SMART Trial: Steroid Dosing by bioMARker Guided Titration in Critically Ill Patients With Pneumonia

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Abstract

Pneumonia is the most common cause of acute hypoxemic respiratory failure. The limited and variable use of corticosteroids in critically ill patients with pneumonia is largely due to an inability to identify patients that will benefit from the use of anti-inflammatory medications. Increased levels of pro-inflammatory mediators are a prominent feature of pneumonia and previous studies have tracked the effect of steroids on inflammatory biomarkers or, more recently, used biomarkers (i.e. C Reactive Protein -CRP) to enroll patients in to clinical trials. The objective of this prospective, single-center pilot trial is to compare individualized, biomarker concordant vs usual care in patients with pneumonia and acute hypoxemic respiratory failure identified in the emergency department whose bedside physicians intend to provide adjunctive corticosteroid treatment. These data will be used to assess feasibility, refine the protocol, and calculate the sample size in preparation for a larger pragmatic clinical trial comparing the two strategies.

Research Plan

I. Specific Aims

Specific Aim 1: To assess the feasibility, safety and preliminary efficacy of individualized, biomarker-guided corticosteroid dosing compared to usual care in critically ill patients with community acquired pneumonia and acute hypoxemic respiratory failure. We hypothesize that, compared to usual care; individualized, biomarker-guided corticosteroid dosing will lead to:

- Lower cumulative exposure to corticosteroids
- Lower incidence of adverse events (hyperglycemia, delirium, and nosocomial infections)
- Improvement in pulmonary organ function based on requirements for oxygen and advanced respiratory support
- Reduced hospital length of stay

This pilot study is being conducted to assess the feasibility of recruiting patients and clinician adherence to steroid protocol, to refine the trial intervention and endpoints, and to calculate target sample sizes in preparation for a larger pragmatic clinical trial comparing the two approaches to corticosteroid administration.

Specific Aim 2: To evaluate the trajectories of C-reactive protein (CRP), pulmonary and non-pulmonary organ failures over time in patients from the two study arms.

In addition to assessing the feasibility of individualized, biomarker guided steroid dosing, this pilot study is necessary to evaluate the usefulness of CRP as a predictive enrichment tool in identifying patients in whom steroid administration will be most beneficial and also as a prognostic enrichment tool (alongside severity of pulmonary and other organ failures) to identify patients at higher risk of poor outcomes. It will inform the target population and will help refine the thresholds for initiation, titration and discontinuation of individualized corticosteroid therapy used to reduce inflammation in patients with pneumonia and acute hypoxemic respiratory failure

Specific Aim 3: To evaluate the role of a biomarker-titrated adjuvant corticosteroid administration compared to usual care in patients admitted to hospital with SARS Co-V 2 (COVID-19) infection. We hypothesize that, compared to usual care, individualized biomarker-titrated dosing will be associated with:

a) Improvement in pulmonary organ function based on requirements for oxygen and advanced respiratory support

b) Reduced hospital length of stay
c) Reduced cardiovascular complications including evidence of myocardial injury, need for inotropes and new/worsening arrhythmias

II. Background and Significance

Pneumonia and acute respiratory distress syndrome (ARDS), are common causes of hypoxemic respiratory failure, morbidity and mortality in the intensive care unit (ICU)(1). Although outcomes from these conditions have improved in recent decades, in part due to improved organ support, earlier antimicrobial treatment and the prevention of iatrogenic lung injury from lung-injurious ventilator practices (2), the impact of pneumonia and ARDS on patient outcomes remains substantial. While inflammation is a hallmark pathologic feature of both pneumonia and ARDS, the pharmacological treatment of these conditions with corticosteroids and other anti-inflammatory medications is controversial, and clinical practice remains heterogeneous.

