VIRTUAL

ART SLUTSKY RESEARCH DAY

Interdepartmental Division of Critical Care Medicine
University of Toronto

ABSTRACT BOOKLET

Tuesday June 22, 2021
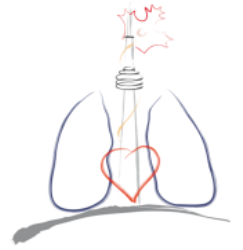
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Basic Science Abstracts

BRACHIAL PLEXUS PALSY COMPLICATING PRONE POSITIONING: DEVELOPING A METHOD TO STUDY FAPS MOLECULAR REGULATION OF MUSCLE FIBROSIS FOLLOWING DENERVATION INJURY IN THE RAT

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Introduction and Objective:

Increased incidence of brachial plexus injury and subsequent complete palsies have been reported in mechanically ventilated patients with SARS-Cov-2 following prone positioning due to sustained abnormal positioning of the arm and shoulder[1]. Muscle denervation results in immediate loss of function, muscle atrophy and progressive fibrosis over time. If re-innervation occurs in the short term, muscle function and mass are fully recoverable due to muscle's robust capacity for regeneration and self-repair. If re-innervation is delayed, regeneration/repair is exhausted and muscle fibroses due to the influx of fibro-adipogenic progenitor cells (FAPs). Initially FAPs mediate muscle repair by supporting the activation of muscle satellite (progenitor) cells (MPs), but with sustained denervation FAPs switch to a pathogenic phenotype and induce endstage fibro-fatty degradation of muscle. Peripheral nerves regenerate 1-2 mm/day; with brachial plexus injury by the time the nerve regrows to its target muscles (e.g. hand), muscles restorative potential is lost and the muscle is non-functional. There is no therapy that can fully prevent, or treat, long term denervation muscle injury. Brachial plexus injury induced by trauma (e.g. heavy industry and motor vehicle accidents, obstetrical brachial plexus palsy) is common and results in significant morbidity and economic consequences.

The molecular mechanism regulating the phenotypic change in FAPs from pro-regenerative to pathogenic is not completely understood. To date mechanistic study of FAPs has been undertaken solely in mouse models of denervation injury using flow cytometry/FACS, and is significantly curtailed by the severe atrophy and thereby inadequate volume of long-term denervated muscle tissue for downstream assays. Use of the rat provides larger volume of muscle for study and superior, validated methods to assess muscle strength and physical function in the awake animal, in contrast to mice. We aimed to develop a method for isolation of FAPs from the rat to enable the study of the molecular regulation of FAPs in long-term denervated muscle.

Methods:

We developed a novel flow cytometry/FACs antibody panel to identify and isolate both FAPs and MPs populations in rat muscle, using a unique panel of antibodies comprised of CD31/CD45 (endothelial and hematopoietic markers respectively), VCAM (myogenic progenitors [MPs] marker) and Sca-1 (FAPs marker). Purported pure FAPs and MPs populations were verified by i) immunostaining of FACS freshly-sorted cells with alternative markers (PDGFRα for FAPs and Pax7 for MPs) and ii) by in vitro culture and differentiation of sorted cells into myotubes, adipocytes and fibroblasts. The validated flow cytometry/FACS antibody panel was used to evaluate the dynamics and phenotype of the FAPs population in short-term and long-term denervated gastrocnemius muscle using the tibial nerve transection model in the rat.

Results:

Application of the novel flow cytometry antibody staining panel and gating strategy effectively isolated rat FAPs (CD31-/CD45-/Sca-1+/VCAM-1-) and MPs (CD31-/CD45-/Sca-1-/VCAM-1+) populations. Validation of the specificity and purity of the population sorts was confirmed by demonstrating i) sole immunostaining of freshly sorted FAPs with secondary marker PDGFRα, and MPs sole staining with secondary marker Pax7, ii) in vitro differentiation of FAPs into fibroblasts or adipocytes with an absence of myotubes and iii) in vitro differentiation of MPs into mature myotubes in the absence of fibroblasts and adipocytes. We next serially assessed the dynamics of FAPs and MPs in the gastrocnemius muscle over a 14-week time course post tibial nerve transection. We demonstrated a changing FAPs phenotype with long term denervation that correlated with the onset of irreversible fibrosis. Initially (2 weeks post denervation), low Sca-1 expressing FAPs dominate during the period of reversible denervation injury. Long term denervation (14 weeks) showed a significant shift to a population of high Sca-1 expression FAPs (from 5% at 2 weeks, to 51% at 14 weeks), suggesting that Sca-1 can delineate a population of FAPs that induce fibrogenesis.

Conclusions:

After successfully developing and validating a novel flow cytometric method for FAPs identification and isolation in rat muscle, we demonstrate a changing FAPs phenotype over time with low and high Sca-1 expressing populations that directly correlated with the transition of denervated muscle to irreversible fibro-fatty degradation. This novel finding paves the way for future

mechanistic studies delineating the biologic relevance of these two FAPs populations, and determining targets for pharmacologic management of muscle denervation injury.

Reference:

1) Miller C, O'Sullivan J, Jeffrey J, Power D. Brachial Plexus Neuropathies During the COVID-19 Pandemic: A Retrospective Case Series of 15 Patients in Critical Care. Physical Therapy. 2020;101(1).

PERIPHERAL BLOOD MICRORNA EXPRESSION IS DEREGULATED IN CRITICALLY ILL COVID-19 PATIENTS

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Introduction and objective:
Coronavirus disease 2019 (COVID-19) has accounted for more than 153 million confirmed cases worldwide and more than 3 million deaths. To date, there is no reliable scoring system or bedside test to aid a clinician in prognosticating whether a patient with COVID-19 will require admission to the Intensive Care Unit (ICU) during the course of their illness. Identifying novel biomarkers in COVID-19 could contribute to the development of prognostic models for patient risk stratification. Blood transcriptomics has emerged in the last decade as a rich source of biomarker discovery with applications in various fields such as sepsis and cancer. The circulating non-coding transcriptome, including microRNAs (miRNAs), has provided beneficial information on disease diagnostics and prognostication, with potential for therapeutic intervention that has reached clinical trials. In the current analysis, the peripheral blood miRNAome was assessed in patients critically ill due to COVID-19 and compared to patients with non-COVID-19 critical illness. We hypothesized that there would be differential expression of certain miRNAs, and that specific miRNA signatures would help differentiate patients according to their disease status and prognosticate outcomes.

Methods:
This project is part of the COLOBILI study (COVID-19 Longitudinal Biomarkers in Lung Injury) being conducted at St Michael's Hospital. Research ethics board approval was obtained for the collection of peripheral blood of critically ill patients with confirmed COVID-19 and control patients with non-COVID-19 critical illness. Detailed clinical data continue to be recorded, which include demographics, severity scores, laboratory markers and outcome measures. For the current analysis, the blood of 24 patients (12 COVID positive and 12 COVID negative) was collected in PAXgene RNA tubes within 48 hours of admission to ICU. Total RNA including miRNAs was extracted using a commercial kit as per manufacturer's protocol. MiRNA expression was analyzed with Nanostring technology using 100ng of total RNA as input for the nCounter human v3 miRNA expression panel. Data was analyzed by ROSALIND® (https://rosalind.onramp.bio/) according to manufacturer instructions. Normalization, fold changes and p-values were calculated using criteria provided by Nanostring.

Results:
MiRNA expression analysis from whole blood of patients with COVID-19 using Nanostring technology was successful from a technical standpoint. 63 miRNAs had a significant (p value < 0.05) differential expression between COVID-19 positive and COVID-19 negative patients. Seven miRNAs were upregulated and 56 were downregulated. The top ten most significantly deregulated miRNAs included: miR-563, miR-340-5p, miR-1285-3p, miR-891A-5p, miR-887-5p, miR-942-5p, miR-3614-5p miR-545-3p, miR-5001-5p and miR-369-3p. Hierarchal clustering analysis using the 63 differentially expressed miRNAs was largely successful in segregating samples appropriately according to their COVID-19 status (positive versus negative).

Conclusion:
The analysis of miRNA expression from the peripheral blood of patients with COVID-19 is feasible. Furthermore, the whole blood miRNAome of patients in the ICU differs according to their COVID-19 status, with particular significant deregulation of 63 miRNAs. One miRNA in particular – miR-340-5p – has been similarly identified as downregulated in the blood of individuals with COVID-19 in the one study published on this topic. The results of our work thus far support the hypothesis that miRNAs are differentially expressed in the blood of patients with COVID-19 and may serve as biomarkers. Further analysis of our data will help to identify if miRNA signatures relate to patient outcomes so as to assess their feasibility as tools for prognostication. The biological value of our work will be verified in a separate validation cohort (samples already collected).

IDENTIFICATION OF NOVEL MICRORNAS REGULATING SKELETAL MUSCLE REGENERATION IN SUSTAINED INTENSIVE CARE UNIT ACQUIRED WEAKNESS

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Introduction/Objectives: Intensive care unit acquired weakness (ICUAW) is a complication of critical illness characterized by skeletal muscle wasting and impaired contractile function that may persist for years after ICU discharge, resulting in physical disability. Satellite cell loss and dysregulation of gene co-expression networks that control muscle repair and regeneration are present in critical illness survivors with persistent muscle wasting and weakness. MicroRNA (miRs) regulate gene expression, at the post-transcriptional level by affecting the translation or degradation of messenger RNA (mRNA). We sought to identify miRs that regulate the failure of muscle regeneration in critical illness survivors with sustained ICUAW.

Methods: From a cohort of critically ill patients (n=14), skeletal muscle strength, mass, and physical function were measured and whole-transcriptome miR and mRNA expression was determined in quadriceps muscle biopsies at Day 7 and Month 6 post-ICU discharge. We then conducted an integrated miR-mRNA analysis to identify dysregulated miR/gene pairs that were robustly correlated with sustained muscle wasting in ICUAW and evaluated their impact on myoblast proliferation and differentiation *in vitro*. The highest ranking, differentially expressed, miRs identified in our miRNA/mRNA analysis were selected for *in vitro* study. Candidate miRs were overexpressed and inhibited in AB1167 human myoblasts and their influence on myoblast proliferation and differentiation were subsequently determined by quantification of cell counts, Ki67 nuclear localization, and expression of proliferating cell nuclear antigen and myosin heavy chain.

Results: At 6 months post-ICU discharge, a fourteen-miR expression signature distinguished patients with a significant increase in muscle mass from those with sustained atrophy. miRs-490-3p and 744-5p, both increased in patients whose quadriceps size normalized (post-ICU discharge) to healthy individuals, were each found to regulate up to 4% of the muscle transcriptome. miR-490-3p overexpression significantly reduced AB1167 myoblast proliferation, and induced contact independent myoblast differentiation to mature myotubes. miR-744-5p overexpression attenuated myoblast differentiation.

Conclusion: MicroRNA profiling identified key miRs involved in the regulation of muscle weakness at Day 7 and in the recovery of muscle mass at 6M post-ICU discharge. We identified miR-490-3p and 744-5p as novel regulators of myoblast proliferation and differentiation, which may play a causative role in the pathogenesis of sustained ICUAW.

A CRISPR-CAS13D STRATEGY TO INTERRUPTING SARS-COV-2 VIRAL GENOME IN LUNG ORGANOIDS

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Introduction and Objectives: Novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to challenge global health, despite extensive vaccination strategies and advanced coronavirus therapeutics evaluation. While many traditional treatment options to prevent SARS-CoV-2 viral infection are focused on facilitating human immune system to recognize viral key checkpoints in SARS-CoV-2 life cycle, other therapeutic strategies such as Clustered Regulatory Interspaced Short Palindromic Repeats (CRISPR) technology are seen as powerful tool for direct viral genome interruption independently from the human immune system. One of those strategies is CRISPR-Cas13d-based strategy named PAC-MAN (Prophylactic Antiviral CRISPR in human cells) that aims to target and cleave SARS-CoV-2 RNA-dependent RNA polymerase (RdRP) and nucleocapsid (N) genes which are found in highly conserved regions in the coronaviruses' viral genome.

We tested the hypothesis that PAC-MAN approach can attenuate SARS-CoV-2 infection by cleaving the viral genome and thus inhibiting replication in human induced pluripotent stem cell (iPSC)-derived lung organoids.

Methods: Human lung organoids were generated from iPSCs according to a stepwise directed differentiation protocol. PAC-MAN system was delivered to lung organoids by lentiviral particles pool containing both Cas13d-FLAG and different validated guide RNA sequencing targeting SARS-CoV-2 nucleocapsid and RdRp genes or non-specific guide RNAs as control. Control and PAC-MAN transduced lung organoids were then infected with SARS-CoV-2 virus. Cytopathic effects of lung organoids were determined evaluated, viral titers were assessed by 50% tissue culture infective dose (TCID50) assay and SARS-CoV-2 envelope gene expression by RT-qPCR and nucleocapsid protein expression using western blot and immunostaining.

Results: The lung organoids transduced with PAC-MAN exhibited lower cytopathic effects defined as less cell shedding and higher cell density compared to the control lung organoids in response to SARS-CoV-2 infection. Viral titers were reduced by 95% (P<0.04) and nucleocapsid protein expression decreased by 73.3% (p<0.005) in the e lung organoids transduced with PAC-MAN as compared to the control organoids after 72 hours of SARS-CoV-2 infection

Conclusion: PAC-MAN can effectively target and cleave RNA sequences of SARS-CoV-2 genome, thus inhibiting SARS-CoV-2 viral replication and infectivity.

DEVELOPMENT OF A NOVEL ANTI-INFLAMMATORY DRUG USING PHENOTYPIC SCREENS IN INFLUENZA-INFECTED ZEBRAFISH: VALIDATION IN MICE AND HUMAN TISSUES

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Introduction and objective: Excessive inflammation contributes to tissue injury in numerous acute illnesses including acute respiratory distress syndrome (ARDS) and ischemia-reperfusion after trauma. Although ARDS is commonly initiated by infection with a viral or bacterial pathogen, treatment with antiviral drugs (e.g. Remdesivir) or antibiotics is often unable to improve mortality. This paradox has been attributed to excessive endothelial and innate immune cell activation during infection, resulting in excessive recruitment of leukocytes, overproduction of pro-inflammatory cytokines and the development of lung and systemic endothelial leakage and multi-organ dysfunction. This suggests that treating these patients with compounds that moderate the aberrant host response could improve outcomes of ARDS and other inflammatory diseases.

Zebrafish are tiny vertebrate organisms that are easy and inexpensive to breed in large numbers. It has previously been shown that the human influenza virus can productively infect larval zebrafish, resulting in fish edema and death. We reasoned that a phenotypic screen of chemical libraries using flu-infected zebrafish could identify promising lead compounds with anti-inflammatory properties.

Methods: Using influenza-infected larval zebrafish, we screened chemical libraries for compounds that reduced virus-induced edema and prolonged fish survival. A promising compound (Drug X) was identified and further tested in a lethal mouse model of human influenza-induced lung injury. Drug X was also evaluated in mouse models of gram negative (*E. Coli*) pneumonia and of ischemia-reperfusion-induced liver injury. The effect of the compound on influenza virus replication as well as on endothelial cell and macrophage activation was determined. RNASeq and ingenuity pathway analysis were used to identify the genetic pathways regulated by Drug X. This was combined with *in silico* protein binding analysis (Ligand Express, Cyclica) to identify the likely molecular target of the compound; this was then confirmed *in vitro* using siRNA knockdown. Finally, knockout mice were used to confirm the importance of the target pathway *in vivo*. Chemical derivatives of Drug X (based on ease of synthesis and better drug-like characteristics) were then designed and evaluated *in vitro* and *in vivo*.

Results: Drug X reduced edema and improved survival of influenza-infected zebrafish; it also improved survival in mice infected with a lethal dose of influenza. Drug X had no antiviral activity, suggesting it acts to improve the host response. Drug X also improved oxygen saturation in mice infected intratracheally with *E. Coli;* it also reduced liver damage in a mouse model of hemorrhagic shock resuscitation (ischemia-reperfusion). Pathway analysis using data from RNASeq in influenza-infected lung endothelial cells revealed induction by Drug X of the Nrf2 antioxidant pathway. By qPCR and Western blotting in endothelial cells and macrophages, we confirmed that Drug X also rapidly induced the loss of Keap1, the natural repressor of Nrf2. This was accompanied by an increase in Nrf2 levels and the induction of Nrf2 anti-inflammatory and anti-oxidant target genes such as HO-1. Knock down of Keap1 by siRNA greatly reduced the effects of the drug. Consistent with the cellular data, NRF2-deficient mice with lung injury or liver injury were not protected by Drug X. A novel derivative of Drug X induced cellular loss of Keap1, induction of Nrf2 and significantly improved the oxygen saturation of *E. Coli*-infected mice.

Conclusion: We have identified a novel anti-inflammatory compound that acts by inducing the Nrf2 pathway. Drug X and its derivatives may be useful for the treatment of acute inflammation from both infectious and non-infectious stimuli. Potential applications include ARDS, ischemia reperfusion, and other acute inflammatory conditions like sepsis.

NEBULIZATION OF SOLUBLE HUMAN ACE2 ATTENUATED SARS-COV-2 INFECTION IN HUMANIZED MICE

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*JL and YO contributed equally to the work.

Introduction and objectives: Angiotensin converting enzyme 2 (ACE2) is expressed primarily on alveolar epithelial cell membrane and acts as an essential SARS-CoV-2 receptor for viral entry by binding the viral spike protein, leading to severe lung injury and COVID-19. We hve previously shown that SARS-CoV-2 can directly infect engineered human blood vessel organoids and human kidney organoids, which can be inhibited by soluble human ACE2 (shACE2). We thus hypothesized that excessive srhACE2 competitively binds with SARS-CoV-2 not only to neutralize the virus, as a decoy receptor, but also rescue cellular ACE2 activity which negatively regulates the renin-angiotensin system (RAS) to protect the lung from injury *in vivo* conditions.

Methods: Humanized ACE2 mice were intranasally challenged with 4×10^5 TCID50/50ul SARS-CoV-2 virus per mouse and were treated with shACE2 (12 mg/kg) via aerosolized delivery 48 h post-infection. Lung, brain, heart, kidney, liver, spleen and ileum were processed to determine viral load 7 days post infection (dpi). Lung and brain tissue were also processed to for virus titration (TCID50 assay) and IL-6 gene expression.

Results:

SARS-CoV-2 infection resulted in near 20% body weight loss in male mice while a transient weight loss seen at 4 dpi was recovered in female mice at 7 dpi (**Fig**). The viral expression (spike and nucleocapsid) in lung and protein present in male mice lung but was absent in female brain was Inhalation of soluble recombinant ACE2 daily for 5 mice. protected male mice from SARS-CoV-2 infection days decreasing viral envelope (E) gene copy numbers in by and brain (**Fig**). An improvement in SARS-CoV-2 the lung symptoms was observed from 16.3±0.8 (Mean±SE) infection 22.3±1.5 (P<0.01) in the srhACE2 treated mice. to
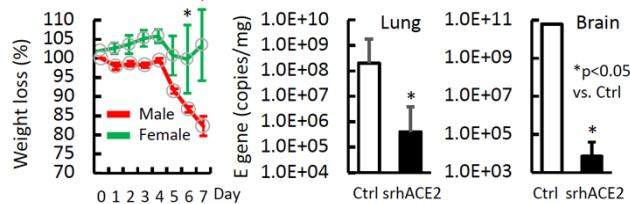
Conclusion: Sex differences may play a role in the severity of SARS-CoV-2 infection. srhACE2 as a decoy receptor is a promising strategy to neutralize SARS-CoV-2 by inhibiting viral entry. Our results suggest that shACE2 has a place in fight against COVID-19.

