1 sign of pneumonia (fever, leukocytosis, or altered mental status with no other cause), as well as at least 1 microbiologic laboratory finding (positive cultures from blood, bronchoalveolar lavage, or pleural fluid specimens) or at least 2 symptoms (purulent sputum, worsening cough, dyspnea or tachypnea, rales or rhonchi, or worsening gas exchange)".

Pneumothorax defined as in: "Air in the pleural space with no vascular bed surrounding the visceral pleura".

Atelectasis, defined as[41]: "Lung opacification with a shift of the mediastinum, hilum, or hemidiaphragm toward the affected area, and compensatory overinflation in the adjacent nonatelectatic lung" (based on radiology reports/medical chart).

Pleural effusion, defined as[41]: "Chest x-ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of the adjacent anatomical structures, or (in the supine position) a hazy opacity in one hemithorax with preserved vascular shadows" (based on radiology reports/medical chart).

Bronchospasm, defined as: "Presence in medical chart of bronchospasm and/or wheezing plus the use of bronchodilators (not bronchodilators alone)".

These pulmonary complications will be identified with information obtained directly from the patient's medical chart. All testing will be performed by and at the discretion of the patient's physicians. No tests will be ordered specifically for this clinical study. The clinical severity of pulmonary and non-pulmonary complications will be graded following accepted scales[44, 45].

Kidney graft outcomes, including postoperative ClCr, daily urine output, need for dialysis postoperatively, diagnosis of delayed graft function, kidney graft rejection. Postoperative hemodialysis is not usually planned and typically reserved for patients with immediate donor graft failure who exhibit signs of congestive heart failure within the first week after transplantation. The need of rescue hemodialysis within the first week after kidney transplantation is an accepted and simple definition of delayed kidney graft function[46].

Hospital resources utilization: hospital floor length of stay (LOS) (days, rounded to half a day), ICU admission and LOS, estimated cost based on average daily cost at a postoperative UCH floor or ICU and/or based on reported estimated costs per PPC[47, 48]

Hypersensitivity adverse events: hypersensitivity signs and symptoms, including but not limited to rash, bronchospasm or anaphylaxis, will be obtained for up to 3 postoperative days directly from the patient and the patient's providers. Their relationship to sugammadex will be assessed by the patient's physicians and the study safety officer. Their confirmatory testing and management will be performed strictly at the discretion of the patient's physicians.

Statistical Methods

The primary hypothesis is that the frequency of patients with one or more episodes of hypoventilation events in PACU (% of patients) is lower in the sugammadex group compared to neostigmine (controls). This will be analyzed by logistic regression which includes as covariates group allocation, total morphine equivalents, and TOF T4/T1 response, and other observed significant and clinically relevant differences between the groups. The odds ratio for the group covariate will be the primary outcome of interest, with the other covariates included in the model to adjust for potential confounders related to hypoventilation.

The secondary analysis comparing delayed efficacy of sugammadex to neostigmine in reducing the incidence of hypoventilation during the first 3 postoperative days will assume the same model and covariates as the primary hypothesis. To compare the incidence of PPCs a logistic regression model will be used with the binary outcome of any PPC and will include covariates for group and total morphine equivalents. Hospital length of stay and costs will be compared between groups using a linear regression model including covariates for group, total morphine equivalents, presence of respiratory comorbidities and other clinical differences that may influence the outcome. Continuous outcomes may be transformed if they violate the normality assumption (e.g., a log-transformation).

Multiplicity

Given only one primary outcome and hypothesis, there is a not a concern for multiplicity. Secondary analyses are considered exploratory in this protocol.

Power/Sample Size:

Based upon a sample size of 40 patients per group, this study has 90% power to detect a 50% difference in hypoventilation incidence in the PACU (from 76% as reported in previous studies[21] to 38%, alpha 0.05), assuming a potential dropout of up to 6 patients per group. The 50% reduction is considered clinically relevant for a decrease in the frequency of hypoventilation, a precursor of more clinically significant complications such as hypoxemia, reintubation or pneumonia. Quantifying the contribution of hypoventilation into more severe complications is challenging, and details of duration and severity of hypoventilation are not well known. Thus, only a significant reduction in hypoventilation incidence (i.e. 50%) may be accepted as relevant. This trial will provide additional detailed information that may provide more insight on the clinical consequences of hypoventilation (e.g. potential association between accumulated minutes of MV <40% expMV and decrease in SpO_2/FiO_2 over the following 30 min).