Observational and clinical trial data show almost 50% of patients with acute hypoxemic respiratory failure and ARDS receive steroids (3). Steroid prescribing practices are highly variable due to uncertainty regarding who will benefit, and whether concomitant processes such as chronic obstructive pulmonary disease (COPD) or septic shock are present. While smaller trials suggested possible beneficial effects of corticosteroid use on patient mortality and ventilator use (4) (5), other trials suggested potential adverse effects (6). A meta-analysis of clinical trials of corticosteroids in ARDS did not show benefit, although subgroup analyses suggested there may be benefit in those who received modest doses of corticosteroids early in the disease course (7). Recent SCCM/ESICM guidelines cautiously recommend the use of corticosteroids in community acquired pneumonia and in ARDS (8). A 5−7 days duration at a daily dose of 1 mg/kg IV methylprednisolone equivalent has been recommended for pneumonia while a higher dose and longer duration has been recommended for patients meeting ARDS criteria (2 mg/kg/day IV methylprednisolone equivalent followed by slow tapering over 13 days).

A major barrier to the more precise and informed use of corticosteroids in patients with pneumonia and ARDS is clinicians' inability to rapidly identify patients most likely to benefit from the use of anti-inflammatory medications. Increased levels of pro-inflammatory mediators are a prominent feature in many patients with pneumonia and ARDS, and distinct hyper-inflammatory endophenotypes have been recently described(9). Prior studies have analyzed the effect of steroids on inflammatory biomarkers in ARDS including C-reactive protein (CRP) which is easily available in the clinical setting and can be completed quickly compared to other biomarkers that are difficult to obtain outside research setting.(10, 11) More recently, studies investigating the treatment of pneumonia have utilized CRP to enrich a population that may benefit from corticosteroids. (12) This enrichment strategy suggested that patients with a high

inflammatory response (pneumonia with an admitting CRP > 150 mg/L) may benefit from modest dose corticosteroid administration. While the clinical practice guidelines specifically state that lower respiratory infections are characterized by persistent systemic inflammation(13) they recommend arbitrary dosing regimens irrespective of the degree of inflammation(8).

Our objective is to better understand the role of steroids in pneumonia and ARDS, and to test the hypothesis that a precise, individualized steroid dosing algorithm will be more effective and safer than standard treatment recommended by controversial expert guidelines(8). Therefore we propose a pilot, prospective, single-center clinical trial to compare a biomarker-driven individualized dosing algorithm to a guideline-based fixed-dose algorithm in emergency room patients with pneumonia and acute hypoxemic respiratory failure whose bedside physicians intend to provide adjunctive corticosteroid treatment.

In response to the emerging COVID-19 (SARS Co-V 2) pandemic, we additionally propose evaluating the role of biomarker-titrated adjuvant corticosteroid dosing in patients with COVID-19. Limited data exists regarding the role of corticosteroids in this setting, and no biomarker-titrated steroid administration has been studied. In a report of 149 patients with COVID-19 in China, 82 had elevated CRP[14]. However, just 5 patients received corticosteroids in this cohort. In a larger cohort of 1099 patients with COVID-19 in Wuhan, China, 204 patients received steroids, with a higher percentage among those with severe disease than non-severe disease (44.5% vs. 13.7%)[15]. Relative survival of those who received steroids versus those who did not was not reported. In another series of 52 patients with severe COVID-19 infection in China, corticosteroids were administered in 30 patients (58%)[16]. Survivors were more likely to receive steroids compared to non-survivors (70% versus 50%).

Furthermore, there is mounting evidence of cardiovascular complications of SARS-CoV-2 infection including acute myocardial injury, shock and arrhythmias associated with worse outcomes[17]. Potential mechanisms of these complications in SARS-CoV-2 infection include exaggerated systemic inflammatory responses, cor pulmonale due to respiratory failure and direct myocardial toxicity/myocarditis thus rational therapeutic options should include anti-inflammatory agents like corticosteroids, antiviral agents, and management of respiratory failure.

Given the limited evidence of adjuvant steroid dosing in this setting, and the absence of any proven treatments for COVID-19, there is an urgent need to evaluate any potential therapies.