NEBULIZER DELIVERY IS SUPERIOR OVER INTRAVENOUS ADMINISTRATION OF SOULUABLE RECOMBINANT ACE2 TO ATTENUATE LUNG INJURY IN A MOUSE MODEL OF SARS-COV-2 SPIKE PRIMING FOLLOWED BY ACID ASPIRATION

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Background

Angiotensin converting enzyme 2 (ACE2) is expressed on lung mucous membrane. ACE2 can bind directly with the spike protein located on the surface of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), leading to the viral entry to cells and the development of coronavirus disease-2019 (COVID-19). We have demonstrated that soluble recombinant human ACE2 (srhACE2), as a decoy receptor, could block SARS-CoV-2 from cell entry in kidney and blood vessel organoids in vitro conditions. Intravenous (IV) administration of srhACE2 is undertaking in multi-center clinical trials to treat patients with severe COVID-19. However, it is unknown whether inhalation of srhACE2 would be more efficient than IV to inhibit SARS-CoV-2 infection in the lung.

Objective

To compare effects of srhACE2 administered by nebulizer (NEB) and intravenously (IV) in a humanized ACE2 mouse of SARS-CoV-2 infection.

Methods

Set #1: Assessment of srhACE2 stability before and after nebulization. srhACE2 (5.7 mg) was distributed into a chamber through a mesh vibrating nebulizer connected to gas blender at bias flow rate of 0.5 l/min at room temperature for 15 min, a setting is used in future mouse model. Condensation fluid in the chamber was collected for protein assay and the size (molecular weight) and quantity of srhACE2 by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Ability of condensation fluid to block SARS-CoV-2 entry to host cells was evaluated by incubating VeroE6 cells with srhACE2 or condensation fluid and SARS-CoV-2 for 15 hours. Viral load was assessed by expression of viral RNA in cell lysate.

Set#2: Comparison of IV vs. nebulization of srhACE2 on inflammation and lung injury in a two-hit model of SARS-CoV-2 spike and acid aspiration. To establish a lung injury model secondary to priming inflammation by SARS-CoV2 spike protein (1.1mg/kg), intratracheal instillation of HCl was administered an hour later in hACE2 mice. The mice were then divided into four groups: 1) PBS-IV; 2) srhACE2-IV (0.4 mg/kg); 3) PBS-NEB; and 4) srhACE2-NEB. srhACE2 was given 30 minutes after spike protein inoculation, and the animals were observed for 5 h.

Results: srhACE2 concentration in the condensation fluid was 85% of the initial concentration prior to nebulization. No proteolysis of srhACE2 was observed after nebulization. Condensation fluid was able to reduce viral load as

same as srhACE2 (Non-treated: 5.3 x 10^{10} $\pm$1.8 x 10^{10} /copies/µl, srhACE2-treated (200µg/ml): 4.2 x 10^8 $\pm$1.8 x 10^8 copies/µl, condensation fluid-treated (200 μ g/ml): 1.9 x 10^8 4.5 x 10^7 copies/µl).

Mice received srhACE2-NEB had reduced BALF PMN count (PBS-IV 6.6 x 10^4 $\pm$2.9 x 10^4 (mean SE) to srhACE2-IV 9.5 x 10^4 $\pm$ 1.8 x 10^4, PBS-NEB 1.4 x 10^5 $\pm$ 5.5 x 10^4 to srhACE2-NEB 2.1 x 10^4 $\pm$5.4 x 10^4 cells/ml) compared against PBS nebulized group while IV srhACE2 had no difference between IV PBS group.

Conclusion
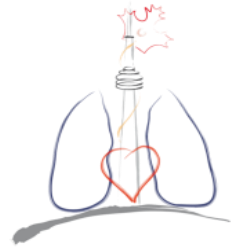
Nebulization of srhACE2 may have a place in the treatment of SARS-CoV-2 infection.

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Clinical/HSR abstracts

THE ASSOCIATION BETWEEN CYTOKINE PROFILES AND POSTOPERATIVE MORBIDITY FOLLOWING THE NORWOOD PROCEDURE

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Introduction and Objective: Cardiopulmonary bypass (CPB) results in a systemic inflammatory response characterized by the initiation of cytokine and coagulation cascades. To date a limited number of cytokines have been evaluated in patients undergoing CPB. We aim to describe the plasma concentrations of an extended panel of cytokine and metabolic mediators following cardiac surgery, with and without CPB. We also aim to determine the relationship between cytokine profiles and clinical outcomes.

Methods: We are performing a prospective longitudinal observational study in patients with hypoplastic left heart syndrome undergoing a Norwood procedure. Our control group is patients receiving an off CPB repair of coarctation of the aorta via lateral thoracotomy. Groups will be matched for age and weight. We are assessing a total of 71 cytokines at 4 time-points: 1) pre-bypass, 2) immediately post bypass, 3) 24 hours post bypass, 4) 72 hours post bypass.

Results: Recruitment began in March of this year and we have currently enrolled 2 patients. No data is available at this point. We anticipate a recruitment time of 2 years to enrol 50 patients to the study arm (Norwood group) and 10 patients to the control arm (coarctation group).

Conclusions: This research seeks to develop a more comprehensive characterization of the cytokine and metabolic alterations following CPB through use of expanded panels not previously available.

ACHIEVING LUNG- AND DIAPHRAGM-PROTECTIVE VENTILATION TARGETS IN ACUTE HYPOXEMIC RESPIRATORY FAILURE: THE LANDMARK I CLINICAL TRIAL

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Introduction & Objective:

Spontaneous breathing during mechanical ventilation in patients with acute hypoxemic respiratory failure (AHRF) can prevent diaphragm disuse atrophy, reduce atelectasis, and improve oxygenation. However, excessive respiratory efforts can injure the lung and diaphragm. The feasibility of optimizing respiratory effort to protect both the lung and the diaphragm in AHRF is unknown. The objectives of this randomized cross-over trial were to determine 1) the feasibility of applying a lung- and diaphragm-protective ventilation (LDPV) strategy, and 2) whether the application of higher PEEP and/or extracorporeal CO_2 removal ($ECCO_2R$) through VV-ECMO increased the probability of achieving LDPV.

Methods:

We included patients with AHRF, defined as PaO_2/FiO_2 <300 mm Hg and receiving invasive mechanical ventilation with or without venovenous extracorporeal membrane oxygenation. Patients were enrolled as early as possible after ICU admission and the study protocol was initiated once the clinical team decided that passive mechanical ventilation was no longer mandatory. Esophageal manometry was employed to measure respiratory effort (quantified as ΔPes) and the dynamic transpulmonary

pressure ($\Delta P_{L,dyn}$). The protocol proceeded in two phases: 1) After enrolment, sedatives and ventilator set rate were adjusted to initiate spontaneous breathing (sedation minimization phase); 2) Once spontaneous breathing was achieved, ventilation and sedation were systematically titrated using a pre-specified algorithm to achieve LDPV targets (ΔPes between −3 to −8 cm H_2O and a $\Delta P_{L,dyn} \leq 15$ cm H_2O) (LDPV titration phase). This titration procedure was performed at both lower and higher PEEP (applied randomly), and in patients on VV-ECMO, at both minimum tolerated sweep gas flow and high sweep gas flow. Pendelluft from spontaneous breathing was quantified by regional ventilation delay measured by electrical impedance tomography. The primary outcome was the proportion of patients in whom the targets were achieved.

Results:

Thirty patients were included in the primary analysis (**Table 1**). Median [IQR] time from enrolment to LDPV titration phase was 1 [1-4] days. Median [IQR] duration of the LDPV titration phase was 1.5 (1-2.5) hours. At enrolment, LDPV targets were not met in any patients (0%, 95% credible interval (CrI) 0%-11%). Once spontaneous breathing was initiated (phase 1) but prior to titration (phase 2), LDPV targets were met in 6/30 (20%, 95% CrI 10%-40%). Following titration, LDPV targets were achieved at either lower or higher PEEP in 20/30 (67%, 95% CrI 49%-81%) patients (**Figure 1A**). The effect of PEEP on ΔPes varied among patients (median change in ΔPes from low to high PEEP was -1 cm H_2O and ranged between -9 and 7 cm H_2O). Patients who had lung recruitment at higher PEEP, had reduced respiratory effort (mean change in ΔPes -3.2 cm H_2O (95% CrI -5-0) and reduced regional ventilation delay (-3% (95% CrI -6-0), but not patients without lung recruitment (posterior probability for interaction 97%). LDPV targets were more likely to be achieved in patients on VV-ECMO compared to patients not on VV-ECMO (OR 10, 95% CrI, 2-81, Figure 1B). Increasing sweep gas flow from 5 l/min (IQR 4-5) to 8 l/min (IQR 7-10) reduced ΔPes by -3 cm H_2O (95% CrI -4 to -1.5). Median (IQR) propofol dose at baseline was 40 µg/kg/min (21-50). Propofol dose was increased in 17/30 (57%, 95% CI 40%-73%) patients. Median (IQR) change in propofol dose from baseline to protocol completion was 15 µg/kg/min (0-37).

Conclusion:

Applying a LDPV strategy is feasible in patients with AHRF. In patients with lung recruitment at higher PEEP, increasing PEEP decreases inspiratory effort and ameliorates pendelluft. Extracorporeal CO_2 removal on VV-ECMO is associated with a higher probability of achieving LDPV targets.

Table 1. Baseline characteristics of the cohort

	Not receiving VV-ECMO (n= 14)	Receiving VV-ECMO (n= 16)	All patients (n= 30)
Age, median [IQR]	58 [55-63]	50 [32-54]	54 [48-60]
Female sex n (%)	4 (29)	6 (37)	10 (33)
APACHE II, median [IQR]	24 [20-29]	18 [17-21]	20 [17-24]
SOFA, median [IQR]	10 [10-11]	10 [10-12]	10 [10-12]
SAS, median [IQR]	1 [1-2]	1 [1-1]	1 [1-2]
Comorbidities, sex, n (%)			
Asthma	0(0)	1 (6)	1 (3)
COPD	2 (15)	1 (6)	3 (10)
Interstitial lung disease	1 (7)	1 (6)	2 (6)
Diabetes	4 (29)	4 (25)	8 (26)
Chronic kidney disease	0(0)	1 (6)	1 (3)
Cause of respiratory failure, n (%)			
Pneumonia	13 (93)	16 (100)	29 (97)
Post-operative respiratory failure	1 (7)	0 (0)	1 (3)
COVID-19 pneumonia, n (%)	6 (46)	7 (54)	13 (43)
PaO_2/FiO_2, median [IQR]*	109 [79-167]	70 [64-117]	88 [64-143]
Ventilatory ratio*	2.0 [1.6-2.7]	2.5 [1.3-2.8]	1.7 [1.4-2.3]
Sweep gas flow (L/min)	-	5 [4-5]	n/a
V_T (ml/kg PBW), median [IQR]	7.5 [6.0-8.0]	5.0 [3.5-6.5]	6.0 [5.0-7.5]
PEEP (cm H_2O), median [IQR]	8 [8-10]	12 [10-15]	10 [8-14]
ΔP (cm H_2O), median [IQR]	17 [12-19]	15 [13-17]	17 [12-19]
Crs (ml/cm H_2O), median [IQR]	28 [21-37]	20 [15-31]	23 [16-37]
Ers (cm H_2O/(ml/kg PBW)), median [IQR]	2.0 [1.8-3.1]	3.3 [2.2-5.1]	2.6 [1.9-5]

*Values of PaO_2/FiO_2 and ventilatory ratio are modified by VV-ECMO and may not be representative of lung function.

Figure 1. Feasibility of achieving lung- and diaphragm-protective ventilation targets in the study population.
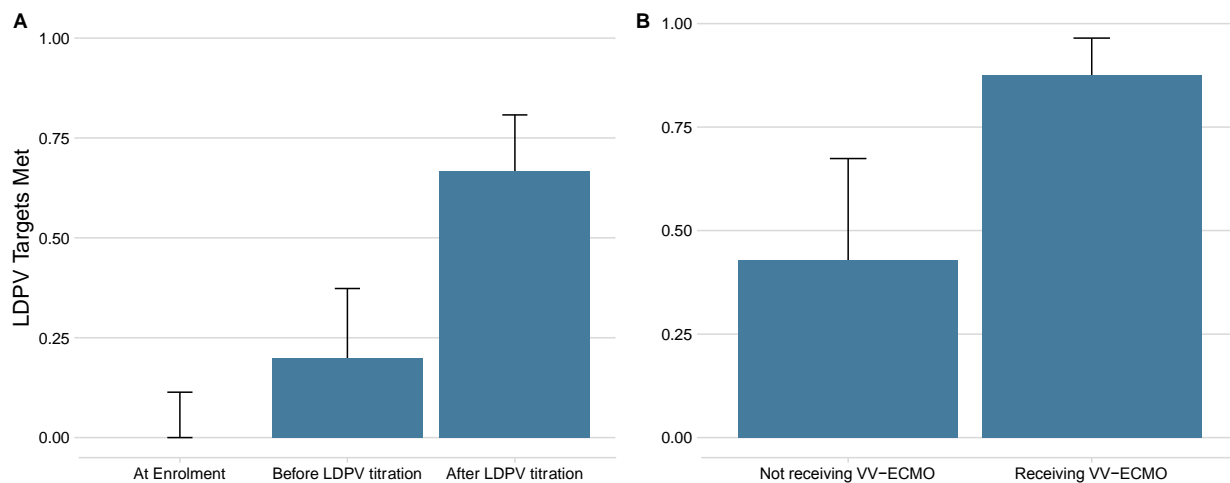
A. Proportion of patients who met LDPV targets at each protocol step. "At enrolment" represents the phase before any intervention was performed. Once patients were consistently triggering the ventilator, the LDPV titration was started. **B.** Proportion of patients who met LDPV targets divided by those not receiving and those receiving VV-ECMO.

CANCOV- Canadian Prospective Cohort of 1-year outcomes in critically ill patients with COVID-19 and their family caregivers

Dragoi L, Robles P, Burns S, Huszti, E, Greenwood S, Del Sorbo, L, Ferguson N, Parotto M, Abbey S, Tan A, Katzberg, H, McCredie, V, Maham N, Fraser I, Warner, M, Sehgal, P, Aulakh, M, Alfilfil, W, Kakho N, Khan S, Bayley M, Flannery J, Goligher E, Lawler P, Flockhart L, Lo V, Cheung A and Herridge M on behalf of the **CANCOV Consortium Investigators**
University Health Network, University of Toronto. Michael Garron Hospital.

Rationale: COVID-19 is a novel multisystem disease with unknown long-term morbidity and mortality. Data on long-term outcomes for critically ill patients after COVID-19 are emerging in the international literature and share many of the previously published functional and neuropsychological morbidities documented in ARDS. CANCOV will offer a comprehensive, granular, multi-centre evaluation of one-year outcomes for Canadian COVID-19 patients and their family caregivers. Very early preliminary data are presented here.

Objectives:
1. To create a definitive, generalizable, granular dataset of Canadian COVID-19 patients and family caregivers by characterizing their short and long-term outcomes including physical, functional, neuropsychological, Health-Related Quality of Life (HRQoL), and pattern and cost of healthcare utilization.
2. To determine clinical risk factors, timing and pace of disease resolution or deterioration.
3. To provide detailed clinical phenotypes for genetic, basic science, translational and multi-omics research inquiry.

Methods: This is a Canadian, multi-centre, ambidirectional cohort study designed to recruit 2000 patients and 500 caregivers across a spectrum of illness. The study includes patients aged 16 and older with documented COVID-19 disease and family caregivers of hospitalized COVID-19 patients. Patients with catastrophic neurologic injury or anticipated death or withdrawal of life sustaining therapies within 48 hours were excluded. Sociodemographic data and data on clinical risk factors were collected at baseline. Standardized follow-up was performed at 7 days and 1,3,6 and 12 months after discharge from ICU and included a battery of patient- and family-centered outcome measures including physical, functional and neuropsychological testing. The current study sample consists of 212 critically ill patients and 47 caregivers.

Results:
From this ambidirectional cohort study sample of 212 patients, we present preliminary descriptive statistics on 125 prospectively recruited ICU patients from UHN (TGH/TWH) and Michael Garron Hospital. Baseline Characteristics include: median patient age 52 (45-59); M:F 82:43 and 87% of patients had at least 1 baseline comorbidity. Most common comorbidities included: diabetes/endocrine 37%; hypertension/cardiovascular 33%; mental illness/substance misuse 23%. Median ICU LOS was 16 d (7,29) and median hospital LOS was 19 d (12, 37). Overall ICU mortality was 44%. Of 125 patients in this sample, 64 required MV only and 61 required MV and ECLS.

ECMO patients were younger and spent more time in the ICU compared to those solely on MV (median age 51 vs 55 p< 0.01; median ICU LOS 24 d vs 9 d p< 0.001 respectively.

ECMO patients had a higher ICU mortality compared to those on MV alone (56% vs 33%). Those ECMO patients who died were younger and had a longer ICU LOS than patients who died on MV (median age 52 vs 62 p< 0.03; median ICU LOS 22d vs 17d p<0.04) respectively.

Follow up data for 7 days, 1 month and 3 months were available for 78 patients. The total FIM score of 74 (53, 93) at day 7 post ICU improved to 112 (91,117) at 1 month and remained stable at 113 (104, 121) at 3 months. Similarly, the MRC total score of 37 (34 ,37) at 7 days increased to 54 (51,59) at 1 month and 57 (52,60) at 3 months.

Conclusion:

Preliminary data on a prospective sample of 125 critically ill COVID-19 patients from the national, multi-centre CANCOV Program show that eighty-seven percent of patients had at least one comorbidity, with diabetes and hypertension being most common. ICU LOS was approximately 2 weeks and hospital LOS almost 3 weeks. ICU mortality for this sample recruited mostly from an ECMO referral centre was 44%. Patients who required ECMO were younger, had a longer ICU stay and a higher ICU mortality (56%) compared to those patients requiring MV alone (33%). Early functional data on post ICU surviving patients suggest that both the FIM score and MRC total score were poor at seven days after ICU discharge and improved to 3 months. Comprehensive data on ICU characteristics and additional multidimensional outcomes are under analysis and will further inform risk stratification and determinants of outcome.

CRITICAL ILLNESS IN PATIENTS WITH HEMATOLOGIC MALIGNANCY: A POPULATION-BASED COHORT STUDY

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Introduction & Objective:
The past decade has seen an evolution in therapies and an improvement in overall survival in patients with hematologic malignancy. As such, candidacy for intensive care unit admission in the setting of critical illness has expanded.
We sought to describe the modern incidence and predictors of ICU admission for adult patients newly diagnosed with a hematologic malignancy.