A sample size of 40 patients per group would also have approximately 80% power (78%) to detect a difference in case the incidence of any hypoventilation events is 60%, instead of the literature-based 76%. The table below provides the sample size per group to achieve a variety of assumptions for the primary outcome, alpha, and power:

Incidence Group 1	Incidence Group 2	Alpha	Power	Sample Size per Group
1. 0.76	2. 0.38	3. 0.01	4. 0.8	5. 39
6. 0.76	7. 0.38	8. 0.05	9. 0.8	10. 26
11. 0.76	12. 0.38	13. 0.01	14. 0.9	15. 48
16. 0.76	17. 0.38	18. 0.05	19. 0.9	20. 34

Although our sample size has been designed based on the frequency of hypoventilation in patients during the PACU stay, we have also estimated the power that a sample size of n=40 patients per group would have to detect a difference on the incidence of residual NMB. In a preliminary sample of 25 patients after general anesthesia and neostigmine used for NMBR at our institution, 9 patients had a quantitative TOF T4/T1 <0.9 in the PACU (36%). This matches the incidence range 10-50% of TOF <0.9 observed in other studies[8, 10, 49]. The reported frequency of qTOF <0.9 after 15min of

sugammadex administration in other surgical populations is <8%[34, 39, 50, 51]. With this incidence of residual NMB, our proposed sample size would have 90% power to detect a reduction to residual NMB to an incidence of 5% (alpha 0.05):

G. Summarize Knowledge to be Gained

This study will fill an important gap of knowledge with immediate clinical applications: 1) determine the efficacy of sugammadex, compared to neostigmine, for NMBR in patients with severe kidney dysfunction undergoing a kidney transplant; and 2) characterize the effect of sugammadex and neostigmine on postoperative ventilation, dependent and independent to residual or recurrent NMB and other contributing factors (e.g. opioids). Our study will describe the effect of NMBR on objective and quantitative assessments of qTOF and minute volume ventilation. Additional measures will include patient's subjective dyspnea scores (with a validated questionnaire), PPCs and kidney graft outcomes, hospital resource utilization and estimated healthcare costs.

H. References

- 1. Fuchs-Buder, T., R. Nemes, and D. Schmartz, *Residual neuromuscular blockade: management and impact on postoperative pulmonary outcome.* Curr Opin Anaesthesiol, 2016. **29**(6): p. 662-667.
- 2. Hayes, A.H., et al., *Postoperative residual block after intermediate-acting neuromuscular blocking drugs.* Anaesthesia, 2001. **56**(4): p. 312-8.
- 3. Fortier, L.P., et al., *The RECITE Study: A Canadian Prospective, Multicenter Study of the Incidence and Severity of Residual Neuromuscular Blockade.* Anesth Analg, 2015. **121**(2): p. 366-72.
- 4. Herbstreit, F., J. Peters, and M. Eikermann, *Impaired upper airway integrity by residual neuromuscular blockade: increased airway collapsibility and blunted genioglossus muscle activity in response to negative pharyngeal pressure.* Anesthesiology, 2009. **110**(6): p. 1253-60.
- 5. Eriksson, L.I., *Reduced hypoxic chemosensitivity in partially paralysed man. A new property of muscle relaxants?* Acta Anaesthesiol Scand, 1996. **40**(5): p. 520-3.
- 6. Eriksson, L.I., et al., *Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers.* Anesthesiology, 1997. **87**(5): p. 1035-43.
- 7. Grosse-Sundrup, M., et al., *Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study.* BMJ, 2012. **345**: p. e6329.
- 8. Murphy, G.S., et al., *Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit.* Anesth Analg, 2008. **107**(1): p. 130-7.
- 9. Berg, H., et al., *Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium.* Acta Anaesthesiol Scand, 1997. **41**(9): p. 1095-1103.
- 10. Errando, C.L., et al., *Residual neuromuscular blockade in the postanesthesia care unit: observational cross-sectional study of a multicenter cohort.* Minerva Anestesiol, 2016. **82**(12): p. 1267-1277.
- 11. McLean, D.J., et al., *Dose-dependent Association between Intermediate-acting Neuromuscular-blocking Agents and Postoperative Respiratory Complications.* Anesthesiology, 2015. **122**(6): p. 1201-13.
- 12. Sasaki, N., et al., *Effects of neostigmine reversal of nondepolarizing neuromuscular blocking agents on postoperative respiratory outcomes: a prospective study.* Anesthesiology, 2014. **121**(5): p. 959-68.
- 13. Fernandez-Bustamante, A., et al., *Postoperative Pulmonary Complications, Early Mortality, and Hospital Stay Following Noncardiothoracic Surgery: A Multicenter Study by the Perioperative Research Network Investigators.* JAMA Surg, 2017. **152**(2): p. 157-166.