III. Progress Report and Preliminary Studies

We performed a retrospective review of patients admitted to the intensive care unit (ICU) at Mayo Clinic, Rochester with pneumonia and acute hypoxemic respiratory failure. In this group, we described current corticosteroid prescribing practices, and compared the efficacy and safety of steroid administration that is biomarker concordant (i.e. patients with a markedly elevated

CRP/procalcitonin who were treated with steroids or patients with a low CRP/procalcitonin who were not treated with corticosteroids), versus treatment that was biomarker-discordant. The threshold for an elevated CRP was 150mg/L and the threshold for an elevated procalcitonin was 2.2ng/ml. After adjusting for severity of illness, early (within 12 hours of ICU admission) steroid administration in patients with pneumonia or ARDS was associated with decreased persistence or progression of pulmonary and other organ failures, reduced hospital and ICU length of stay and decreased hospital mortality(table 1). Patients with biomarker-concordant and biomarker-discordant corticosteroid treatment had similar baseline severity of illness. Biomarker-concordant corticosteroid treatment was associated with faster recovery of hypoxemia (table 2). No significant differences in mortality or hospital/ICU length of stay were seen between the biomarker-concordant versus the biomarker discordant group.

Table1. Impact of early corticosteroid use on outcomes in ICU patients with pneumonia and ARDS

	Steroids ≤ 12h after ICU admission (N=1047)	**Steroids > 12h after ICU admission(N=567)**	**P value**
SOFA Day 1	5 (3-8)	6 (4-8)	0.006
SOFA Day 2	4 (2-6)	5 (3-8)	<0.001
SOFA Day 3	4 (2-7)	5 (3-8)	0.009
PaO_2/FiO_2 at ICU admission	173 (117-250)	161 (108-240)	0.16
PaO_2/FiO_2 after 24h	196 (143-265)	183 (122-255)	0.03
PaO_2/FiO_2 after 48h	209 (145-284)	191 (129-255)	0.03
ICU length of stay	1.98 (1.07-4.0)	3.69 (1.95-7.24)	<0.001
Hospital Length of stay	7.57 (4.55-14.07)	10.4 (6.08-20.8)	<0.001
ICU Mortality	102 (9.7%)	69 (12.2%)	0.15
Hospital Mortality	188 (17.9%)	132 (23.3%)	0.01

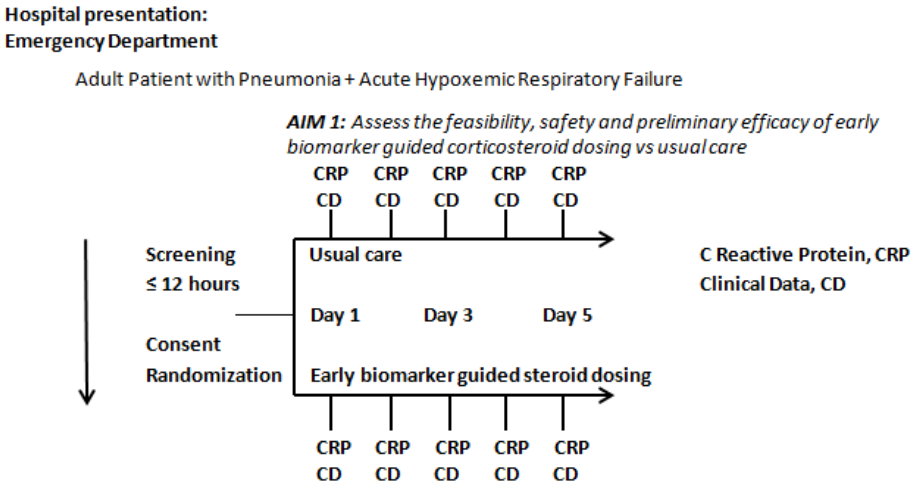
Table 2: **Impact of steroid use that was concordant versus discordant with markers of inflammation on outcomes in critically ill patients with pneumonia**