Methods
We performed a population-based cohort study of adult patients with a new diagnosis of a hematologic malignancy (April 1, 2006-March 31, 2017) in the province of Ontario, Canada. We describe baseline demographic, clinical and laboratory predictors of ICU admission and subsequent mortality. The primary outcome was the incidence of ICU admission within one-year of hematologic malignancy diagnosis. We assessed predictors of ICU admission using Cox-proportional models that accounted for the competing risk of death and reported as subdistribution hazard ratios (sHR) with 95% confidence intervals (CI). The receipt of hematopoietic cell transplantation was included as a time-varying predictor.
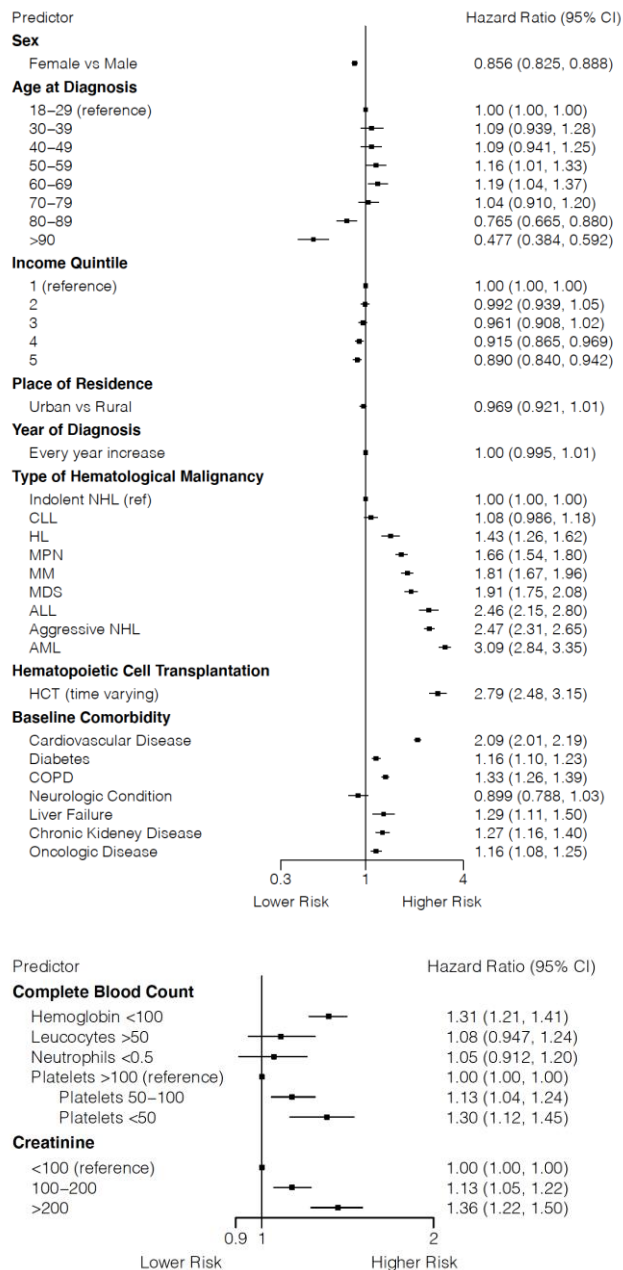
Results
During the study period, a total of 87965 patients (mean [SD] age, 67.8 (15.7) years) were diagnosed with a hematologic malignancy. The incidence of ICU admission within one year was 13.9% (median time 35 days), ranging from 7.3% in patients with indolent lymphoma to 22.5% in patients with acute myeloid leukemia. After multivariable adjustment, compared to indolent lymphoma, acute myeloid leukemia (sHR, 3.09; 95% CI, 2.84-3.35), aggressive non-Hodgkin lymphoma (sHR, 2.47; 95% CI, 2.31-2.65) and acute lymphoblastic leukemia (sHR, 2.46; 95% CI, 2.15-2.80) had the highest risk of ICU admission. Comorbidities such as cardiovascular disease (sHR, 2.09; 95% CI, 2.01-2.19) chronic obstructive pulmonary disease (sHR, 1.33; 95% CI, 1.26-1.39), baseline anemia (sHR, 1.31; 95% CI, 1.21-1.41), thrombocytopenia (sHR, 1.13; 95% CI, 1.04-1.24 [platelet count $50-100 \times 10^9$/L versus $>100 \times 10^9$]; sHR, 1.30; 95% CI, 1.12-1.45 [platelet count $<50 \times 10^9$/L versus $>100 \times 10^9$]) and high creatinine (sHR, 1.13, 95% CI 1.05-1.22 [creatinine 100-200μmol/L versus <100μmol/L]; sHR, 1.36; 95% CI 1.22-1.50 [creatinine >200μmol/L versus <100μmol/L]) were also associated with ICU admission. Treatment with hematopoietic cell transplant also increased the risk of ICU admission (sHR, 2.79; 95% CI, 2.48-3.15). Among ICU patients, 36.7% required invasive mechanical ventilation. Overall ICU and hospital mortality were 20.0% and 31.0%, respectively.

Conclusion
The occurrence of critical illness in patients with a newly diagnosed hematologic malignancy is frequent and occurs early after diagnosis. Certain baseline characteristics at diagnosis and during follow-up can help identify those patients at the highest risk of critical illness.

Figure. Association of Patients' Characteristics and Risk of ICU Admission

Predictor	Hazard Ratio (95% CI)
Sex	
Female vs Male	0.856 (0.825, 0.888)
Age at Diagnosis	
18–29 (reference)	1.00 (1.00, 1.00)
30–39	1.09 (0.939, 1.28)
40–49	1.09 (0.941, 1.25)
50–59	1.16 (1.01, 1.33)
60–69	1.19 (1.04, 1.37)
70–79	1.04 (0.910, 1.20)
80–89	0.765 (0.665, 0.880)
>90	0.477 (0.384, 0.592)
Income Quintile	
1 (reference)	1.00 (1.00, 1.00)
2	0.992 (0.939, 1.05)
3	0.961 (0.908, 1.02)
4	0.915 (0.865, 0.969)
5	0.890 (0.840, 0.942)
Place of Residence	
Urban vs Rural	0.969 (0.921, 1.01)
Year of Diagnosis	
Every year increase	1.00 (0.995, 1.01)
Type of Hematological Malignancy	
Indolent NHL (ref)	1.00 (1.00, 1.00)
CLL	1.08 (0.986, 1.18)
HL	1.43 (1.26, 1.62)
MPN	1.66 (1.54, 1.80)
MM	1.81 (1.67, 1.96)
MDS	1.91 (1.75, 2.08)
ALL	2.46 (2.15, 2.80)
Aggressive NHL	2.47 (2.31, 2.65)
AML	3.09 (2.84, 3.35)
Hematopoietic Cell Transplantation	
HCT (time varying)	2.79 (2.48, 3.15)
Baseline Comorbidity	
Cardiovascular Disease	2.09 (2.01, 2.19)
Diabetes	1.16 (1.10, 1.23)
COPD	1.33 (1.26, 1.39)
Neurologic Condition	0.899 (0.788, 1.03)
Liver Failure	1.29 (1.11, 1.50)
Chronic Kideney Disease	1.27 (1.16, 1.40)
Oncologic Disease	1.16 (1.08, 1.25)

0.3   1   4
Lower Risk   Higher Risk

Predictor	Hazard Ratio (95% CI)
Complete Blood Count	
Hemoglobin <100	1.31 (1.21, 1.41)
Leucocytes >50	1.08 (0.947, 1.24)
Neutrophils <0.5	1.05 (0.912, 1.20)
Platelets >100 (reference)	1.00 (1.00, 1.00)
Platelets 50–100	1.13 (1.04, 1.24)
Platelets <50	1.30 (1.12, 1.45)
Creatinine	
<100 (reference)	1.00 (1.00, 1.00)
100–200	1.13 (1.05, 1.22)
>200	1.36 (1.22, 1.50)

0.9 1   2
Lower Risk   Higher Risk

The plots shows the subdistribution hazard ratio for time to ICU admission for each predictor. All variables included in the model have are included in the plot. .

Abbreviations: ICU, intensive care unit; CI, confidence interval; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; MPN, myeloproliferative neoplasm; MM, multiple myeloma; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HCT, hematopoietic stem cell transplantation; COPD, chronic obstructive pulmonary disease

CHARACTERIZATION OF EPINEPHRINE DURING EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION

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Introduction and Objectives: Despite improvements in resuscitation science and ECMO technology, there remain questions about how to deliver ECPR to optimize survival and neurologic outcomes. Epinephrine has been the vasoactive of choice during conventional CPR in pediatrics. There is no evidence to guide its dose or delivery after launching ECPR. The potential negative impact of elevated afterload following ECPR cannulation during the post cardiac arrest care phase can limit a centrifugal ECMO pump's ability to push blood forward through the vasculature, causing a decrease in circuit flow. Faced with this paradox, many critical care physicians have started to modify epinephrine delivery during ECPR. Actual practice has not been broadly characterized. This retrospective study will seek to describe the pattern of epinephrine administration at a single institution during ECPR and evaluate its association with post-cannulation ECMO parameters in an attempt to determine if a relationship exists between epinephrine use and clinical outcomes following ECPR.

Methods: A single-center, retrospective observational study consisting of patients aged 0-18 years old who underwent cannulation for ECPR over a six-year time period. Patients were included if cannulation occurred in the PICU, CCCU, operating room, or cardiac catheterization lab. Patients were excluded if cannulation had been started before cardiopulmonary arrest or if incomplete resuscitation record. The primary exposure is time form last dose of epinephrine to time of ECMO cannulation, with secondary exposures of total amount of epinephrine and epinephrine per minute. The primary outcome was the recorded blood pressure each hour for the first six hours after cannulation. Secondary outcomes include initial ECMO flow rate, initial ECMO pump speed in RPMs, time to target flow, first post-ECPR lactate and time to clearance, highest vasoactive-inotropic score (VIS) within the first hour and first six hours after cannulation, and the vasodilator requirement within the first hour and the first six hours after cannulation.

Results: This study is currently underway, having finished initial data collection. A total of 92 events from 87 unique patients were queried. An average of 74 mcg/kg (range 0-269 mcg/kg) of epinephrine was given during resuscitation with an average time from ECMO cannulation of 10 minutes (range 0-55 minutes). Blood pressures have been recorded, along with VIS and vasodilator requirements. Initial interpretation do not suggest any correlation between time between last epinephrine dose to cannulation and initial BP ($r=-0.27$) or VIS ($r=0.07$). Further results will be available by the presentation day.

Conclusion: At this time, the study has completed data gathering for new data and will be merged with prior data pertaining to demographics, laboratory results, and long-term clinical outcomes and mortality. No conclusion can be made at this time.

CODE STATUS DOCUMENTATION IN OLDER HOSPITALIZED MEDICAL PATIENTS AT HIGH RISK FOR FRAILTY: A MULTI-CENTRE COHORT STUDY

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Introduction and Objective: Hospitalized medical patients are required to determine their code status in the event of a clinical deterioration. Ideally, the code status of a patient will be based on their values, preferences and prognosis. The objective of this study was to determine the code status of patients at the time of hospital discharge, as well as the association between prognosis and changes in code status over the course of their hospitalization.

Methods: We conducted a multi-centre retrospective cohort study of 200 patients admitted to medicine at one of four hospitals participating in the General Medicine Inpatient Initiative (GEMINI) from 2015-2019. Prognosis was estimated using the hospital frailty risk score (HFRS), which stratifies patients into high, moderate and low frailty risk. Study inclusion criteria included: age 75 years and older, and at least one prior admission to medicine within the preceding 12 months at one of the participating GEMINI hospitals. Previous admission was required to calculate patients' HFRS from the prior admission discharge diagnosis. Manual chart review was undertaken to collect whether a code status was documented, the details of the code status discussion and if this code status changed during admission.

Results: Of the 200 patients, 91% (n=181) of patients had a code status documented during their admission. Comfort care was the most common final code status in the chart, representing 30% (n=55) of all final code statuses. Comfort care was most common in both high and moderate frailty risk patients, representing 30% (n=18) and 35% (n=22) of final code statuses, respectively. Full code was the most common final code status in low frailty risk patients, representing 37% (n=22). The proportion of patients with code statuses that had a documented code status discussion in the chart was 64% (n=116). When comparing the 4 different hospital sites (Hospitals A, B, C and D), Hospital D, which uses primarily typed notes, had the highest percentage of patients with documented code status discussions, at 84% (n=42). Code status changed in 48% (n=87) of patients at some point during their admission. To highlight the changes that occurred from first to final documented code status, 5% (n=9) of patients were initially comfort care and 30% (n=55) of patients ended their admission as comfort care.

Conclusion: While the majority of older medical patients had a code status documented in their chart, documented code status discussions were more variable between frailty risk categories and hospital sites. Electronic charting may facilitate documentation of discussions, as the hospital site with typed notes had the highest proportion of documented code status discussions. Furthermore, changes in code status during admission were common, particularly in patients with an intermediate prognosis. Early, high-quality communication in patients deemed to have intermediate and poor prognoses may modify the need for frequent meetings to discuss code status and are essential for ensuring goal-concordant care is received.

MANAGEMENT PRACTICES AND OUTCOMES ACROSS PATIENTS PRESENTING WITH HIGH RISK ACUTE MYELOID LEUKEMIA

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Abstract

Introduction: Approximately 10% to 20% of patients with Acute Myeloid Leukemia (AML) patients present with hyperleukocytosis. Hyperleukocytosis can result in leukostasis leading to end organ dysfunction and critical illness. Institutional practices vary on the management of patients with hyperleukocytosis and leukostasis including location of chemotherapy administration and thresholds for ICU admissions. There is paucity of data on the management and short- and long- term outcomes of these patients – particularly across those managed on in-patient wards vs. ICUs.

Objectives: To describe the characteristics of patients with hyperleukocytosis and factors associated with ICU admission and 60-day mortality.

Methods: We conducted a retrospective cohort study of consecutive admissions to Princess Margaret (PM) Cancer Center or Mount Sinai Hospital Intensive Care Unit (ICU for PM) between 2014-2019. Any adult patients with a white blood cell count >50 10_9/L and a new diagnosis of AML were included. Their clinical and laboratory data were evaluated across their first 5 days of hyperleukocytosis. Our primary outcome was ICU admission and our secondary outcome was 60 day mortality.

Results:

One-hundred and sixty-nine patients were admitted with a diagnosis of AML and hyperleukocytosis. Mean age was 58 (SD 15) and 59% were male with 43% having greater than 2 comorbidities. Median WBC on the first day of hyperleukocytosis was 103 (IQR 67-152), with 55% having a WBC >100$10_9$/L and 15% having a WBC >200 10_9/L On the first day of hyperleukocytosis, 63% had hypoxemic requiring supplemental oxygen therapy, 25% (43) had biochemical tumor lysis syndrome, and 49% were diagnosed with acute kidney injury (8% requiring dialysis) (*Table 1*). ICU admission was required in 44% of the cohort (75/169 patients) and the median time to ICU was 1 (IQR 0-3) days. Across entire cohort, median change in WBC from day 1 to 2 was – 17 (IQR -31 - -1), the median greatest decrease in WBC over a 24 hour period across the first 5 days was 58 (31-88). Drop in WBC in first 5 days was higher in those not admitted to ICU and across survivors. (Table 1). Across the ICU cohort, 59% required invasive mechanical ventilation, 76% had acute kidney injury and 48% require vasopressors (Table 2). Across those admitted to the ICU, 81% were admitted within 4 days of hyperleukocytosis. Sixty-day mortality across the whole cohort was 30% (57% across the ICU cohort and 8% across the non-ICU exposed). ICU mortality was 82% across those who required invasive mechanical ventilation during the first 5 days of hyperleukocytosis.

Hospital admission factors associated with ICU admission included a lower PaO2/FiO2 on day 1 of hyperleukocytosis (PaO2/FiO2 OR 0.97 (95% CI 0.96-0.98, p<0.001) and acute kidney injury (OR 12.2 95% CI 1.8-83, p 0.011). Factors associated with 60-day mortality included male sex, WBC >100, lower PaO2/FiO2, any invasive mechanical ventilation and a lower drop over a 24 hour period in the WBC across the first 5 days. (Table 2)

Conclusions: The vast majority of patients with hyperleukocytosis were managed on the inpatient wards and had a mortality rate of 8%; however, the subset admitted to ICU and particularly requiring invasive mechanical ventilation on admission did poorly.

TABLE 1	Entire Cohort (N=169)	ICU Cohort (N=75)	No ICU (N=94)	60-day Mortality (N=50)
DEMOGRAPHIC VARIABLES				
Age	58 SD 15	59 (15)	58 (14)	59 (16)
Comorbidities	1 (IQR 0-2)	2 (IQR 1-3)	1 (IQR 0-2)	2 (IQR 1-3)
Sex-Male	100 (59%)	48 (64%)	52 (55%)	38 (76%)
# Comorbidities	0 – 48 (29%) 1 – 47 (28%) ≥2 - 73 (43%)	0 – 14 (19%) 1 – 14 (19%) ≥2 – 47 (63%)	0 - 34 (37%) 1 – 33 (35%) ≥2 – 26 (28%)	0 - 11 (22%) 1 – 13 (26%) ≥2 – 26 (52%)
Days from hospital admission to ICU admission	1 (0-3)	1 (0-3)	N/A	
WBC DETAILS				

WBC >100 on presentation	92 (55%)	44 (59%)	48 (52%)	31 (65%)
WBC >200	25 (15%)	16 (21%)	9 (10%)	12 (24%)
WBC day 1	103 (67-152)	106 (61-187)	102 (69-143)	114 (71-195)
WBC day 2	85 (60-125)	87 (63-150)	76 (56—120)	98 (73-153)
WBC day 3	61 (37-110)	71 (129-46)	61 (37-109)	65 (38-100)
WBC day 4	32 (15-74)	18 (5-88)	37 (19-64)	43 (18-83)
WBC day 5	14 (3-38)	15 (2-51)	14 (5-36)	19 (9-59)
Change D2-D1	-17 (-31 - -1)	-9 (-25 – 10)	- 21 (-35- -9)	-1 (-21- 23)
Change D3-D2	-18 (-35 - -7)	-26 (-60 - -9)	-18 (-33- -6)	-23 (-35- -11)
Greatest decrease in 24 hours over first 5 days*	58 (31-88)	48 (18-91)	62 (37-87)	48 (21-80)
CLINICAL VARIABLES				
ICU admission	75 (44%)	N/A	N/A	43 (86%)
PaO2/FiO2 Day 1	280 (IQR 140-450)	168 (112-251)	452 (442-461)	145 (108-206)
Any hypoxia day 1	80 (63%)	71 (96%)	9 (11%)	
Highest oxygen support on day 1	Room Air 75 (48%) NP 27 (17%) HFNC 4 (3%) NIV 6 (4%) Inv Mech Vent 43 (28%)	4 (5%) 18 (24%) 4 (5%) 6 (8%) 43 (57%)	71 (89%) 9 (11%)	3 (6%) 8 (17%) 0 1 (2%) 36 (75%)
PTT day 1	28 (25-33)	31 (28-39)	26 (23-29)	32 (28-43)
Potassium (dialysis excluded) day 1	3.8 (3.3-4.3)	4.5 (3.9-4.9)	3.5 (3.2-3.9)	4.3 (3.8-5)
Uric Acid day 1	363 (221-540)	356 (170-640)	363 (227-539)	402 (226-742)
Biochemical TLS day 1	43 (26%)	42 (56%)	1 (1%)	30 (60%)
AKI day 1	82 (49%)	54 (72%)	28 (31%)	39 (79%)
Dialysis day 1	14 (8%)	14 (19%)	0	10 (20%)
GCS day 1	14-15: 136 (81%) <14: 31 (19%) 3: 14 (8%)	14-15: 44 (59%) <14: 31 (41%) 3: 14 (19%)	14-15: 94 (100%)	14-15: 28 (57%) <14: 22 (43%) 3: 12 (25%)
Shock day 1	33 (20%)	32 (43%)	1 (1%)	21 (43%)
WORST CLINICAL STATUS BY DAY 5				
Invasive mechanical ventilation by day 5	44 (27%)	44 (59%)	N/A	
AKI by day 5	88 (52%)	57 (76%)	35 (38%)	39 (79%)
Dialysis by day 5	14 (8%)	14 (19%)	0	
Shock by day 5	36 (22%)	36 (48%)	1 (1%)	
Time to ICU admission	Direct-25 (15% ICU) w/i 4 days-60 (37%)	25 (33%) on day 0 62 (81%) by day 4 68 (88%) by day 7		14 (32%) on day 0 36 (82%) by day 4 40 (90%) by day 7
TREATMENT IN FIRST 5 DAYS				
Hydroxyurea	140 (84%)	51 (68%)	89 (97%)	32 (65%)
Cytarabine	81 (49%)	30 (41%)	51 (55%)	23 (48%)
OUTCOMES				
60-day mortality	50 (30%)	43 (57%)	7 (8%)	N/A
Death across ICU exposed cohort	44/75 (59%)	42 (56%)	N/A	N/A

60-day mortality excluding ICU admissions	7/93 (8%)	N/A	7 (8%)	N/A
Death within 24 hours	11 (7%)	11 (15%)	0	11 (22%)
Death within 48 hours	21 (12%)	21 (28%)	0	21 (46%)

*(excluding 17 pts no decrease and 24 with missing data/death)

TABLE 2: FACTORS ASSOCIATED WITH ICU ADMISSION			
Variable	**OR**	**95% CI**	**P**
Age	0.97	0.92-1.02	0.21
Sex	4.2	0.64-28	0.13
WBC Greater than 100 on day 1	1.7	0.33-7.6	0.58
# Comorbidities	1.21	0.67-2.19	0.54
PaO2/FiO2* on day 1	**0.97**	**0.96-0.98**	**<0.001**
AKI on day 1	**12.2**	**1.8-83.4**	**0.011**

FACTORS ASSOCIATED WITH 60 DAY MORTALITY			
Variable	**OR**	**95% CI**	**P**
Age	1.03	0.98-1.08	0.31
Sex -Female	**0.03**	**0.002-0.02**	**0.003**
WBC Greater than 100 on day 1	**10.16**	**1.24-82.88**	**0.03**
# Comorbidities	0.73	0.39-1.35	0.31
PaO2/FiO2* on day 1	**0.99**	**0.98-0.997**	**0.007**
Tumor Lysis Syndrome on day 1	1.18	0.16-8.61	0.87
Any AKI	0.55	0.12-2.37	0.43
Any Invasive Mechanical ventilation	**26.85**	**1.67-434.34**	**0.02**
Greatest drop in WBC in first 5 days	**0.96**	**0.93-0.99**	**0.02**

(*SaO2/FiO2 with adjustment factor used for patients without PaO2 available)

EARLY PREDICTION OF MECHANICAL VENTILATION-FREE SURVIVAL IN PATIENTS ADMITTED WITH TRAUMATIC SPINAL CORD INJURY: A REGISTRY-BASED OBSERVATIONAL STUDY

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Introduction & Objective: The need for mechanical ventilation (MV) greatly impacts life expectancy and quality of life of patients with spinal cord injury (SCI) but predictors of weaning from MV have not been systematically assessed. Using a registry-based observational study, our aims were: i) to investigate the probability of survival free of MV at hospital discharge (weaning success), ii) to develop and validate a prediction score for weaning success and iii) to estimate the time to weaning and identify its predictors in ventilated patients with SCI.