- 14. Piccioni, F., et al., *An acceleromyographic train-of-four ratio of 1.0 reliably excludes respiratory muscle weakness after major abdominal surgery: a randomized double-blind study.* Can J Anaesth, 2014. **61**(7): p. 641-9.
- 15. Tawfic, Q.A. and G. Bellingham, *Postoperative pain management in patients with chronic kidney disease.* J Anaesthesiol Clin Pharmacol, 2015. **31**(1): p. 6-13.
- 16. Mehta, J.H., et al., *The relationship between minute ventilation and end tidal CO2 in intubated and spontaneously breathing patients undergoing procedural sedation.* PLoS One, 2017. **12**(6): p. e0180187.
- 17. Williams, G.W., 2nd, et al., *A Comparison of Measurements of Change in Respiratory Status in Spontaneously Breathing Volunteers by the ExSpiron Noninvasive Respiratory Volume Monitor Versus the Capnostream Capnometer.* Anesth Analg, 2017. **124**(1): p. 120-126.
- 18. Voscopoulos, C., et al., *A risk stratification algorithm using non-invasive respiratory volume monitoring to improve safety when using post-operative opioids in the PACU.* J Clin Monit Comput, 2017. **31**(2): p. 417-426.
- 19. Gonzalez Castro, L.N., et al., *Quantification of respiratory depression during pre-operative administration of midazolam using a non-invasive respiratory volume monitor.* PLoS One, 2017. **12**(2): p. e0172750.
- 20. Cavalcante, A.N., et al., *Low minute ventilation episodes during anesthesia recovery following intraperitoneal surgery as detected by a non-invasive respiratory volume monitor.* J Clin Monit Comput, 2017.
- 21. Galvagno, S.M., Jr., et al., *Evaluation of respiratory volume monitoring (RVM) to detect respiratory compromise in advance of pulse oximetry and help minimize false desaturation alarms.* J Trauma Acute Care Surg, 2016. **81**(5 Suppl 2 Proceedings of the 2015 Military Health System Research Symposium): p. S162-S170.
- 22. Min, K.C., et al., *Pharmacokinetics of sugammadex in subjects with moderate and severe renal impairment.* Int J Clin Pharmacol Ther, 2017. **55**(9): p. 746-752.
- 23. Staals, L.M., et al., *Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: a pharmacokinetic study.* Br J Anaesth, 2010. **104**(1): p. 31-9.
- 24. Panhuizen, I.F., et al., *Efficacy, safety and pharmacokinetics of sugammadex 4 mg kg-1 for reversal of deep neuromuscular blockade in patients with severe renal impairment.* Br J Anaesth, 2015. **114**(5): p. 777-84.
- 25. Staals, L.M., et al., *Multicentre, parallel-group, comparative trial evaluating the efficacy and safety of sugammadex in patients with end-stage renal failure or normal renal function.* Br J Anaesth, 2008. **101**(4): p. 492-7.
- 26. de Souza, C.M., et al., *Efficacy and safety of sugammadex in the reversal of deep neuromuscular blockade induced by rocuronium in patients with end-stage renal disease: A comparative prospective clinical trial.* Eur J Anaesthesiol, 2015. **32**(10): p. 681-6.
- 27. Illman, H.L., et al., *The duration of residual neuromuscular block after administration of neostigmine or sugammadex at two visible twitches during train-of-four monitoring.* Anesth Analg, 2011. **112**(1): p. 63-8.
- 28. Khuenl-Brady, K.S., et al., *Sugammadex provides faster reversal of vecuronium-induced neuromuscular blockade compared with neostigmine: a multicenter, randomized, controlled trial.* Anesth Analg, 2010. **110**(1): p. 64-73.
- 29. Gaszynski, T., T. Szewczyk, and W. Gaszynski, *Randomized comparison of sugammadex and neostigmine for reversal of rocuronium-induced muscle relaxation in morbidly obese undergoing general anaesthesia.* Br J Anaesth, 2012. **108**(2): p. 236-9.
- 30. Hristovska, A.M., et al., *Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults.* Cochrane Database Syst Rev, 2017. **8**: p. CD012763.
- 31. Kaufhold, N., et al., *Sugammadex and neostigmine dose-finding study for reversal of residual neuromuscular block at a train-of-four ratio of 0.2 (SUNDRO20)dagger.* Br J Anaesth, 2016. **116**(2): p. 233-40.
- 32. Jette, M., K. Sidney, and G. Blumchen, *Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity.* Clin Cardiol, 1990. **13**(8): p. 555-65.