	Biomarker Concordant (N=130)	**Biomarker Discordant(N=114)**	**P value**
FIO_2 at ICU admission	40 (30, 60)	40 (30, 60)	0.47
FIO_2 Day 2	35 (28, 50)	40 (31, 50)	0.07
FIO_2 Day 3	31 (21, 40)	37 (29, 50)	0.004
FIO_2 Day 4	28.0 (21.0, 37.5)	35 (28, 50)	<.001
FIO_2 Day 5	28 (21, 36)	28 (24, 45)	0.03
ICU free days (Median estimate (95%CI)	1.97 (-0.50, 4.45)	0.00 (Ref)	0.12
Hospital free days (Median estimate (95%CI)	1.79 (-0.98, 4.57)	0.00 (Ref)	0.21
ICU Mortality (Hazard Ratio with 95% CI)	0.93 (0.31, 2.74)	1.00 (Ref)	0.89
Hospital Mortality (Hazard Ratio with 95% CI)	0.75 (0.36, 1.59)	1.00 (Ref)	0.45
Delirium	36 (27.7%)	34 (29.8%)	0.71
Hyperglycemia	30 (23.8%)	26 (23.4%)	0.94

Team experience: Dr. Hemang Yadav is an Assistant Professor and Senior Associate Consultant in the Division of Pulmonary and Critical Care at the Mayo Clinic. He has expertise in ARDS epidemiology research and the incorporation of biomarkers in ARDS risk prediction. Dr. Yewande Odeyemi is a clinical fellow in Critical Care at Mayo Clinic, Rochester with an interest in critical care outcomes research. Dr. Herasevich is a research trainee at Mayo Clinic, Rochester also with an interest in critical care outcomes research. Dr. Erin Barreto is an assistant professor and clinical pharmacist at Mayo Clinic, Rochester with an interest in individualizing pharmacotherapy for critically ill patients with infections. Dr. Gajic is an internationally renowned leader in ARDS research and founder of our multidisciplinary clinical research laboratory (METRIC), and Director of Critical Care Research at Mayo. Within this group, we have adequate resources, expertise and training to achieve our scientific objectives.

IV. Research Design and Methods

Figure 1 summarizes study design. A two-arm multicenter randomized trial



A. Study Design or Overview

Specific Aims 1 and 3: We plan to perform a two arm multi-center pilot phase II clinical trial. 44 patients with pneumonia (additional strata to include patients with COVID-19 for specific aim 3) and acute respiratory failure defined by $SpO_2/FiO_2 < 315$ ($SpO_2 < 90\%$ on room air or $< 97\%$ on 2L/min O_2) will be included.

- Control arm: Usual care
- Intervention arm: individualized, biomarker concordant steroid use: dosing, titration and duration according to CRP level (Table 3).

Table 3. Biomarker-concordant steroid treatment

CRP (mmol/L)	Methylprednisolone (daily)
<50	None
51 - 100	0.5 mg/kg
101 - 150	0.75 mg/kg
151 - 200	1 mg/kg
>200	1.5 mg/kg
	*per ideal body weight

Randomization will be stratified based on the need for high flow nasal cannula oxygen, noninvasive or invasive ventilator support.

Definitions

Pneumonia is defined as an acute infection of the lung parenchyma that is associated with clinical symptoms of community acquired pneumonia (cough, fever, pleuritic chest pain, and dyspnea) and a new radiographic infiltrate(18). ARDS complicating community acquired pneumonia will be defined in accordance with the Berlin Definition as acute respiratory failure with a PaO_2/FiO_2 ratio < 300 and the need for positive end expiratory pressure > 5 mmHg and bilateral pulmonary infiltrates within 1 week of the diagnosis of community organized pneumonia (19).

Suspected COVID-19 defined as anyone in whom COVID-19 testing is requested

Confirmed COVID-19 is defined as a patient with positive COVID-19 PCR on either nasopharyngeal swab or microbiological testing from lower respiratory sample sites (e.g. tracheal secretions, bronchial washings, bronchoalveolar lavage).

Participating sites

Mayo Clinic Rochester, Minnesota

Mayo Clinic Health System, Mankato, Minnesota

B. Study Subjects

Inclusion criteria: Patients with pneumonia and acute respiratory failure defined by SpO_2/FiO_2 < 315 (SpO_2 < 90% on room air or < 97% on 2L/minute O_2).