Methods: We obtained data from the Trauma Registry at St. Michael's Hospital. We included adult patients with traumatic SCI requiring MV, admitted to the trauma-neuro intensive care unit of St. Michael's Hospital between January 2005 and December 2019. Multivariable logistic and competing risk regression analyses were used, respectively, to identify early predictors of weaning success and time to liberation. We developed and internally validated via bootstrap a prediction score based on regression coefficients; its ability to discriminate between weaning success/failure was assessed using ROC curve analysis and compared to the Injury Severity Score (ISS) through pairwise testing. To estimate the time to liberation and its predictors while accounting for the competing risk of death, cumulative incidence curves were plotted, and Fine-Gray competing risk regression models were built.

Results: Of 257 patients requiring MV after SCI, 178 (69.3%) experienced MV-free survival and 40 (15.6%) died. Factors relevant for weaning success included: age (OR 0.97, p= 0.003), number of comorbidities (OR 0.8, p= 0.045), blunt injury (OR 7.09, p= 0.005), cervical level lesion (OR 0.98, p= 0.084) and ISS (OR 0.35, p= 0.005). A score based on these covariates had much better performance predicting weaning success than the ISS (AUROC= 0.78, 95%CI 0.70 – 0.83, *vs* 0.57, 95%CI 0.50 – 0.66, p< 0.0001). Median crude time to liberation from MV was 15 days; the cumulative incidence of weaning was lower in patients with a cervical SCI level compared to patients with either a thoracic (p< 0.01) or lumbar (p< 0.004) level (Figure). The same factors relevant for weaning success, along with the presence of complete SCI (p= 0.004), also predicted time to liberation.

Conclusion: 69.3% of patients were discharged alive and-free of MV after SCI. A newly developed score based on readily available patient characteristics on admission could predict weaning success with good discriminative properties in internal validation. External validation will be conducted during on-going research.
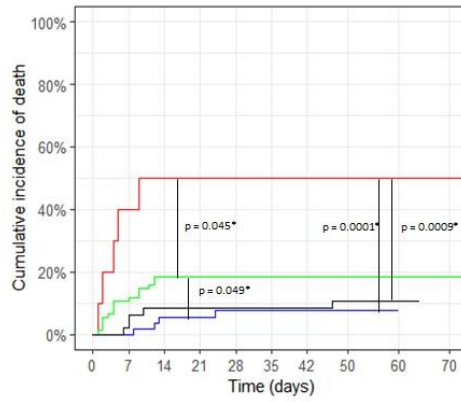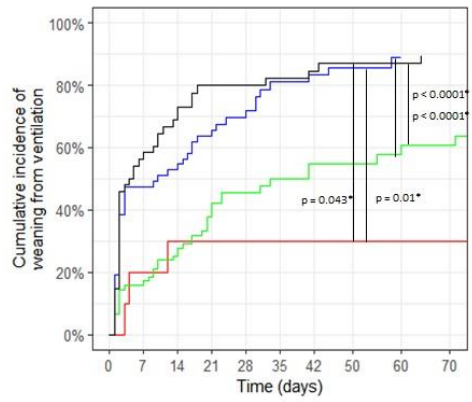
IDENTIFYING CLINICAL SUBPHENOTYPES IN SEPSIS-SURVIVORS WITH DIFFERENT ONE-YEAR OUTCOMES:
A SECONDARY LATENT CLASS ANALYSIS OF THE FROG-ICU COHORT

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ABSTRACT

Introduction and objective:

Late mortality risk in sepsis survivors persists for years with high readmission rates, and low quality of life. The present study seeks to link the sepsis-survivors heterogeneity with late adverse events using an unsupervised analysis.

Methods:

In the original prospective, observational, multicenter FROG-ICU study, intensive care unit (ICU) patients with sepsis on admission (Sepsis-3) were identified (n=655). Among them, 467 were discharged alive from the ICU and included in the current study. Latent class analysis (i.e., unsupervised machine learning) was applied to identify distinct sepsis-survivors clinical subphenotypes using routine data at ICU discharge. The primary endpoint was one-year mortality after ICU discharge.

Results:

At ICU discharge, two distinct subphenotypes were identified (A and B) using 17 clinical and routine biological data **(Figure 1A)**. Patients assigned to subphenotype B (41% of the studied population) had more impaired cardiovascular and kidney functions, hematological disorders, and inflammation at ICU discharge than subphenotype A. Sepsis-survivors in subphenotype B had significantly higher one-year mortality compared to subphenotype A (respectively, 33.5% vs 18.4%, p< 0.001) **(Figure**

1B). When adjusted for standard long-term risk factors (e.g., age, comorbidities and duration of ICU stay), subphenotype B was independently associated with increased one-year mortality (adjusted hazard ratio=1.50 (1.02-2.21); p=0.04). A reduced six-variable classification model could also be used to discriminate the two subphenotypes.

Conclusion:

A subphenotype with sustained organ failure and inflammation at ICU discharge can be identified from routine clinical and laboratory data and is independently associated with poor long-term outcome in sepsis-survivors.

Trial registration: ClinicalTrials.gov NCT01367093.

Keywords: Sepsis; Post intensive care syndrome (PICS); biomarkers; latent profile analysis; prognostic enrichment, personalized medicine

Figure 1.

(A) Comparison of subphenotype-defining variables. Description: continuous variables were plotted after natural log transformation. Every normalized variable was standardized such that all means are scaled to 0 and SDs to 1. Group means of standardized values are shown by subphenotype (A and B). A value of +1 for the standardized variable (y-axis) indicates that the mean value for a given subphenotype was one SD higher than the mean value in the whole sepsis survivors cohort (n=467). Abbreviations: SD, standard deviations; BUN, blood urea nitrogen; CRP, C-reactive protein; SBP, systolic blood pressure; WBC, white blood cell.
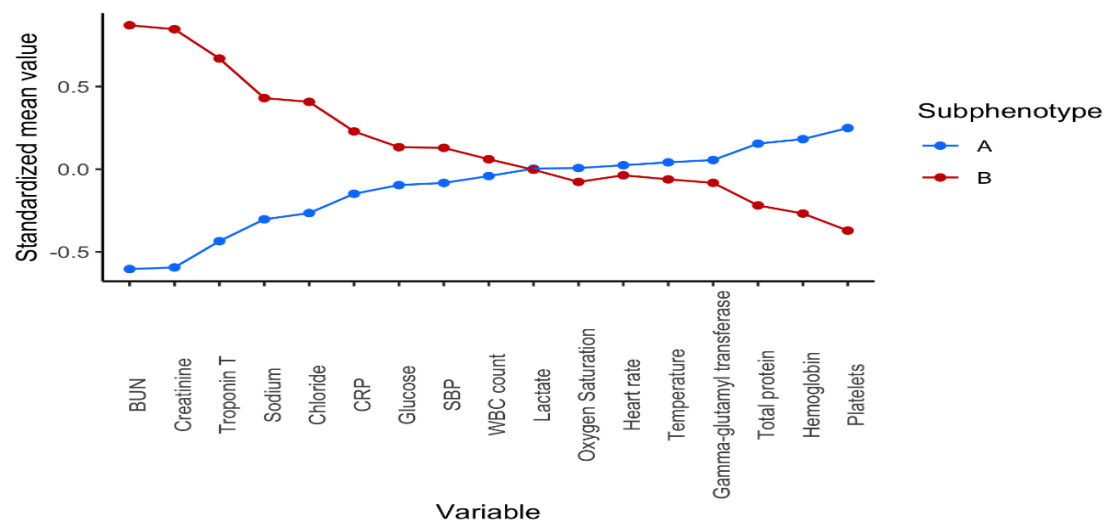
(B) One-year post-ICU survival curves according to subphenotype membership. The log-rank test between the survival curves of the two subphenotypes at ICU discharge showed a p<0.001.
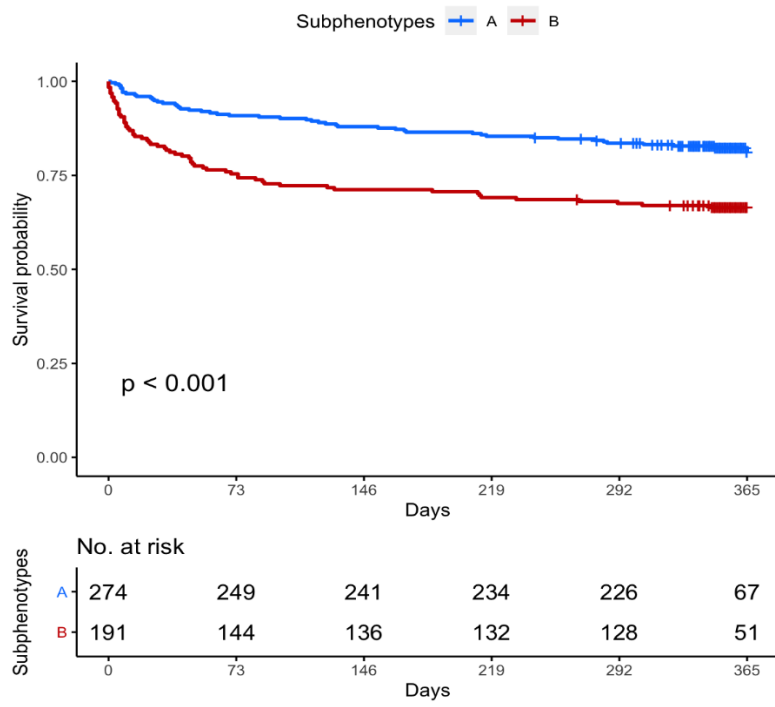
STANDARDIZED LIBERATION TRIALS IN PATIENTS WITH COVID-19 ARDS TREATED WITH VENO-VENOUS EXTRACORPOREAL MEMBRANE OXYGENATION

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Introduction and Objective:

Current strategies for liberation from veno-venous extracorporeal membrane oxygenation (VV ECMO) rely on physician preference and practice, leading to under-recognition of readiness for liberation or unsafe initiation of liberation attempts, increasing the risk for prolonged ECMO runs and associated complications. The purpose of the study was to assess the feasibility of adopting a standardized liberation protocol for patients with COVID-19 ARDS treated with VV-ECMO.

Methods:

This was a single-center, retrospective cohort study of adult patients treated with VV ECMO for COVID-19 ARDS at Toronto General Hospital between May and October 2020. The study was approved by the Research Ethics Board of the University Health Network. Liberation from VV-ECMO at our center typically consists of a slow progressive wean of sweep gas flow (SGF), while the patient is kept on systemic anticoagulation and different levels of sedation. Starting May 2020 an alternative approach to weaning was introduced, including screening for eligibility for daily ECMO liberation trials, emulating spontaneous breathing trials for ventilated patients. Entry criteria included at least 12 hours of treatment for ARDS, absence of neuromuscular blockade, hemodynamic stability, reasonable mechanical ventilation parameters, and extracorporeal blood flow $\leq$ 5 L/min and SGF $\leq$ 4 L/min. Patients meeting entry criteria were then assessed for readiness for liberation by conducting a sweep off trial (SOT). SOTs consisted in interrupting SGF (i.e., 4L/min to 0L/min) while monitoring hemodynamics, respiratory mechanics, surrogates of respiratory drive and effort, and gas exchange. If the SOT was successful, the patient would be maintained with sweep gas off until ready for decannulation (usually within 24 hours). Patients who failed the SOT would continue to be trialed on daily basis until decannulation, as long as they met entry criteria. Differences in ventilatory, clinical and blood gas parameters were compared between differing SOT outcomes using Mann-Whitney U test.

Results:
Sixty-one SOTs were performed in 31 patients, with 19 SOTs (31%) leading to decannulation. Sixty three percent of patients were liberated with $\leq$ 2 SOTs, and 73% of patients were liberated earlier than expected (SGF $\geq$ 2 L/min). Two patients (3%) experienced SOT related complications (respiratory acidosis and atrial fibrillation). One patient was recannulated 48 hours after a successful SOT due to worsening respiratory failure and was later decannulated after treating for ventilator associated pneumonia. Four patients (21%) died after decannulation, with a median time to dead of 7.5 days (2 died of non-respiratory causes, 1 died of pulmonary hemorrhage and 1 died of hypoxemic respiratory failure). At trial termination, failed SOTs had significantly higher (median [IQR]) plateau pressure (34 [27-38] vs 29 [24-32] cmH$_2$O; p = 0.009), driving pressure (24 [19-27] vs 16 [14-22] cmH$_2$O; p = 0.002), surrogates of increased work of breathing (P$_{OCC}$ -33 [-44, -28] vs -25 [-28, -15] cmH$_2$O; p = 0.01) (P0.1 -8 [-11,-6] vs -3 [-5,-3] cmH$_2$O; p = <0.001), and higher ventilatory ratio (3 [2-3] vs 2 [2-3]; p = 0.021), lower PaO$_2$ (70 [62-89] vs 104 [78-116] mmHg; p = 0.001) and PaO$_2$/FiO$_2$ (118 [96-197] vs 203 [166-258]; p = 0.002). The median time to SOT failure was 0.25 hours (0.25 [0.25-1.50]). The most common reasons for failing the SOT were hypoxemia (40%) and increased work of breathing (36%).

Conclusions:
Incorporating a standardized liberation protocol with SOTs in patients with COVID-19 ARDS treated with VV ECMO is feasible, and provides an alternative strategy to current practice. The utility of standardized SOTs in expediting liberation from VV ECMO warrants further research.

DECLINE IN VENTILATORY RATIO AS A PREDICTOR OF MORTALITY IN ADULTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME RECEIVING PRONE POSITION

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Introduction and objective: Prone position is an adjuvant treatment for patients with moderate to severe acute respiratory distress syndrome (ARDS). Despite proven mortality benefit, it remains unclear which physiological changes after prone positioning are translated into better clinical outcomes. We sought to determine the association between relative changes in physiological parameters at twenty-four hours of prone positioning and outcomes (mortality and liberation from invasive ventilation) in adult patients with ARDS. Our study hypothesis was that certain relative changes in physiological parameters at twenty-four hours would help identify those patients with improved clinical outcomes after prone positioning.

Methods: Using the VENTILA data base, a prospective cohort of adults with ARDS that received invasive mechanical ventilation in 349 intensive care units from 23 different countries, we performed a retrospective cohort study including patients receiving prone positioning during the first 7 days of invasive mechanical ventilation. Using multivariable logistic regression, we assessed the association between relative changes in physiological parameters at 24 hours of prone positioning (Pa_{O2}/Fi_{O2} ratio, dynamic driving pressure, $PaCO_2$ and ventilatory ratio) with ICU mortality (primary outcome). Relative changes were estimated as: value day 2-value on day 1/value day1. Measures of association are reported as odds ratios (OR) with 95% confidence intervals (CI). We used proportional-hazard models accounting for the competing risk of death and reporting subdistribution hazard-ratios (sHR) and 95% CI to assess for association between relative changes at 24 hours with time to liberation from mechanical ventilation (secondary outcome). We replicated our analyses in a propensity-score matched population of patients not receiving prone positioning as a negative control.

Results: The cohort consisted of 1124 patients with ARDS admitted from 2010 to 2016, of which 156 patients met inclusion criteria. ICU mortality occurred in 82 (53%) of the patients. After adjusting by baseline confounders, a relative decline in the ventilatory ratio at twenty-four hours was associated with lower ICU mortality (OR 0.80; 95% CI 0.66-0.97, every 10% decrease). Relative changes in Pa_{O2}/Fi_{O2} (OR 0.89; 95% CI 0.77-1.03, every 25% increase), $PaCO_2$ (OR 0.97; 95% CI 0.82-1.16, every 10% decrease) and dynamic driving pressure (OR 0.98; 95% CI 0.89- 1.07, every 10% decrease) were not associated with ICU mortality. Relative changes in ventilatory ratio (sHR 1.12; 95% CI 1.01-1.24) and Pa_{O2}/Fi_{O2} (sHR 1.06; 95% CI 1.01-1.12) were associated with time to liberation from mechanical ventilation. These findings were not replicated in a propensity-score matched population of patients not receiving prone positioning.

Conclusion: In patients with ARDS receiving prone positioning, a relative decline in the ventilatory ratio at twenty-four hours is associated with lower ICU mortality. These findings might have important implications to assess response to prone positioning in this population.

Appendix

Figure 1. Relative Changes on Respiratory Physiologic Parameters and Mortality
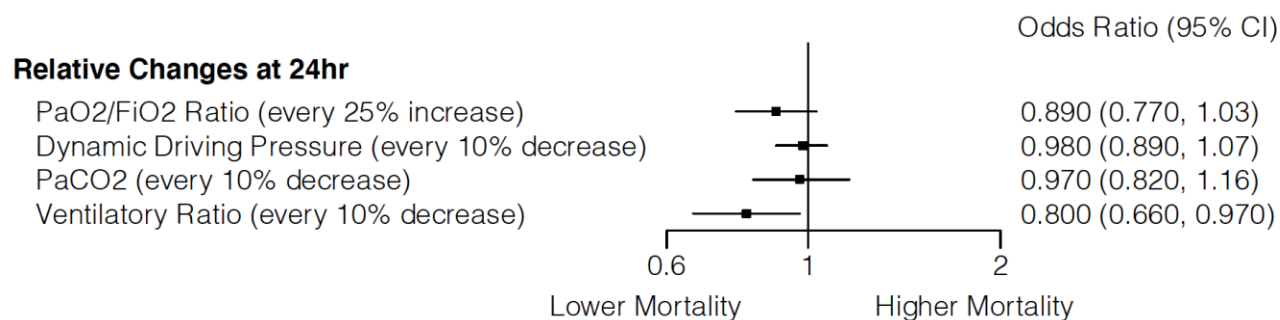
The Figure shows results of four different multivariable logistic regression models. Each model includes the key exposure represented in the figure and the following potential confounders: age, sex, SAPS II score, presence of shock, PaO_2/FiO_2 at baseline and dynamic driving pressure at baseline. Models where the exposure are relative changes in dynamic driving pressure and PaO_2/FiO_2 do not include these respective variables at baseline.
* Abbreviations: CI, confidence interval. PaO_2/FiO_2, ratio of arterial Oxygen partial pressure to fractional inspired Oxygen. $PaCO_2$, Partial pressure of Carbon dioxide in arterial blood.