- 33. Aldrete, J.A., *The post-anesthesia recovery score revisited.* J Clin Anesth, 1995. **7**(1): p. 89-91.
- 34. Brull, S.J. and A.F. Kopman, *Current Status of Neuromuscular Reversal and Monitoring: Challenges and Opportunities.* Anesthesiology, 2017. **126**(1): p. 173-190.
- 35. Murphy, G.S., *Neuromuscular Monitoring in the Perioperative Period.* Anesthesia & Analgesia, 2018. **126**(2): p. 464-468.
- 36. Thilen, S.R. and S.M. Bhananker, *Qualitative Neuromuscular Monitoring: How to Optimize the Use of a Peripheral Nerve Stimulator to Reduce the Risk of Residual Neuromuscular Blockade.* Curr Anesthesiol Rep, 2016. **6**: p. 164-169.
- 37. Mehta, J.H., et al., *Assessment of perioperative minute ventilation in obese versus non-obese patients with a non-invasive respiratory volume monitor.* BMC Anesthesiol, 2017. **17**(1): p. 61.
- 38. Voscopoulos, C., et al., *Non-invasive respiratory volume monitoring to detect apnea in post-operative patients: case series.* J Clin Med Res, 2014. **6**(3): p. 209-14.
- 39. Brueckmann, B., et al., *Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study.* Br J Anaesth, 2015. **115**(5): p. 743-51.
- 40. Thiele, R.H., et al., *Standardization of care: impact of an enhanced recovery protocol on length of stay, complications, and direct costs after colorectal surgery.* J Am Coll Surg, 2015. **220**(4): p. 430-43.
- 41. Canet, J., et al., *Prediction of postoperative pulmonary complications in a population-based surgical cohort.* Anesthesiology, 2010. **113**(6): p. 1338-50.
- 42. Cassidy, M.R., et al., *I COUGH: reducing postoperative pulmonary complications with a multidisciplinary patient care program.* JAMA Surg, 2013. **148**(8): p. 740-5.
- 43. ARDS Definition Task Force, T., *Acute Respiratory Distress Syndrome: The Berlin definition.* JAMA: The Journal of the American Medical Association, 2012. **307**(23): p. 2526-2533.
- 44. Clavien, P.A., et al., *The Comprehensive Complication Index (CCI(R)): Added Value and Clinical Perspectives 3 Years "Down the Line".* Ann Surg, 2017. **265**(6): p. 1045-1050.
- 45. Dindo, D., N. Demartines, and P.-A. Clavien, *Classification of Surgical Complications.* Annals of Surgery, 2004. **240**(2): p. 205-213.
- 46. Mallon, D.H., et al., *Defining delayed graft function after renal transplantation: simplest is best.* Transplantation, 2013. **96**(10): p. 885-9.
- 47. Shander, A., et al., *Clinical and economic burden of postoperative pulmonary complications: patient safety summit on definition, risk-reducing interventions, and preventive strategies.* Crit Care Med, 2011. **39**(9): p. 2163-72.
- 48. Lawrence, V.A., et al., *Incidence and hospital stay for cardiac and pulmonary complications after abdominal surgery.* J Gen Intern Med, 1995. **10**(12): p. 671-8.
- 49. Esteves, S., et al., *Incidence of postoperative residual neuromuscular blockade in the postanaesthesia care unit: an observational multicentre study in Portugal.* Eur J Anaesthesiol, 2013. **30**(5): p. 243-9.
- 50. Della Rocca, G., et al., *Reversal of rocuronium induced neuromuscular block with sugammadex or neostigmine: a large observational study.* Acta Anaesthesiol Scand, 2013. **57**(9): p. 1138-45.
- 51. Ledowski, T., et al., *Introduction of sugammadex as standard reversal agent: Impact on the incidence of residual neuromuscular blockade and postoperative patient outcome.* Indian J Anaesth, 2013. **57**(1): p. 46-51.