Exclusion criteria:

- Contraindications or unwilling to use steroids by patient or provider
- Refractory septic shock(20)defined as a requirement of norepinephrine dose or equivalent above >0.1 mcg/kg min or 2 or more vasopressors
- Pre-admission chronic use of steroids or other immunosuppressive medications
- Recent or past history of bone marrow or solid organ transplantation
- Adrenal insufficiency, as noted in the problem list/medical history
- Comfort care
- Hospital admission in the previous 30 days for severe community acquired pneumonia patients

- Leukopenia <1000/mm or neutropenia <500/mm (except if attributable to pneumonia) and HIV positive with a CD4 count <100
- Suspected flare of Interstitial lung disease (infectious and non-infectious)
- Positive influenza testing or high suspicion for influenza

Protocol: Patients who meet inclusion criteria will be randomized into usual care or the individualized biomarker-concordant arm. Patients will be eligible for inclusion if they have received an initial dose of steroids by the primary service. In this situation they would either be randomized to usual care (continued steroid administration at discretion of primary service) or the individualized CRP-guided protocol outlined in Table 3.

In the individualized, biomarker-concordant arm, all patients will receive steroids once at the time of admission, then a daily morning dose In order to account for varying turnaround time at different laboratories, CRP levels will be drawn with early morning labs, and used to determine the steroid dosing for the day. Patients will receive daily CRP measurements for the first 5 days of the hospitalization, or until hospital discharge. Steroid administration will be facilitated using standardized computerized physician order entry. Steroid order sets will include 6 hourly point of care glucose monitoring, and an insulin sliding scale for glucose levels to facilitate glucose management. The need for insulin drip will be determined by the treating physician. Additional testing including serum and urine ketones will be informed by the glucose level, serum anion gap and bicarbonate levels in routine basic metabolic panels and determined by the treating physician. Glucose levels, new or worsening infections within 30 days of start of steroid (positive blood/sputum/urine culture) and Confusion Assessment Method in the ICU will be documented in case report forms.

In the usual care arm, patients will receive daily CRP measurements for the first 5 days of the hospitalization, or until hospital discharge. However, these CRP measurements will not be accessible to the treating physicians.

An oxygen titration protocol will be utilized to standardize oxygen weaning in both arms (please see appendix).

Daily Troponin measurements will be added in both arms

Primary outcomes:

- Feasibility: a percentage of eligible patients adhered to the timely initiation and daily treatment according to ESICM/SCCM clinical practice guideline (control group) or biomarker concordance (intervention group)

Secondary outcomes

- Death
- Progression of disease as defined by the need for high flow nasal cannula oxygen, noninvasive or invasive ventilation. Given the proliferation of high flow nasal cannula oxygen use in lieu of mechanical ventilation, instead of ventilator-free days we opt for

using advanced respiratory support free days where “advanced respiratory support” includes both invasive and noninvasive mechanical ventilation and the high flow nasal cannula oxygen.

- Evolution of respiratory and other organ failures measured by SOFA at time of ICU admission, after 24 hours, after 48 hours and after 72 hours and by the organ failure free days. In the absence of daily arterial blood gas analysis, for respiratory component of SOFA, PaO2/FiO2 ratio will be replaced by SpO2/FiO2 ratio

- Need and duration of vasopressors and inotropes use (based on cardiovascular SOFA sub-score)
- New onset/worsening arrhythmias
- Evidence of myocardial injury determined by daily troponin peak and/or new diagnosis of LV dysfunction (LVEF <40%) or new diagnosis of cor pulmonale (≥moderate RV dysfunction)
- Re-hospitalization for a primary cardiovascular diagnosis within 30 days

- Side effects of steroid (Safety) including

    - Hyperglycemia and its complications- Diabetic ketoacidosis (DKA) and Hyperosmolar hyperglycemic syndrome (HHS), the need for insulin

    - Delirium (measured by CAM-ICU) and

    - New infections in patients with pneumonia and/or ARDS

- Length of ICU and hospital stay

- Time to discontinue oxygen or return to baseline oxygen use

- Requirement and duration of non-invasive and invasive mechanical ventilation

- ICU, and 30, 60 and 90-day mortality

- Discharge, 30, 60, and 90-day disposition (home vs other)

C. Sample Size and Power: In this pilot study, we do not have the power to test the efficacy of the intervention on patient-centered outcomes. However, this pilot data will provide us with potential effect size data necessary for sample size determination for the future phase II/III study.