Figure 2. Relative Changes on Respiratory Physiologic Parameters and Time to Liberation from Mechanical Ventilation
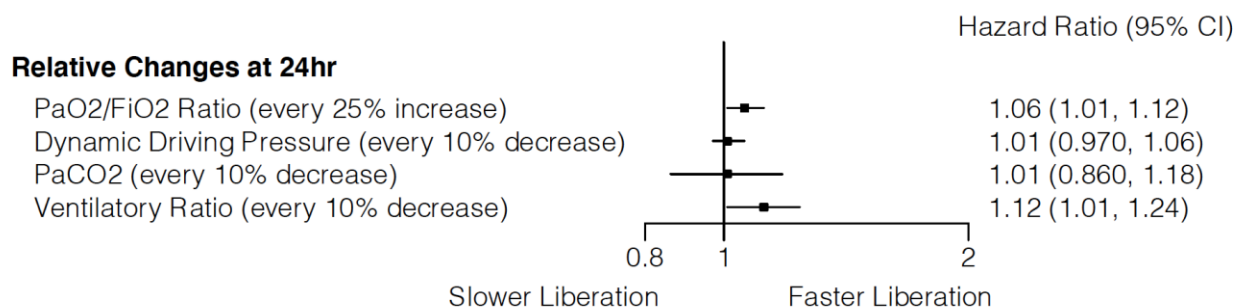
The Figure shows results of four different proportional-hazards regression models which account for the competing event of death before liberation from mechanical ventilation. Each model includes the key exposure represented in the figure and the following potential confounders: age, sex, SAPS II score, presence of shock, PaO_2/FiO_2 at baseline and dynamic driving pressure at baseline. Models where the exposure are relative changes in dynamic driving pressure and PaO_2/FiO_2 do not include these respective variables at baseline.
* Abbreviations: CI, confidence interval. PaO_2/FiO_2, ratio of arterial Oxygen partial pressure to fractional inspired Oxygen. $PaCO_2$, Partial pressure of Carbon dioxide in arterial blood.

Figure 3. Association between the change in ventilatory ratio and mortality in patients with ARDS in supine versus prone position
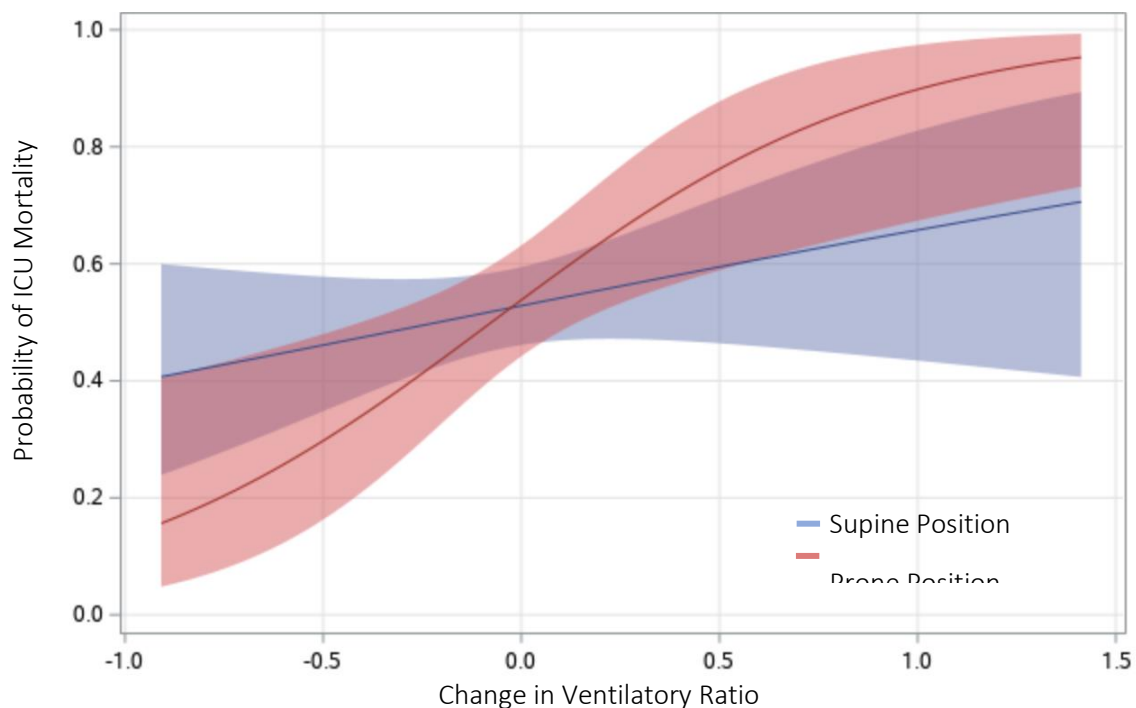
The Figure represents the results of the association between relative changes in ventilatory ratio and the probability of ICU mortality in the study cohort including proned and propensity score matched supine patients. The plot represents a post-estimation effect fit plot. As depicted in the Figure, there is an interaction between changes in ventilatory ratio and patients' position in its association with ICU mortality. Changes in ventilatory ratio of 0 or less imply an improvement within 24 hours, whereas a change in ventilatory ratio of 0 or more implies no change or worsening.

LONGITUDINAL MULTI-OMICS IN CRITICALLY ILL COVID-19 PATIENTS

U Trahtemberg[1], MJ Fritzler[2], R Rottapel[3,4], AS Slutsky[5,6], L Brochard[1,6], V di Giovanni[7], CC dos Santos[1,5,6]* and AJ Baker[1,5,6]*, the COVID-19 longitudinal biomarkers in lung injury.

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Introduction and Objective: COVID-19 is a multifaceted disease that remains only partially comprehended by the medical and scientific community. Our objective is to study critically ill COVID-19 patients with lung injury, to better understand the immune and physiological networks underpinning the disease, its progression and outcomes. Importantly, given the translational nature of our study, we apply four key methodological aspects to enrich our analysis: use of an appropriate control group, longitudinal follow up, extensive multi-omic data, and rigorous standard operating procedures.

Methods: Patients with respiratory failure were recruited on admission to the ICU and divided into COVID+ and COVID- cohorts by PCR, providing a well-matched control group of similar severity. Detailed clinical data (demographics, severity scores, chart data, lung injury-specific measures and clinical laboratory) and blood sampleswere collected longitudinally (admission and days 3, 5, 7, 10, 15, 22 and then biweekly) until death, hospital discharge or up to 3 months following ICU admission. Blood samples were analyzed by cytokine panel, lung injury biomarkers, autoimmune and anti-SARS-CoV2 serology, RNA sequencing, miRNA (subgroup), methylomics, proteomics (subgroup), antigenemia, viremia, metabolomics (subgroup), and immunophenotyping. Our collaborators are conducting studies on lipidomics, variant-specific antibodies, endothelial and vascular dysfunction, glycocalyx disruption, RNA sensors, microfluidic devices, COVID-19 markers in saliva, long term outcomes in COVID-19 and muscle organoids. Finally, data and samples are part of the Uof T COVID-19 biobank consortium.

Results: We recruited St. Michael's first ICU COVID-19 patient in March 2020. Subsequently, we recruited 80 COVID+ and 80 COVID- patients admitted directly to the ICU, as well as 30 "delayed" COVID+ patients that were admitted to the ICU later in their course or for non-respiratory reasons. Our study includes patients with the original strain and variants of concern, patients treated with/without dexamethasone and with/without anti-IL6. We recently published on autoantibodies in a cohort of 20 COVID+ and 20 COVID-, showing no statistical difference (1,2), refuting previous studies that used inappropriate controls and ascribed autoimmunity to COVID-19. We also showed a lack of association of anti-cardiolipin autoantibodies with thrombotic events in this cohort. Conversely, we showed a high prevalence and incidence of autoantibodies among respiratory failure patients irrespective of COVID-19 status, and an association with disease severity. We are currently analyzing results of 115 patients from the larger cohort which we will present at the conference (including but not only autoimmune serology).

Conclusions: The autoantibodies studied to date are a feature of critical disease and are not COVID-19 specific but can be associated with disease severity. Our study will elucidate the immune and physiological dynamics of respiratory failure in COVID and non-COVID critically ill patients.

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VENOVENOUS EXTRACORPOREAL MEMBRANE OXYGENATION IN PATIENTS WITH ACUTE RESPIRATORY FAILURE FROM COVID-19

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Introduction & Objective: The optimal indications for extracorporeal membrane oxygenation (ECMO) and modifiers of treatment effectiveness in patients with acute respiratory failure from COVID-19 are currently unknown. Established protocols are largely based on a randomized controlled trial in patients without COVID-19. We emulated a pragmatic clinical trial using observational data from the COVID-19 Critical Care Consortium to determine the effectiveness of ECMO therapy compared to conventional mechanical ventilation and to analyze different clinical criteria for the decision to initiate ECMO in patients with acute respiratory failure from COVID-19.

Methods: Patients were included in the analysis if they were admitted to participating Intensive Care Units with clinically suspected or laboratory-confirmed SARS-CoV-2 infection between January 3, 2020, and January 26, 2021. We compared the receipt of usual care, which included treatment with ECMO if deemed clinically indicated, to treatment with conventional mechanical ventilation without the use of ECMO. The primary outcome was hospital mortality up to 60 days after intensive care unit admission. Adherence-adjusted estimates were calculated using marginal structural models with inverse probability

weighting, accounting for baseline and time-varying confounding, as well as for competing events (death versus hospital discharge).

Results: A total of 3,248 patients from 25 countries were eligible for analysis. Hospital mortality was 38.2% (95% confidence interval [CI]: 36.1% to 40.3%) under usual care compared to 40.7% (95% CI: 35.7% to 45.8%) had patients received conventional mechanical ventilation without ECMO (risk ratio 0.94; 95% CI 0.84 to 1.05). ECMO therapy would have been most effective if provided to patients with age ≤ 65 years and ratio of arterial partial pressure of oxygen-to-fraction of inspired oxygen (PaO_2/FiO_2) ≤ 80 mmHg (risk ratio 0.58, 95% CI: 0.45 to 0.76) or with driving pressures > 15 cmH_2O (risk ratio 0.73, 95% CI: 0.60 to 0.89) during the first 10 days of mechanical ventilation.

Conclusion: Age and severity of hypoxemia, as well as the duration and intensity of mechanical ventilation should be considered when deciding to initiate ECMO in patients with COVID-19.

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Physiology Abstracts

100 PV: A MULTI-PATIENT VENTILATOR

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The ongoing COVID-19 pandemic has brought out a severe shortage of ventilators around the world. As a result, a number of new basic emergency-use designs have emerged, most of which lack patient-ventilator synchrony capabilities. Patient-ventilator synchrony allows the patient to trigger the inhalation and exhalation cycle, which would normally be time triggered. This triggering is used in Pressure Support and CMV Mode, the ventilation modes used to wean recovering patients off of mechanical ventilation. To address this problem, our team has designed a cost efficient ventilator which would have patient-ventilator synchrony capabilities.

The design is a multi-patient ventilator which uses a single gas processing system. Through a single air compressor and oxygen source, our ventilator can provide mechanical ventilation to multiple patients in parallel. Each patient has his/her own control system which provides patient-ventilator synchrony capabilities and a unique ventilation settings catered to the individual's needs. A dedicated flow and pressure sensor detects patient inhalation or exhalation efforts. For cost effectiveness, the ventilator utilizes off the shelf components.

A prototype was constructed and tested with an artificial lung (Quick Lung). The ventilator was initially tested for the basic pressure control mode, where the inhalation and exhalation cycles are time triggered by the ventilator. The ventilator successfully ventilated the patient with the inputted inhalation and exhalation times. To test patient support mode, both inhalation and exhalation triggering were tested. Through physical manipulation of the artificial lungs, the ventilator was triggered and switched from inhalation to exhalation or exhalation to inhalation as desired. With this patient triggering simulation, we have shown the patient-ventilator synchrony capabilities within our design. The overall per patient cost of the ventilator was around $2000.00 CAD, significantly cheaper than the regular $25000 CAD ventilators. Our ventilator has shown patient ventilator synchrony capabilities while also being cost effective. Further testing is to be conducted with multiple parallel patient lines to see the effects of multiple patients.

REGIONAL PHRENIC NERVE BLOCK IN PATIENTS WITH ARDS AND HIGH SPONTANEOUS BREATHING ACTIVITY – A PILOT STUDY

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Abstract

Introduction and Objective

The use of assisted ventilation in patients with acute respiratory failure may improve hemodynamics and oxygenation. These benefits, however, may be overshadowed by strong spontaneous inspiratory efforts that ultimately lead to the loss of protective mechanical ventilation, possibly causing lung injury. In this scenario, some may reinstate deep sedation and even neuromuscular blockade. These strategies, nevertheless, may have serious adverse effects. Our objectives were to evaluate both in an animal model and in patients with acute respiratory distress syndrome (ARDS) the feasibility and safety of phrenic nerve blockade with the administration of perineural lidocaine under ultrasound guidance in order to reduce tidal volume and peak transpulmonary pressure in spontaneously breathing patients.

Methods

An established animal model of ARDS was used first in a proof-of-concept study. We then evaluated the effect of the technique in nine mechanically ventilated patients under pressure support with a driving pressure greater than 15 cmH$_2$O or a tidal volume (V$_T$) superior to 10 ml/Kg of predicted body weight. Ultrasound imaging together with a nerve stimulator were used to identify the phrenic nerve. Perineural lidocaine was administered first in the left and then 10 minutes later in the right phrenic nerve. Subjects were followed until return to baseline.

Results

In pigs and humans, all variables decreased significantly after bilateral phrenic nerve block. In pigs, V$_T$ decreased from 8.1±1.3 to 5.9±0.9 ml per kg of predicted body weight (p<0.001), peak ΔPL from 25.0±6.7 to 17.2±5.1 cmH$_2$O (p<0.001), and driving pressure from 24.6±8.7 to 17.8±5.1 cmH$_2$O (p<0.001). In humans, V$_T$ decreased from 9.7±2.8 to 6.7±1.5 ml per kg of predicted body weight (p<0.01), peak transpulmonary pressure from 28.0±11.8 to 20.1±6.2 cmH$_2$O (p<0.05), driving pressure from 29.1±11.8 to 19.9±6.9 cmH$_2$O (p<0.01). Esophageal pressure swings and electrical activity of the diaphragm also decreased. All variables returned to baseline after 12.7 [6.7-13.7] hours.

Conclusions

Phrenic nerve block is feasible, lasts around 12 hours, and reduces tidal volume and driving pressure in patients under assisted ventilation.
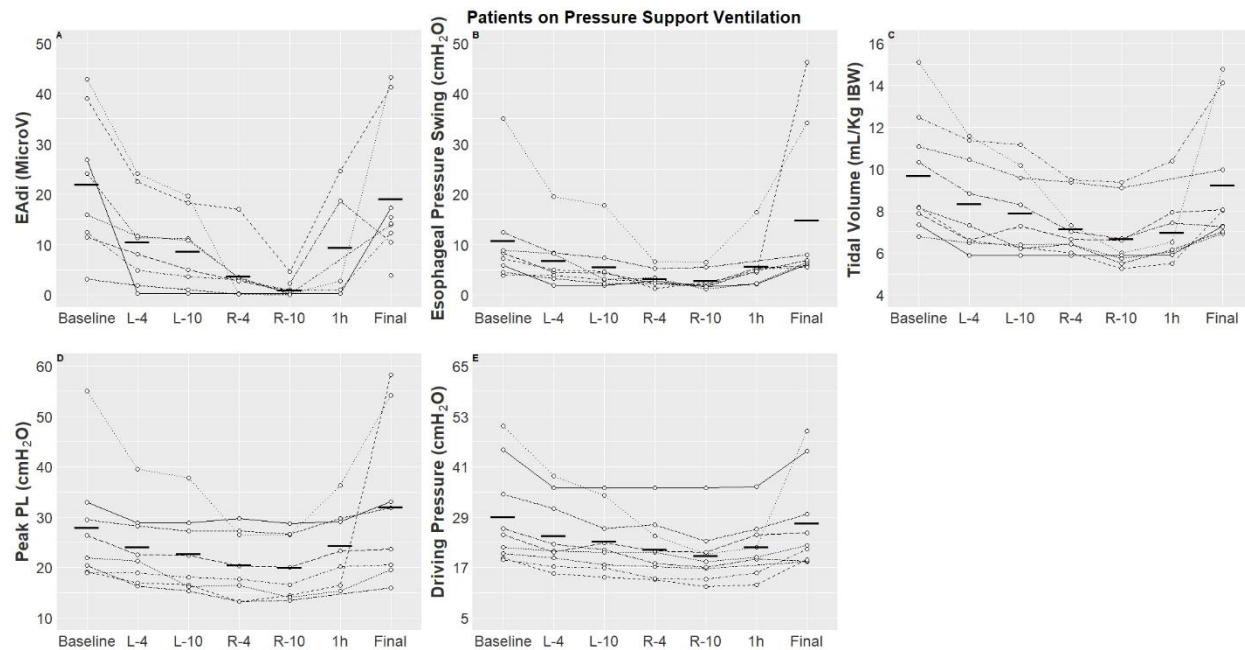
Figure – Progress of respiratory variables in patients on pressure support ventilation

DIAPHRAGM ELECTRICAL ACTIVITY DURING EXPIRATION IN CRITICALLY ILL PATIENTS – THE EFFECT OF REVERSE TRIGGERING.

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Introduction & objectives.

Our main objective was to investigate the intensity and pattern of the diaphragm electrical activity (Edi) during reverse triggering (RT) as an example of patient-ventilator dyssynchrony. The timing of diaphragmatic activity during the inspiratory and expiratory phase of the mechanical ventilator could have various physiological consequences. Additionally, we aimed to characterize the prevalence of mandatory breaths with and without RT, double cycling and triggered breaths in mechanically ventilated critically ill patients early in the course of mechanical ventilation and the association with sedation.

Methods.

Study design. Secondary analysis of a prospective observational study in critically ill patients (DIVIP; NCT02434016; REB#15-073). Edi was continuously recorded after intubation until recovery of full spontaneous breathing, extubation, death or 120 hours. A 1-hour waveform of Edi, airway pressure and flow recording was collected daily and used for this study.

Offline analysis.

Breath's classification. Each breath was classified as triggered by the patient, mandatory with or without RT or double cycling. Triggered breaths were identified by an Edi >0.5 µV above baseline or a drop < -0.33 cmH$_2$O (Neurosync criteria) at the beginning of the mechanical insufflation and a peak Edi (Edi$_{PEAK}$) >2 µV. Mandatory breaths with and without RT were identified according to the presence or absence of an increasing Edi after the beginning of a mandatory insufflation with an Edi$_{PEAK}$ >2 µV, respectively. Double cycling was identified as the second breath triggered by the patient due to an inspiratory effort that persisted beyond the inspiratory phase of the ventilator. Breaths lasting less than 0.5 seconds were considered artifacts and excluded from the analysis.

Patient-ventilator synchrony. Edi peak and offset (Edi$_{PEAK}$ and Edi$_{OFF}$, respectively) were identified for each breath. Edi$_{PEAK}$ was the higher Edi activity in µV, Edi$_{OFF}$ was defined as when Edi decreased by 30% after reaching Edi$_{PEAK}$ (NAVA criteria). To compare patient-ventilator (dys)synchrony during inspiratory-to-expiratory cycling between the different types of breaths, we compared the % of breaths in which Edi$_{PEAK}$ and Edi$_{OFF}$ occurred during the expiratory phase of the ventilator between each type of breath.

Edi intensity and Pattern. The inspiratory and expiratory phases of the mechanical ventilator were divided into quartiles and the mean Edi (µV) during each quartile was calculated and compared between the different types of breaths. Phase angles (θ) were calculated to characterize RT as per the standard equation: θ= ([Edi onset time – ventilator onset time] / total time of the ventilator cycle) * 360. Mandatory breaths without RT had no significant Edi activity (≈ 0.5 µV).

Sedation use was recorded from the hospital records and the average of the 24h before the Edi recordings was calculated. Each day was then classified as having 1) $\geq 10\%$ of RT; 2) $<10\%$ RT and mostly triggered breaths; 3) $<10\%$ RT and mostly mandatory non-RT breaths. Sedation use was compared between each of these 3 classifications.

Results.

Patients' characteristics. This preliminary analysis reports data from 12 patients aged (mean ± standard deviation) 64±22 years, 60% female, APACHE II 25±8. Reasons for mechanical ventilation were 75% respiratory. Patients had 2.5±1.3 days of recordings, totaling 45 days of recordings and 62885 breaths.

Prevalence of breath types. 52% of all breaths were triggered breaths, 39% were mandatory breaths without RT, 5% were RT (ranging from 10% in day 1 to 0.03% in day 5) (θ: median[25%-75%IQR] 72[37-107]º) and 4% were double cycling (*P*<0.01 between all).

Inspiratory-to-expiratory cycling synchrony. Edi$_{PEAK}$ occurred during the ventilator expiratory phase in 20% of the breaths triggered during assist-control and 8% during pressure support. Edi$_{OFF}$ occurred during the expiratory phase of the ventilator in 59% of the breaths triggered during assist control and 47% during pressure support. Edi$_{PEAK}$ occurred during the ventilator expiratory phase in 76% of the RT and 17% during double cycling. Edi$_{OFF}$ occurred during the expiratory phase of the ventilator in 90% of the RT and 39% during double cycling (*P*<0.01 between all).

Edi intensity. Edi$_{PEAK}$ was (median[25%-75%IQR]) 5[4-15] µV during RT, 8[6-15] µV during triggered breaths and 9[4-23] µV during double cycling (*P*<0.01 between all). Overall, double cycling had greater Edi intensity than triggered breaths and

RT ($P<0.01$). Figure 1 shows the average Edi intensity at the different moments of the respiratory cycle for each type of breath. The high Edi intensity on the first inspiratory quartile of the second breath of double cycling reflects that the breath was triggered before the previous breath reached Edi_{OFF}. Triggered breaths had greater Edi intensity than RT ($P<0.01$).

Sedation use. Table 1 shows sedation use was greater in days which mandatory non-RT breaths were the most prevalent. Days with more than 10% of RT had less use of sedation than days with most mandatory non-RT breaths and more than days with most triggered breaths (Table 1).

Conclusion.

Patients have the offset of the neural inspiratory drive occurring during the expiratory phase of the ventilator in approximately 50% of breaths. Double cycling was associated with greater inspiratory drive and worse patient-ventilator synchrony during the previous breath. Our preliminary data confirm the high prevalence of reverse triggering in mechanically ventilated patients, mostly in the initial course of mechanical ventilation, and support the hypothesis that reverse triggering might occur during the transition phase between deep sedation and the onset of the patient triggering the ventilator.

Table 1. Mean sedation use adjusted by body weight 24h before the Edi recordings according to the most prevalent type of breath during the recording period of each day.

	Days with most mandatory breaths with less than 10% of RT	Days with more than 10% of RT	Days with most triggered breaths and less than 10% of RT
Number of days	13	8	24
Mandatory breaths without RT (%)	97 ± 6	28 ± 21*	5 ± 6*¥
Mandatory breaths with RT (%)	1.7 ± 2	24 ± 28*	0.3 ± 2.7 ¥
Triggered breaths (%)	2.5 ± 5	47 ± 31*	94 ± 7*¥
Double cycling (%)	0 ± 0	0.4 ± 0.5	2 ± 3
Propofol (mg/hour/kg)	2.79 ± 2.90	0.91 ± 1.32	0.26 ± 0.49*
Midazolam (mg/hour/kg)	6.48 ± 5.31	0 ± 0*	0.26 ± 0.90*
Fentanyl equivalent (mcg/hour/kg)	3.78 ± 3.79	0 ± 0	0.09 ± 0.22

*$P<0.05$ vs. Days with mandatory breaths with less than 10% of RT. ¥ $P=0.03$ vs. Days with more than 10% of RT.
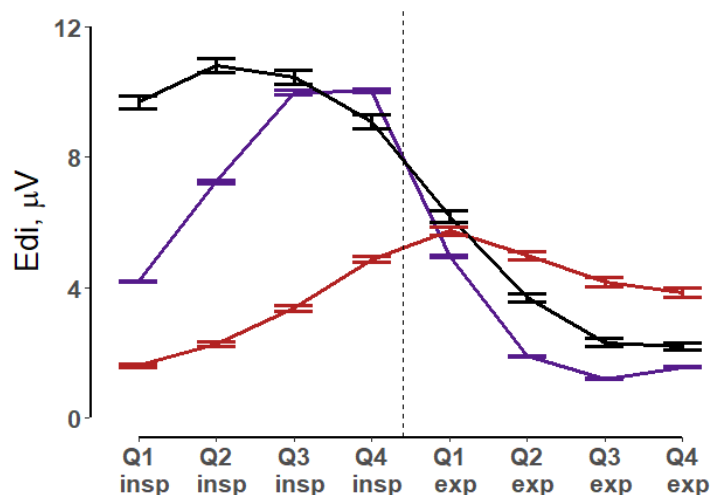
Figure 1. Mean Edi intensity (μV) during inspiratory and expiratory quartiles of the ventilator cycle. $P<0.01$ for all between-group comparisons. Red line: RT breaths; Purple line: triggered breaths; black line: double cycling. Q1 insp – Q4 insp: 1st - 4th quartile of the inspiratory phase of the mechanical ventilator; Q1 exp – Q4 exp: 1st – 4th quartile of the expiratory phase of the mechanical ventilator. The dashed line represents the end of the inspiratory phase of the mechanical ventilator defined by the zero-crossing line of the flow signal.

THE OPTIMAL PEEP STUDY: LUNG COLLAPSE VERSUS LUNG OVERDISTENSION – *PROTOCOL AND PRELIMINARY RESULTS*

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Introduction: The use of Positive End-Expiratory Pressure (PEEP) has been associated with reduction in lung collapse and increased oxygenation in some ventilated patients with Acute Respiratory Distress Syndrome (ARDS). An individualized approach proposed for setting PEEP in ARDS patients is the crossing point between the relative lung collapse and relative overdistension, assuming that both phenomena are equally harmful. However, some studies have suggested that to prevent overdistention is more important than to prevent collapse.

Objective: To address the impact of setting PEEP based on the crossing point of collapse and overdistension, compared to PEEP set at low collapse and PEEP set at low overdistension, on the lung inflammation, respiratory function and hemodynamics, during long-term mechanical ventilation in ARDS.

Methods: This is an experimental randomized controlled study in a porcine ARDS model. We use Electrical Impedance Tomography (EIT) to measure relative lung collapse and overdistension. After lung injury, the pigs are randomized in one of three intervention groups: low PEEP group (low overdistension), the pig is ventilated with PEEP set at 0-3% of overdistension; middle PEEP group, PEEP set at the crossing point of collapse and overdistension; or high PEEP group (low collapse), PEEP set at 0-3% of collapse. The pigs are ventilated for 12 hours with the randomized PEEP. We collect blood samples and respiratory and hemodynamics variables, including esophageal pressure, EIT measurements, cardiac output and pulmonary arterial pressure, every three hours. At the end of the protocol, we also do biological and histological analysis.

Preliminary results: We conducted a preliminary analysis in nine pigs, three per group. One pig (33%) in the low PEEP group died when we set the randomized PEEP. Median and Interquartile Range (IQR) PEEP was 8 (6-9) for low PEEP group, 11 (10-11) for middle PEEP group, and 14 (13-15) for high PEEP group. We computed the change of driving pressure driving pressure over time (Delta DP = DP final – DP initial), to calculate our sample size. The mean delta DP was 1.5 ± 2.1 cmH$_2$O for low PEEP group, -0.3 ± 2.1 cmH$_2$O for middle PEEP group, and -1.3 ± 0.6 for high PEEP group. We also computed the mean wet-to-dry ratio, it was higher for the low PEEP group (7.32 ± 0.39), and lower for the high PEEP group (6.50 ± 0.38). Based on these preliminary data, we are going to include a total of 32 pigs, 12 per group. The results of this study may help to understand better the role of collapse and overdistension in ventilator-induced lung injury in ARDS.
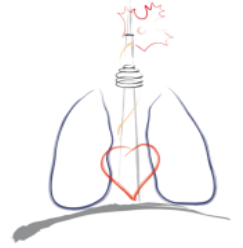
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Quality ImprovementAbstracts

SURVEY OF ANTIBIOTIC DURATION IN CRITICALLY ILL PATIENTS WITH BLOODSTREAM INFECTIONS BETWEEN CRITICAL CARE AND INFECTIOUS DISEASES SPECIALISTS IN KUWAIT

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Introduction & Objectives: Antibiotic duration for bloodstream infections is an area of controversy and uncertainty in critically ill patients due to the scarcity of an evidence based from randomised controlled trials. Our primary objective is to assess antibiotic treatment durations recommended by critical care and infectious diseases specialists in Kuwait. Our secondary objective is to assess (i) practice heterogeneity; (ii) equipoise for a trial of shorter versus longer therapy; and (iii) the influence of pathogen and host characteristics on treatment duration recommendations.

Methods: Kuwaiti infectious diseases, critical care specialists and anaesthetists with critical care experience were surveyed regarding their recommended antibiotic treatment durations for five common bacteraemic syndromes. Questions with various host and pathogen characteristics were provided to estimate their influence in antibiotic duration decisions.

Results: In total, 112 clinicians responded to the survey giving a 68% response rate (36% ID, 17% critical care and 47% anaesthesia). The median (interquartile range, IQR) for antibiotic duration of each syndrome was similar: central vascular catheter-related bloodstream infection, 10 days (IQR 7); bacteraemic pneumonia, 10 days (IQR 7); bacteraemic urinary tract infection, 10 days (IQR 7); bacteraemic intra-abdominal infection, 10 days (IQR 7); and bacteraemic skin and soft-tissue infection, 10 days (IQR 7). The median antibiotic duration for the following bacteria were: Staphylococcus aureus, 14 days (IQR 4); ESBL Escherichia coli, 10 days (IQR 7); MDR Pseudomonas aeruginosa, 14 days (IQR 4); MDR Acinetobacter baumanni, 14 days (IQR 4); VRE Enterococcus faecalis, 14 days (IQR 4); carbapenem resistant Klebsiella pneumoniae, 14 days (IQR 4); and Coagulase negative Staphylococcus 7 days (IQR 3). However, we also found for all infectious syndromes and individual organisms, duration responses often followed discrete choices of 5 days, 10 days and 14 days. 70% of respondents would prescribe longer duration of antibiotic therapy for patients who are immune suppressed.

Conclusion: This survey highlights significant practice variation in antibiotic duration therapy for bloodstream infections found in a previous similar survey done in Canada. These findings also support the need in Kuwait for an adequately powered randomized controlled trial assessing optimal antibiotic duration for bacteraemic syndromes and pathogens.

FACILITATION OF "HIDDEN" CLINICAL INFERENCES IN THE PEDIATRIC INTENSIVE CARE UNIT: PRELIMINARY EVALUATION OF A TASK-BASED VISUAL ANALYTICS TOOL CALLED IN-SIGHT

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Introduction and Objective: Clinical decision-making in the Pediatric Intensive Care Unit (PICU) is challenging due to patient complexity and data integration demands that impose a significant cognitive load on clinicians. Inefficient data integration can result in patient harm. The current electronic health record (EHR) fails to effectively present data to support clinical decision-making and thus important patient inferences may be "hidden" to clinicians. Visual analytics tools are needed that present data in ways that make data integration and "hidden" inferences easier for clinicians to see. Our objective was to develop and evaluate a novel visual analytics tool – In-Sight – that displays key clinical data and their relationships to drive patient inferences in a more efficient, accurate, and user-friendly way than the current EHR. We focused on displaying fluids, electrolytes, and nutrition (FEN) data in our prototype due to the known complexity and interdependence of data elements within this care domain and the importance of this domain to every ICU patient every day.

Methods: In-Sight was designed by our team of PICU clinicians and computer scientists. We first performed a task analysis to determine how a visual analytics tool could best augment FEN inferences at the bedside. We then developed a novel interactive web application that displays interrelated FEN high-level trends, detailed data elements, and suggested inferences (https://clinicalvis-ver7.herokuapp.com/intro-video). After multiple rounds of development sprints informed by clinician focus groups and split run testing, we performed an asynchronous multicenter evaluation. Users were asked to use In-Sight to identify 3 intended inferences for a simulated patient case and provide feedback about task-specific (e.g. identification of fluid overload) and overall (e.g. user-friendliness) usability on a 1 - 10 scale compared to their current EHR. Wicoxon rank sum and Kruskall-Wallis tests evaluated for differences between groups, as appropriate.

Results: Forty-eight participants (31% residents, 31% fellows, and 31% staff) from 4 centers completed the evaluation. The simulated case was rated moderately realistic (median 4 interquartile range (IQR) 3 - 4) and moderately difficult (median 4, IQR 3 - 5) by users on a 1 - 5 Likert scale (1 = very unrealistic/easy; 3 = neutral; 5 = very realistic/challenging). Overall, 83% of participants determined at least 2 of the 3 intended inferences. The median time spent on the inference task ranged from 32 seconds (IQR 11 - 44) in residents to 77 seconds (IQR 12 - 97) in fellows. Residents were least likely to identify all 3 intended inferences (7%) compared to fellows (53%) and staff (47%) (p = 0.02, fig. 1A) and least likely to choose the most beneficial action (residents 54%, fellows 93%, staff 87%, p = 0.02). In-Sight was rated superior to the current EHR in every specific task workflow (all p < 0.001) and overall (all p < 0.0001, figs. 1B and 1C). There were no differences between roles in the task-specific ratings, but residents had lower overall ratings of In-Sight than fellows or staff, p = 0.02).

Conclusion: In-Sight efficiently facilitated inferences in a challenging simulated patient case and was rated more favorably than the EHR at four different centers in both workflow-specific and overall domains. In-Sight performance and ratings differed by level of experience/role. Further research is needed to understand how best to optimize In-Sight for all end-users and integrate the tool into clinical workflows.
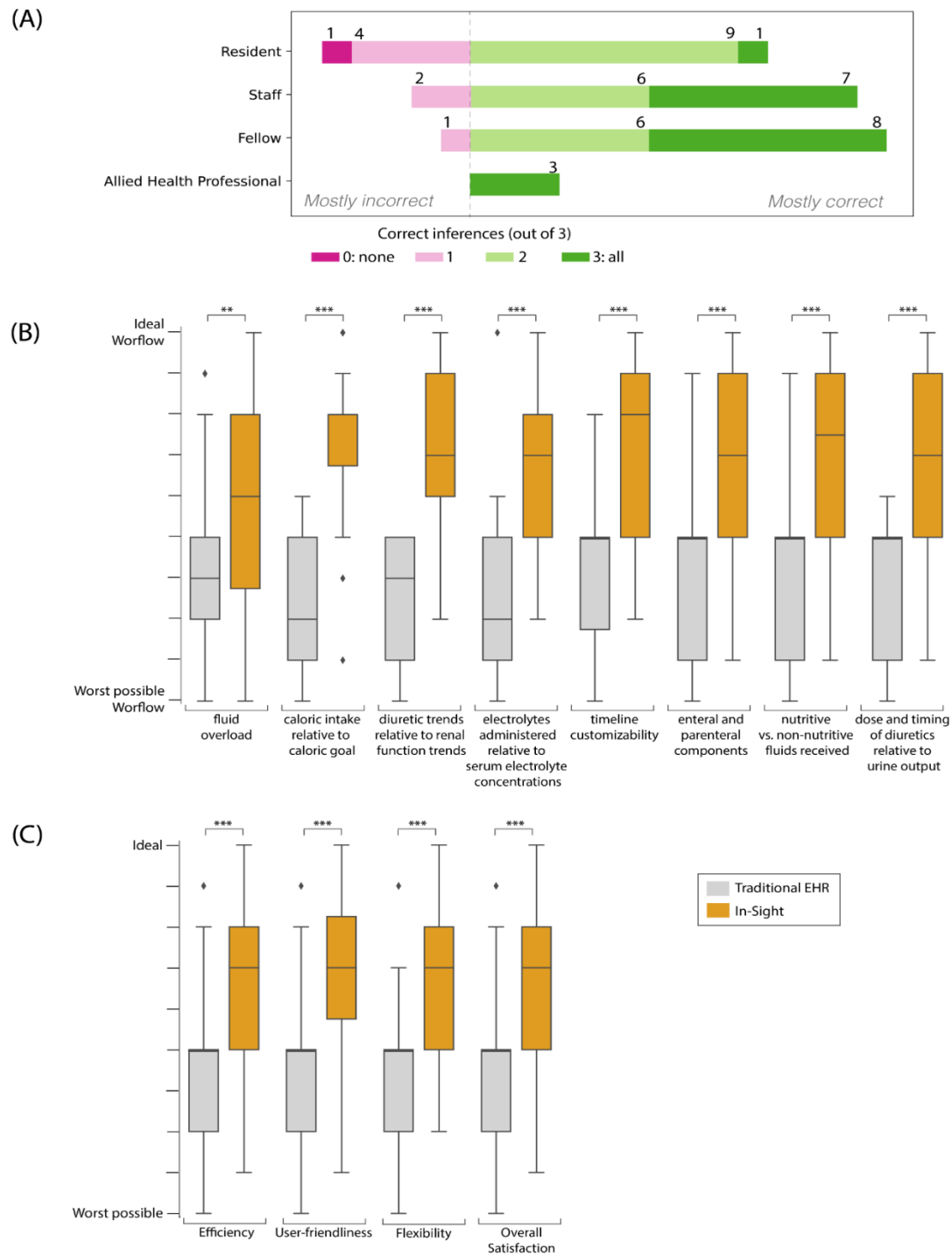
Figure 1. A) Correct inferences by role; B) Ratings of In-Sight vs. current EHR on specific task workflows and C) Ratings of In-Sight vs. current EHR on overall metrics of usability. ** p < 0.001, *** p < 0.0001

AN ANALYSIS OF CHILDREN ADMITTED TO PICU VERSUS THOSE DIVERTED TO ANOTHER CARE SETTING FOLLOWING TRANSPORT BY AN INSTITUTIONALLY-BASED PAEDIATRIC TRANSPORT TEAM

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Introduction & Objectives:

Critically ill children have improved outcomes when they are treated at dedicated pediatric tertiary care centers and when they are transported to these centers by pediatric transport teams. However, there is an increasing recognition that there are some children referred to Paediatric Intensive Care Units (PICU) who do not require Critical Care, and who would benefit from care closer to home. A previous study demonstrated that only 50% of remote consultation calls to SickKids are admitted directly to a PICU. Given the substantial resources utilized during transport, we aim to determine which patients require transport to a tertiary care center for assessment and observation, and which could be appropriately cared for by their local community hospital. Our primary objective is to determine risk factors for admission to the PICU within 24h of external consultation and transport among children who are initially diverted to the Emergency Department or Pediatric ward at SickKids. Secondary objectives include comparing severity of illness and mortality between those admitted directly to PICU vs those children requiring ICU admission within 24h and 72h of initial diversion.

Methods:

This is a retrospective cohort study of all patients included in the Sick Kids Critical Care Bridge Call database between 01-01-2016 to 31-12-2020 inclusive. This database includes all external patient consultations by our paediatric consultation service and all transports logs by our institutionally based transport team. Approximately 5000 participants will be included. Clinical data from ICU admission will be linked to transport and consultation data. Descriptive statistics will be used to describe the cohort. A multivariable logistic regression model will be used to identify risk factors associated with increased odds of PICU admission within 24h of initial diversion among all patients diverted after transport. Candidate risk factors will include sex, age, principal diagnosis, severity of illness at triage, referring center characteristics (rural/urban, capacity) and duration of transport. Secondary outcome endpoints will include odds of requiring mechanical ventilation, odds of mortality, PRISM III score and PICU length of stay. Analyses will be performed with Stata/IC 15.1.