D. Data Collection: Case Report Forms will be completed by research coordinators and entered in a REDCap database.

E. Data Handling:

-Protected health information will be preserved by having patient data be de-identified and given a study number.
-This data will be recorded using REDCap and JMP. Any written data will be stored in storage files in a locked access building.
-Data will only be accessible to investigators/participating personnel.
-The computers where the data will be stored meet strict security requirements imposed by Mayo Clinic.
-No data containing PHI will be transported on data sticks or laptops without being encrypted or
password protected.
-No hardcopy information containing PHI will be transported/removed from the Mayo campus.
-Any hard copies of archival source documentation will be stored in a locked, secure location only
accessible to the study personnel.
-No data will be disclosed to another institution and all identifiers linking to the patient will be destroyed after data collection is complete.

f. Data Analysis

Aims 1and 3: Continuous outcomes will be compared between treatment arms using linear regression and binary outcomes using chi-square or fishers exact tests. Secondary outcomes will be tested without adjustment for multiple comparisons. Data from this study, including estimated effects of the intervention and sample variation in outcomes, will provide valuable information to plan a well-powered subsequent phase II trial.

Aim 2: The correlation between CRP levels and corticosteroid dosing in those who receive individual-dose steroids versus usual care will be examined using Pearson's correlation coefficient. The effect of CRP levels on the secondary outcomes will be evaluated using multivariable analysis adjusting for severity of illness. The data from this study will help evaluate the usefulness of CRP as a predictive and prognostic enrichment tool and thus help inform and refine the thresholds for initiation, titration and discontinuation of corticosteroids in the subsequent larger study.

Decision to proceed with a larger study: The decision to proceed with a phase II/III study will be based on the following criteria:

- Ability to enroll an adequate number of eligible patients early in the course of illness. The expected hurdles include delayed identification of potentially eligible patients, provider/patient refusal, non-adherence to protocol, and inability to obtain CRP levels in a timely manner.

- Safety; i.e. absence of significant adverse events.

- Preliminary efficacy: ability to show reduction in steroid use, reduced episodes of hyperglycemia and favorable trajectory of pulmonary organ dysfunction.

The data collected will be essential to adequately plan the future study, estimate power and sample size, refine exclusion/inclusion criteria and determine the number and characteristics of future study sites.

g. Feasibility and Time Frame:
We believe that our project is feasible in the time frame of the grant; we hope to use the preliminary data generated from this pilot study to decide about moving forward with a phase II/III study involving a larger study group and more centers (Table 5).

h. Strengths – This is a well-designed pilot study to examine the feasibility of this approach. Data from this study, including estimated effects of the intervention and sample variation in outcomes, will provide valuable information to plan a well-powered subsequent phase II/III trial.

i. Limitation – Subject enrollment is dependent on availability of research coordinators, therefore we aim to enroll 44 patients within a 2 year period. Randomization by stratification might limit wide generalizability and feasibility if a high proportion of subjects with chronic obstructive lung disease are enrolled. We also acknowledge the fact that the lack of blinding of treating attending physicians and physicians in training is a strong limitation in our study.

V. Human Subjects

Informed consent: All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study.

The risk profile would justify deferred consent for those who are unable to give consent and have no legally authorized representative available within the short timeframe.

Our inclusion and exclusion criteria have been carefully selected to maximize potential benefit and minimize risk to study subjects.

For suspected/confirmed COVID-19 subjects: Due to the high infectivity of COVID-19, and the strict need to minimize contact between suspected COVID-19 patients and study staff, we propose consent be obtained verbally via telephone or via video.

Patients would still receive a copy of the consent form describing the study. This would be given to the patient by the room nurse to be coordinated with other routine cares.

For all other subjects: The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

Potential risks:. We will include a detailed description of potential risks and benefits of corticosteroid administration while obtaining patient consent.

All the tests and procedures that will be included in the study are consistent with standard clinical care; there will no extra costs to the subjects who consent to study participation. CRP would be taken during routine daily lab draws; there may be one additional blood draw on the day of consent. All clinical assessments will be done through EMR.

Potential benefits: The potential benefits include the importance of the knowledge to be gained from this study with the possibility of reduced adverse side effects of steroids associated with a lower dosing and shorter duration in the individualized arm.

VI. Gender/Minority Mix

This study will include minority patients and both gender.

VII. References:

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Appendix 1

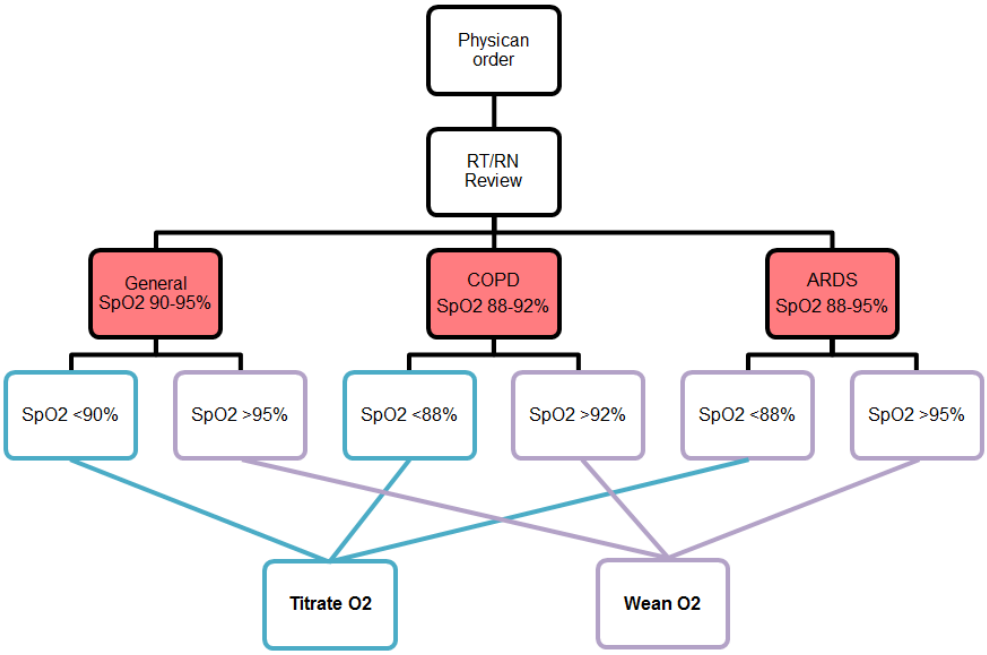
Oxygen Titration Protocol

- Consult the patient specific SpO2 targets (per diagnosis category)
- SPO2 target range 90-95%
  - COPD in exacerbation: SPO2 preferred target 88-92%
  - ARDS: SPO2 preferred target 88-95%
- Decision support tool should be utilized in stabilized patients only
- Assess for titration minimally every 60 mins (with vital sign assessments)
- Overall goal: Discontinue oxygen or wean to baseline need (NC, CPAP)

	SpO2	NC, NP, SFM	CPAP/BPAP	High flow NC	Invasive mechanical ventilation
Hyperoxia	SpO2>95% COPD SpO2>92%	Reduce flow rate by 1 L/min or if SpO2>98% reduce by 2 L/min	ł Reduce FiO2 by 0.1	Reduce FiO2 by 0.1	Reduce FiO2 by 0.1 Follow ARDSnet PEEP/FiO2
Target Range	SpO2 90-95% COPD SpO2 88-92% ARDS SpO2 88-95%	No Change	No Change	No Change	No Change
Hypoxia	SpO2<88%	Titrate per order	Titrate per order	Titrate per order	Titrate per order

NC: Nasal Cannula, NP: Nasal Pendant, SFM: Simple face mask, Severe COPD: GOLD III or IV, ARDS: Acute Respiratory Distress Syndrome.

ł After FiO2 <0.4. Decrease EPAP/CPAP per RT, (Minimum EPAP/CPAP 5 cm H20)


Physican order
RT/RN Review
General SpO2 90-95%
COPD SpO2 88-92%
ARDS SpO2 88-95%
SpO2 <90%
SpO2 >95%
SpO2 <88%
SpO2 >92%
SpO2 <88%
SpO2 >95%
Titrate O2
Wean O2