Results:

Data analysis remains ongoing and results are not yet available.

Conclusion:

We hypothesize that there are significant demographic and clinical differences between patients admitted directly to PICU and those who are diverted elsewhere, particularly those who require admission within 24h of diversion. Identification of risk factors for admission will help guide recommendations about inter-facility transport suitability and will help identify a group of children who require observation in a tertiary care center with immediate access to Critical Care.

TIMELY INTUBATION IN SEVERE TRAUMATIC BRAIN INJURY: AN INDICATOR OF TRAUMA CENTER PERFORMANCE

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Introduction & Objective: Timely intubation of patients with severe traumatic brain injury (TBI) is critical to reducing secondary brain injury. We sought to determine whether time to intubation for patients with severe TBI is a useful process measure in the assessment of the quality of trauma care and to describe trauma centers who performed consistently well.

Methods: We used data derived from ACS TQIP over 2017-19 and identified adults with severe TBI who underwent intubation upon trauma center arrival. We calculated each center's 75th percentile of time to intubation from ED arrival and characterized them as average, or as a fast or slow outlier. Outliers were centers whose 75th percentile for time to intubation were >2 standard deviations from the overall cohort.

Results: We identified 13,369 patients in 423 centers. Of these, 92 (22%) and 142 (34%) centers were classified as fast and slow outliers, respectively (figure). Fast outliers were more often level II centers (59% vs 43%, $p<0.001$), and were more frequently high-volume centers with >400 beds (72% vs 47%, $p<0.001$). Slow outliers were more frequently non-profits (94% vs 70%, $p<0.001$) or teaching hospitals (89% vs 78% p= 0.0140) and had more patients who were Black (18.3% vs 15.0%, $p<.0001$), or without commercial insurance (65.3% vs 59% $p<.0001$).

Conclusion: Time to intubation in severe TBI is a useful marker of hospital process. Non-profit hospitals with marginalized patient populations appear over-represented in the slow outlier group. Factors influencing the timeliness of intubation in this high-risk population should be evaluated to understand if the lack of resources might contribute adversely to this process measure.

Figure 1: Funnel plot representing 75th percentile intubation times versus volume of severely injured patients per center
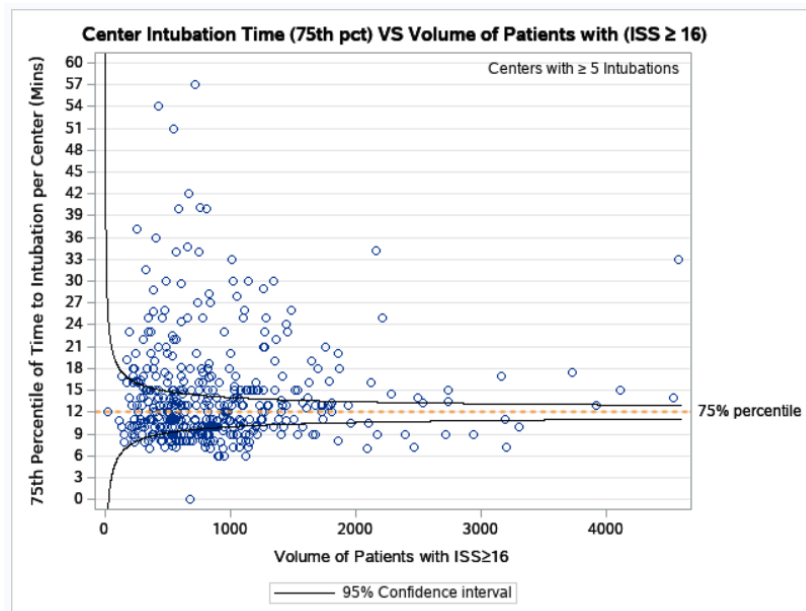
ERROR REDUCTION IN TRAUMA CARE: LESSONS FROM AN ANONYMIZED, NATIONAL, MULTICENTER
MORTALITY REPORTING SYSTEM

Doulia M. Hamad[1,2], D.M, Mandell, S.P.[3], Stewart, R.M.[4], Patel, B.[6], Guttman, M.P.[1,2], Williams, P. [1,2], Jerath, A.[2], Bulger, E.M,[3] Nathens, A.B[1,2,6].

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Introduction & Objective: The importance of system solutions to overcome human fallibility and prevent medical errors has been recognized as critical for a safer healthcare system. Yet over time rates of preventable deaths, particularly in trauma care, have not changed. We developed a mortality reporting system (MRS) to aggregate deaths with an opportunity for improvement from > 300 trauma centers. This study evaluates provider and system level strategies used by participating centers to prevent future harm.

Methods: Deaths are reported to the MRS if there is an identified opportunity for improvement, along with a mitigation strategy to avoid recurrence of the error. Using a validated framework based on the hierarchy of intervention effectiveness (figure) and consensus by three independent reviewers, we mapped mitigation strategy effectiveness from person-focused to system-oriented interventions.

Results: Over a 2-year period, 395 deaths were reviewed. 33.7% of mortalities were unanticipated, and frequently occurred after failure to rescue (36.1%). Errors frequently pertained to management (50.9%), clinical performance (54.7%) and communication (56.2%). Human failures were involved in 61% of errors. Person-focused strategies like education were common (56%), while more effective strategies such as automation, standardization and fail-safe approaches were seldom used. In 7% of cases, centers were unable to identify a specific strategy to prevent future harm.

Conclusion: Most strategies to reduce errors in trauma centers focus on changing the performance of providers rather than system-level interventions. Higher-level interventions may help reduce variability in clinical care. Centers require additional support to develop more effective mitigation strategies that will prevent recurrent errors and patient harm.

Figure 1. Thematic Analysis Framework Based on the Hierarchy of Intervention Effectiveness.
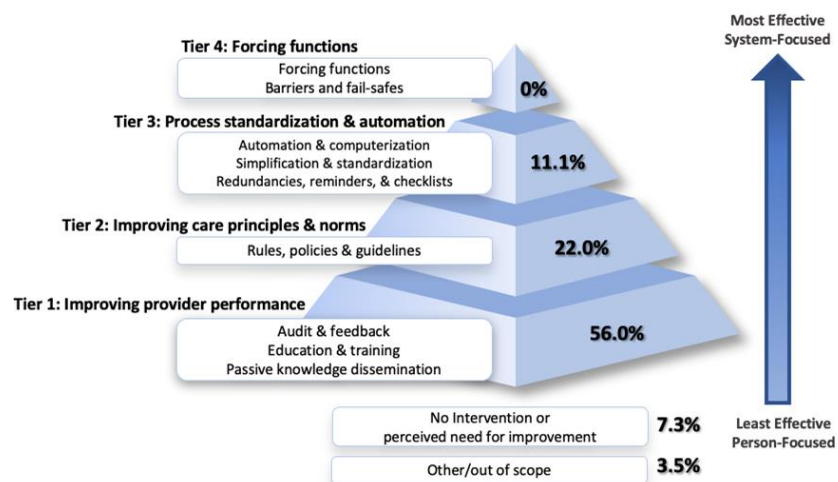
BAG-VALVE-MASK (BVM): A PERFORMANCE EVALUATON REPORT

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Introduction: Bag-valve-mask (BVM) devices, also known as manual resuscitators, are critical equipment in acute care, and are used routinely for short term manual ventilation as well as for pre-oxygenation prior to short procedures (such as ECT) or endotracheal intubation and initiation of mechanical ventilation. Unanticipated results during an unrelated experiment raised concerns regarding the performance of new BVM models in use at our centre during the COVID-19 pandemic.

Objective: We sought to evaluate the inspiratory resistance and competence of the inspiratory-expiratory control valve in in three common BVM models: Ambu Bag Spur II, CAREstream CARE-BVM and Laerdal LSR.

Methods: We evaluated inspiratory resistance and competence of the inspiratory-expiratory valve in using 3 samples of each model. Inspiratory flow and resistance were measured with expiratory ports open vs. blocked. If device valves are competent the state of the expiratory port should have no impact on inspiratory flow resistance. In the event significant changes in inspiratory resistance with obstruction of the expiratory port, flow through the expiratory port during simulated inspiration was directly measured. Testing was consistent with procedure outlined in CSA-Z10651-4-08 (R2018): Lung ventilators — Part 4: Particular requirements for operator-powered resuscitators, section A.4.8 (CSA revision of ISO 10651-4:2002), with the addition of testing under blocked expiratory port condition that is not included in the CSA/ISO standard.

Results: All samples from two models (Laerdal LSR, Ambu Spur II) showed anticipated behaviour with no effect of expiratory port blockage on inspiratory flow and resistance, though several of the samples from these two models had inspiratory pressure drops that measured as much as 10% above the maximal limit of 5 cm H_2O prescribed by CSA-Z10651-4-08(R2018).

All three samples of CARE-BVM showed lower values of inspiratory pressure drop [mean (SD)= 3.0(0.26) cm H_2O] but showed consistent and significant increases in inspiratory resistance when the expiratory port was blocked, with pressure drops of 7.8(0.72) cm H_2O, significantly exceeding the 5 cm H_2O limit. This suggests significant entrainment of outside air during negative pressure inspiration, via a leaking expiratory valve. To confirm this, we directly measured entrained air flow from the expiratory port. At 50 L/min of inspiratory flow 43-74% of inspiratory gas consisted of room air from the expiratory valve instead of flowing through the self-inflating reservoir of the BVM. This corresponds to a calculated delivered oxygen fraction of 40-60% assuming a perfect face seal and 100% oxygen flow from the BVM reservoir.

Conclusion: Our results raise a significant safety concern regarding the performance of CARE-BVM devices in spontaneously breathing patients suggesting that these patients may often be receiving a significantly lower concentration of oxygen than assumed by care providers. However, the technical standard (ISO/CSA-Z 10651-4-08) required by Health Canada and FDA does not explicitly mandate competence of the valves and only requires delivery of 35% oxygen at an external oxygen flow 15 L/min into the device, meaning that the CARE-BVM devices appears to meet the explicit requirements regarding inspiratory resistance and oxygen provision. There is significant inconsistency between clinician expectations, device performance and regulatory requirements for BVM devices.

TITLE: THE LABATT FAMILY HEART CENTER INSTITUTIONAL MEMORY PROJECT: BETTER DECISIONS WITH DATA

RM Muhame[1], O Honjo[2], C Haller[2], M Mazwi[1], MA Moga[1]

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Introduction: Paediatric cardiology patients comprise a small but distinct population with complex and diverse spectrums of diagnoses and interventions associated with decisional uncertainty, high risk of morbidity and mortality. Currently, institutional experience when required for decision making is largely supported by individual recall. We are leveraging technology to create integrated infrastructure, informed by a deep understanding of users and their environment, to support data driven decision making in this unique group.

Methods: 25 one-on-one interviews were conducted using design thinking methodology and artificial intelligence enabled thematic analysis to understand users' experiences, their environment and identify use cases.
Infrastructure development: Data definitions were abstracted from 7 multi-center cardiac registries and are being integrated into a novel, highly adaptable database that will be 'the single source of truth'.

Results: From the interviews, we found that decisions are emotional; data trust is key and overall experience with data matters. Ease of use, customizability and high impact visualizations are expected of the data infrastructure. Cardiac surgical Performance Rounds was identified as first use case to be powered by this infrastructure.

Conclusion/ Impact: This approach is scalable, will improve system efficiency, data accessibility and actionability. Customized visualizations will represent relevant data in a manner that facilitates reflection, drives insight and results in beneficial action at critical decision points, ultimately impacting quality of care and patient outcomes.

THE AIRWAY DOME "CANOPPE": A NOVEL NEGATIVE PRESSURE BARRIER ENCLOSURE FOR AIRWAY MANAGEMENT IN AEROSOL-GENERATING PROCEDURES.

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2 Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael´s Hospital, Toronto, ON, Canada
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Background and Objective

The efficacy and safety of aerosol barrier enclosure systems to protect healthcare workers from airborne contaminants have been questioned. The Airway Dome (CANOPPE) is a novel system with improved ergonomics and negative pressure. We tested the efficacy at retaining (0.12μ) aerosolized particles and the safety during normal breathing and High-Flow Nasal Cannula (HFNC).

Methods

A mannequin with airway connected to a breathing simulator was placed inside the CANOPPE (RR=25bpm, VT=390mL, peak cough flow=220L/min), HFNC was set at flow rates of 30 and 60L/min. Negative pressure inside the CANOPPE was generated using regular vacuum wall suction. Under this configuration, we simulated CO_2 production (6L/min 5% CO_2) and washout (capnography) from the CANOPPE, and containment of nebulized fluorescent micro particles (Glo Germ Oil). HFNC ventilation inside the CANOPPE was assessed experimentally and clinically using flow rate of 30 and 60L/min. Suction of 80L/min was used to produce negative pressure inside the CANOPPE while latex aerosol micro particles of 0.12μm diameter (compatible with the SARS-CoV-2 Virus) were introduced into the CANOPPE in an airtight aerosol chamber; air was sampled inside and around the CANOPPE for particle leak. Clinical assessment of the CANOPPE was performed with two healthy volunteers during normal breathing and HFNC. Minute-ventilation of the volunteers were assessed through Electrical Impedance Tomography and CO_2 production through capnography.

Results

No fluorescent particles leaked from the CANOPPE with the suction flow of 80L/min, regardless of the HFNC flow rate. Moreover, latex aerosol particles (0.12μm diameter) did not leak from the CANOPPE under similar conditions. CO_2 accumulation inside the CANOPPE correlated with the suction flow rate in all conditions tested (normal breathing and HFNC of 30 and 60L/min), with higher flow rate leading to lower CO_2 pressure. Accordingly, CO_2 accumulation during normal breathing by a healthy volunteer rapidly decreased to approximately 2mmHg with negative pressure (suction flow of 80L/min). Lastly, to prevent CO_2 accumulation during HFNC ventilation the suction flow rate needed to be 20L/min higher than the HFNC flow rate; as expected, CO_2 accumulation led to higher minute ventilation by the volunteers.

Conclusion

The CANOPPE effectively prevented leak of particles 0.12μm in diameter (compatible with the SARS-CoV-2 Virus) during aerosol-generating procedures when suction flow rate was set at 80L/min. Moreover, during HFNC ventilation the CANOPPE suction flow rate needed to be at least 20L/min above that of the HFNC flow rate to prevent aerosolized particle leak and CO_2 accumulation.
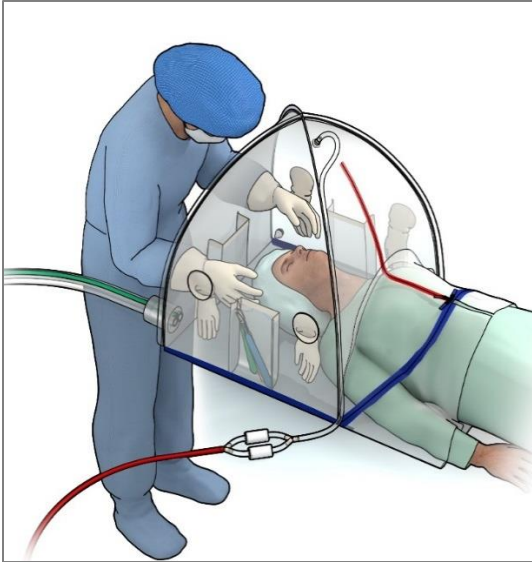
CANOPPE with sealed ports and its 6 different gloved access sealed sites.
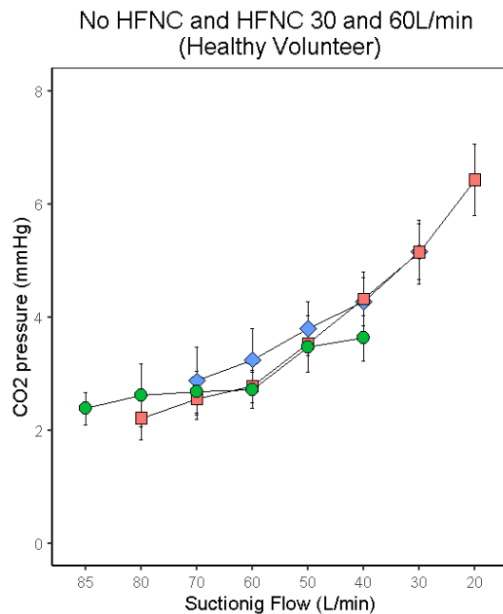
Blue Diamond= No HFNC; Green Circle= HFNC 60L/min; Red Square= HFNC 30L/min
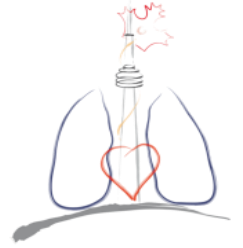
VIRTUAL

ART SLUTSKY RESEARCH DAY

Interdepartmental Division of Critical Care Medicine
University of Toronto

System Review/Case reports Abstracts

A RETROSPECTIVE REVIEW OF CRITICALLY ILL PREGNANT PATIENTS WITH COVID-19: A SINGLE CENTRE EXPERIENCE

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Introductions and Objectives

Pregnant women appear to be at increased risk of developing severe COVID-19 disease, and there does appear to be an increased risk of hospitalization, ICU admission and respiratory failure. About 10-20 % of patients develop moderate to severe disease requiring a period of hospitalization. Literature on the effects and management of COVID-19 in pregnant patients is relatively limited, with few descriptions of the severity related to variants, disease progression, and practice trends regarding mechanical ventilation. We have noted an increased rate of ICU admission of pregnant patients during the 3rd COVID-19 wave in Ontario, Canada, in our tertiary referral centre. Our goal is to describe the management of severe COVID-19 pneumonia and mutations (Variants of Concern - VOC) and ARDS in pregnant women in our high-volume centre. We also evaluated the outcomes associated with COVID-19 pneumonia and VOC during pregnancy through a retrospective patient chart review and data collection from March 1st, 2020, to April 20th, 2021.

Methods

A retrospective case series and chart review of women who tested positive for SARS-CoV-2 were admitted to Mount Sinai Hospital ICU between March 1st, 2021 and April 20th, 2021. Data collected from the chart review included: patient demographics, pre-existing comorbidities, prenatal course, COVID-19 admission and hospital course, and ICU admission and hospital course. In addition, maternal and neonatal outcomes, including data on delivery, morbidity and mortality, were also collected. Summary statistics were calculated, and quantitative and nominal data were expressed as the mean+SEM and percentages respectively.

Results

Eighteen patients were studied who had completed their ICU course at the time of analysis. Five were admitted during the first two COVID waves in Canada (March 2020 to February 2021) and eleven during the 3rd wave (March-May 2021) (Figure). Of the thirteen patients admitted during this latter period, 11 were positive for VOC (results were unavailable in 2). Nine were identified as B.1.1.7 (UK variant), one B.1.351 (South African variant), and one as P.1 (Brazil variant). The mean gestation at the time of ICU admission was 29 weeks. All except one patient (admitted March 2020) were treated with steroids for COVID-19 pneumonitis. Remdesevir was administered to two patients before ICU admission, and eleven patients received a single dose of tocilizumab. Invasive mechanical ventilation was required in eleven patients, the remainder treated with HFNO or non-rebreather masks. None received noninvasive ventilation. The mean duration of mechanical ventilation was ten days. The highest PEEP settings ranged from 12 to 20 cmH2O. Of the eleven patients ventilated, ten received neuromuscular blockade, five were treated in the prone position, and four received inhaled nitric oxide. One patient required ECLS. Five patients were electively delivered for obstetric indications during their ICU stay, no maternal mortality occurred, but two women were left with significant morbidity: one with anoxic brain injury and one with dialysis-dependent renal disease.

Conclusion

Our retrospective review demonstrated an increase in ICU admission and disease severity associated with VOC in the 3rd wave. Our approach was not to deliver purely for maternal respiratory benefit, and there was no significant increase in maternal or neonatal mortality. Management of COVID-related ARDS was similar to the non-pregnant population.

WHO AM I? – PERSONAL AND PROFESSIONAL JOURNEYS IN CRITICAL CARE

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Introduction and Objective

Clinicians in Intensive Care Units practice a liminal medicine, bearing witness to countless yet unique patient and family experiences at the fragile border between life and death, experiences laden with suffering and tragedy which cannot fail to impact the clinicians themselves. Arguably, an ability to situate and articulate these intensely human experiences is an unwritten prerequisite for professional belonging in intensive care, and certainly any mind-less effort to ignore the unavoidably self-affecting realities of this profession will yield an abbreviated or at best unsatisfying career. Yet the total experience of ICU care provision is a particularly challenging world to make sense of; the professional journey of intensivists is inextricably bound to their personal effort to reconcile discordant realities: tragic deaths, mundane everyday frustrations, academic stimulation, and moments of joy in a death averted. Unique insights into this journey are afforded by narratives written by clinicians to articulate their personal effort to find reason and meaning amidst the profession of intensive care medicine and its attendant human experiences. Such narratives illuminate key transformative moments in clinicians' professional lives, moments in which the personal experience of professional realities establishes, ratifies, or transforms their professional identity. The goal of this study was to analyze narratives written by ICU clinicians to determine which experiences most profoundly impact their conception of professional identity.

Methods

After surveying 31 intensive care journals, we identified one journal that has published ICU clinician narratives monthly since 2013. These 85 narratives constituted our data source. The research team consisted of a clinician educator, an art historian and an anthropologist, who analyzed these pieces using a narrative analysis technique identifying major themes and subthemes. Once the research team agreed on a thematic structure, a clinician-ethicist and a trainee read all the pieces for analytic validation.

Results

The main theme that emerged across all these pieces was the experience of existing at the heart of the dynamic tension between life and death. We identified three further sub-themes: the experience of bridging the existential divide between dissimilar worlds and contexts, fulfilling divergent roles and the concurrent experience of feeling dissonant emotions.

Conclusions

Our analysis sheds light on personal identity formation among intensive care clinicians. By understanding how the otherwise disorienting experience of working at the boundary of life and death can foster or undermine clinicians' well-being, medical educators will be better equipped to guide reflection and cultivate constructive professional identity formation as trainees adapt to their career paths. The unexamined life has become untenable as clinician burnout soars amidst increasing stressors on our healthcare systems, while a healthy professional identity formation has become an increasingly invaluable asset for personal growth and moral resilience. Our study paves the way for tangible post-graduate and continuing education interventions that foster mindful personal growth within the profession of critical care medicine.

Preliminary Report: Systematic Review and Meta-Analysis of Continuous Renal Replacement Therapy for Cytokine Removal or Blood Purification on Survival in Critically Ill Patients with Systemic Inflammatory Response Syndromes.

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Interdepartmental Division of Critical Care Medicine,
University of Toronto, Canada

Introduction

Systemic inflammatory response syndrome in critical illness can result in cytokine 'storms' and contribute to high morbidity and mortality. Management of inflammation using Continuous Renal Replacement Therapy (CCRT) may reduce cytokines and improve survival.

Methods

We performed a systematic review and meta-analysis. Eligible studies were randomized trials that enrolled critically ill patients and compared CRRT as a modality primarily for cytokine removal with usual care. The primary outcome was mortality.

Searches of MEDLINE, EMBASE, the Cochrane Central library and ongoing trials in ClinicalTrials.gov were combined. Two investigators independently reviewed title and abstracts to identify eligible studies using DistillerSR®. Statistical analysis used STATA®. Risk of bias was assessed using the Revised Cochrane risk-of-bias tool for randomized trials tool.

Results

Preliminary searches identified 7216 unique records. Sixty-two studies underwent full text review from which 23 studies of 1415 patients were amenable for meta-analysis. Half (48%) were published after 2010. Most (22) were of adult patients, 10 pertained to sepsis/septic shock, 4 pertained to burns, 4 pertained to severe acute pancreatitis, 7 studies had high risk of bias; 5 had low risk of bias, and the rest had unclear risk of bias.

The median (IQR) sample size was 40 (24-76). Overall, 725 patients received CRRT and 690 received usual care. Three studies demonstrated absolute benefit and none demonstrated harm. Most studies showed indeterminate outcomes. Meta-analysis found mortality occurred in 276 (38.1%) patients with CRRT, and 325 (47.1%) patients randomized to usual care. Overall, there was a survival benefit from CRRT: Pooled Odds ratio (95% CI) 0.58 (0.4 - 0.82); p=0.001, I^2= 31.34 %.

Conclusion

This preliminary report of 23 RCTs found that treatment with CRRT for cytokine removal improves survival in critically ill patients and suggests that treating 8 patients saves one life. Additional high-quality randomized controlled trials may be conducted to confirm these findings in contemporary patients with SIRS treated with anti-inflammatory medications.

THE "RIPPLE" EFFECT: A NOVEL APPROACH TO CONTINUING PROFESSIONAL DEVELOPMENT

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[1] *Interdepartmental Division of Critical Care, University of Toronto*
,[2] *Sunnybrook Health Sciences Centre*

Introduction & Objective:

Continuing professional development (CPD) has been defined as self-directed learning and reflective practice aimed to improve personal and professional growth. The Royal College of Physicians and Surgeons of Canada's Maintenance of Competence program requires physicians to accrue credits from CPD activities. However, completing CPD activities does not always translate into improvements in practice as many activities are passive and without direct feedback on performance. Continuing professional development activities with opportunities for self-assessment, timely external feedback, and interactions with peers and experts in a safe learning environment are still uncommon. We know that effective strategies most likely to influence physician behavioral changes include interactive interventions and activities in a small-group format. Our needs assessment also revealed that 15% of community physicians routinely lack access to an expert consultant.

We developed the Rounds for ICU Practicing Physicians for Lifelong Education (RIPPLE) workshop to address these gaps. The objective of the event was to create a forum where practicing physicians could interact with peers and experts about common clinical challenges in a safe learning environment.

Methods:

RIPPLE was a novel CPD event with attendance limited to practicing academic and community intensive care unit physicians. The four-hour session was endorsed by the Canadian Critical Care Society and the Critical Care Canada Forum, and piloted as a pre-conference event. Potential participants completed a pre-workshop needs assessment that, along with known practice gaps in critical care, informed the four clinical cases we designed on respiratory failure, neuro-prognostication, right heart failure and chronic ventilation weaning. Each case included 4 to 5 questions to probe participants' understanding and rationale of management. The attendees could access the cases 48 hours ahead of the session. During the workshop, the four cases were discussed successively (Figure 1): participants first reviewed the clinical vignette and questions individually, then discussed answers in a small group of peers, followed by a larger, interactive group discussion facilitated by the expert who exchanged their views on case management with participants. Due to the COVID-19 pandemic, the workshop was delivered online with breakout rooms to facilitate small-group interactions.
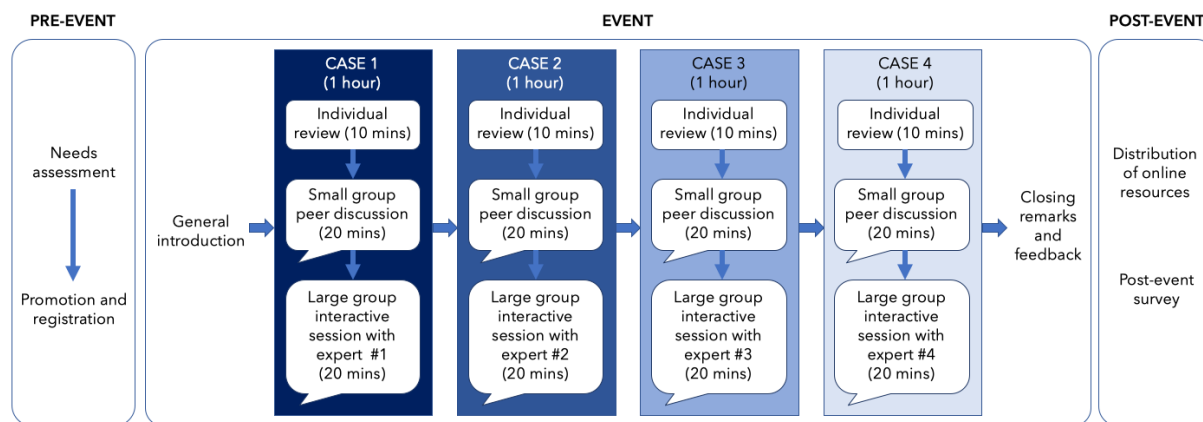
Figure 1: Flow-diagram of RIPPLE workshop.

Results:

We set a registration cap of 40 participants to optimize interactivity. The seven intensivist attendees were a mix of community and academic intensivists from Canada and the United States. Due to technical delays, one session was shortened. From the post-event survey, five of seven participants wished for more time with expert panelist and no time for individual review. Six participants have shared the post-event resources with their colleagues and trainees. Five participants wished to submit their own cases for future events.

Conclusions:

WThe RIPPLE workshop added to the current CPD landscape and was innovative in numerous ways. It provided participants with opportunities to engage with authentic scenarios and to commit to a management plan, to interact directly with peers and experts and discuss their practices in a non-threatening learning environment, to receive immediate feedback on case management, and to share new knowledge and resources with their local peers and trainees. The use of a virtual platform facilitated participation of international attendees, and offers the possibility to upscale the event for a national or international audience in the future. In order to continue this "ripple effect" of professional development, our advice to educators who wish to adapt this event include: completing a needs assessment of the local physicians' practice needs, engaging local experts early, and encouraging broad dissemination of the workshop's educational material in person or online via an e-platform.

Challenges faced in this inaugural event included low attendance despite high registration numbers, time allocation, and technical delays. As for improvements for future sessions, we plan to (1) distribute cases in advance to maximize live interaction time with peers and experts, (2) allow submission of topics or cases by attendees, (3) shorten the event to three cases, and (4) increase registration fees to ensure commitment to workshop attendance.

ASSOCIATION OF PEEP SELECTION STRATEGIES WITH ALL-CAUSE MORTALITY IN ADULT PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME:
A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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# Dr. Angriman and Dr. Goligher contributed equally to this abstract.

Introduction and objective: The most beneficial positive end expiratory pressure (PEEP) in patients with acute respiratory distress syndrome (ARDS) remains contentious, and current practice is variable. Our main objective was to compare different PEEP selection strategies with all-cause mortality in adult patients with moderate to severe ARDS.

Methods: MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE and LILACS were searched from inception to May 2021. No limits were applied to language, sex or race. We included randomized clinical trials enrolling adult patients with moderate to severe ARDS, comparing any available PEEP selection strategy: a) low PEEP, b) higher PEEP, c) open lung approach (any strategy that included a lung recruitment maneuver using intermittent increases in airway pressure), and d) esophageal pressure (P_{es}) guided PEEP selection. The primary outcome was all-cause mortality, up to 90 days. Two reviewers independently extracted individual study data and evaluated studies for risk of bias using the Cochrane Risk of Bias tool. Network meta-analyses using a Bayesian framework to derive risk ratios (RRs) with 95% credible intervals (CrI) were conducted. Grading of recommendations assessment, development, and evaluation methodology was used to rate the interventions.

Results: 18 randomized trials (4690 participants) were included (median $PaO_2:FiO_2$, 133). In comparison to the low PEEP strategy, the median relative risk for mortality with higher PEEP was 0.78 (95% CrI, $0.61 - 0.99$; posterior probability of benefit 98%, moderate certainty), the median relative risk for the P_{es}-guided strategy was 0.72 (95% CrI, $0.46 - 1.13$; posterior probability of benefit 92%, moderate certainty), and the median relative risk for mortality with the open lung approach strategy was 0.94 (95% Crl: $0.81 - 1.06$; posterior probability benefit 84%, low certainty). In comparison to a higher PEEP strategy, the median relative risk for the P_{es}-guided strategy was 0.92 (95% CrI $0.60 - 1.40$; posterior probability of benefit 65%, moderate certainty) and the median relative risk for mortality with the open lung approach was 1.20 (95% CrI $0.90 - 1.59$; posterior probability of harm 90%, very low certainty). Finally, in comparison to the open lung approach, the median relative risk for the P_{es}-guided strategy was 0.77 (95% CrI $0.47 - 1.20$; posterior probability of benefit 88%, very low certainty). These findings remained robust across sensitivity analyses.

Conclusions and relevance: In this network meta-analysis of PEEP selection strategies in adult patients with moderate to severe ARDS, there was a high probability that the use of a higher PEEP strategy or P_{es}-guided strategy was associated with lower risk of all-cause death in comparison to a low PEEP strategy. The use of an open lung approach using staircase recruitment maneuvers is potentially harmful when compared to a higher PEEP strategy. Future studies should aim to identify subgroups of patients that may benefit from different PEEP titration strategies.

COMPLICATIONS ASSOCIATED WITH THE USE OF INVASIVE MECHANICAL VENTILATION IN THE TREATMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME: A SYSTEMATIC REVIEW

L. Ishaq[1]; W. Wang[1]; B. Lam[1]; T. Pettenuzzo[1]; S. Sharma[1]; E. Lee[2]; M. Azam[1]; K. Gorsky[3]; M. Englesakis[4]; S. Munawer[1]; E. Fan[1]

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Introduction
The cornerstone of supportive therapy in Acute Respiratory Distress Syndrome (ARDS) is the use of invasive mechanical ventilation (IMV) to maintain gas exchange. Though lifesaving in patients with ARDS, the use of IMV is associated with a number of potential harms. We conducted a systematic review to characterize the range and frequency of adverse effects associated with the use of IMV in ARDS.

Methods
We used a sensitive search strategy developed by an information specialist to query the following databases from inception to September 2019: 1) Medline 2) Embase 3) CCTR 5) CDSR 6) Clinicaltrials.gov. We included studies in which adult patients (Age >18) with ARDS received IMV, with the exception of case reports, editorials, and conference abstracts. We excluded studies with a small sample size (n <50). Outcomes of interest included barotrauma, ventilator-associated pneumonia (VAP), and all other adverse effects potentially related to IMV. Quality assessments were done using the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies. The review was registered with PROSPERO (CRD42020161960).

Results
7816 unique articles were identified by our search strategy, of which, 136 met the eligibility criteria (38198 patients). There were 51 RCTs, 81 observational studies, and 4 quasi-experimental studies published between 1993 and 2019. The risk of bias varied across articles. The most frequently described complications were barotrauma and VAP. The median (IQR) reported rate of barotrauma was 8.1% (4.0%-12.1%, n=23196). It declined from a median (IQR) of 11.5% (8.0%-16.0%) in articles published from 1990-1999 (35 articles, n=7380), to 6.0% (4.0%-10.8%) in 2000-2010 (33 articles, n=9701), to 5.6% (2.9%-10.2%) in 2010-2019 (24 articles, n=6115). The median rate of barotrauma did not correlate with the severity of ARDS. The median rate (IQR) of VAP was 28.0% (16.4%-44.5%, n=17582). The rate was stable over time, but in 10 studies (n= 1489) whose populations had more severe ARDS, the median (IQR) rate was higher compared to the 30 studies (n=14692) with moderate ARDS and 1 study (n=238) with mild ARDS (40.7% [23.5%- 48.7%] vs 27.5% [15.7%- 43.2%] vs 21.0%, respectively). Complications involving other organ systems were less frequently described and not clearly attributed to IMV.

Conclusions
Barotrauma and VAP in patients with ARDS undergoing IMV are relatively common, and differ according to severity of underlying lung injury, and may be changing over time. The reduction in barotrauma over time may reflect increasing use of lung protective ventilation in patients with ARDS. In contrary, the rates of potential complications from IMV involving other organ systems are not as well described.

EXPLORING AND SUPPORTING THE PROCESS OF PROFESSIONAL IDENTITY FORMATION OF CRITICAL CARE CLINICIANS THROUGH MEDICAL HUMANITIES

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Presenter: Catherine Proulx

Introduction & Objective:
A growing acknowledgment of the reality and consequences of burnout in medicine has brought a new focus upon ways to promote moral resilience. This is particularly relevant to the specialty of critical care, which has one of the highest burnout rates. Professional identity formation is known to be associated with resilience, self-regulation and development of an "inner compass" to help navigate the moral dilemmas inherent to medical practice. An extensive literature has examined the nature of physicians' professional identity and factors that influence its development: some of the most powerful include role models, mentors, and mindful accumulation of experiences. Reflecting on critical formative experiences can help clinicians use their experiences to construct meaning and clarify values to promote a new way of being. Humanities, by facilitating reflection and creation, encourage meaning-making, and contribute to self- awareness and growth in achieving a more accurate understanding of the profession in the full scope of its complexity and ambiguity. By nurturing professional identity formation, humanities may foster clinician's emotional resilience and wellness. Currently, humanities are inconsistently utilized or studied as a sustainable path towards clinicians' professional identity formation.

The aim of this study is to explore longitudinal professional identity formation through reflections of participants in a medical humanities curriculum through investigating (a) key transformative experiences that impact professional identity formation, (b) how reflection through art and humanities can support the process of professional identity formations, and (c) how mentors and peers can guide the process for a supportive professional identity formation that promotes emotional resilience.

Methods:
This is a qualitative study using phenomenology as an approach to explore the experiences of Pediatric Critical Care Medicine clinicians participating in a medical humanities curriculum. Our group created a longitudinal Medical Humanities Curriculum where trainees and faculty meet in small groups on a regular basis to create a space for them to reflect on, explore, and integrate their experiences. A range of themes are used to guide discussion and introspection with the help of a varied group of facilitators (clinician, educator, ethicist, art historian, and anthropologist).

Over 24 months, we will conduct ethnographic observations, collect humanities artefacts (from varied arts), and conduct interviews with participants to develop important insights into the process of professional identity formation. Our interdisciplinary research team will analyze the data (observations, art pieces, and interviews) iteratively and interpretatively until a final thematic analysis will be developed to provide a framework for our areas of explorations.

Results (in progress):
Preliminary data is derived from our observations from participants' discourses and art/artefacts brought during the evenings. Participants' interviews have not been conducted yet. As of now, our informal observation have shown that reflections mediated

through different art forms and humanities focus on practicing medicine at the border of life and death, and its consequences for clinicians. Other major themes were life between a personal and professional world; the ability to form a group among whom vulnerabilities are welcomed and relationships trusting and caring; the ability of art to enable healing and a sense of pleasure and fulfillment when we create it or appreciate the pieces created by others.

Conclusions:

The project is ongoing. We expect that reflecting on personal and professional experiences through art and the humanities nurtures the longitudinal process of professional identity formation. We are confident that a medical humanities curriculum can positively contribute to clinicians' moral resilience and wellness.

[a]Appendix 1: Scheme of the Medical Humanities Curriculum already in use at Department of Critical Care Medicine of The Hospital for Sick Children

Appendix 1
Medical Humanities Curriculum

Introduction of the curriculum to trainee and faculty

| Workshop on reflective writing | Discussion on music | Workshop on painting photography and visual details |

EVENINGS OF ART AND HUMANITIES

| Writing sessions facilitated by a professional editor and their peers | Participants playing instruments or bringing a musical piece | Participants tell a Piece of Medical History | Reading to your colleagues Bring your favorite piece | "Immortalize" an experience in any form of Art | Painting & Photography your own or someone else's that is meaningful |

End of year event to share work and reflections

REAL COMMUNICATION IN A VIRTUAL WORLD: LEARNING FROM A PANDEMIC, TEACHING FOR THE FUTURE

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Presenter: Catherine Proulx

Introduction & Objective:
Deficiencies in communication negatively impact patient care, exacerbate healthcare inequities, and contribute to moral distress. Nevertheless, there is a paucity of clinical communication training in Paediatric Critical Care programs where difficult conversations are the norm. The COVID-19 pandemic has underlined the need for clinicians to meet increasingly complex communication challenges, to be nimble in their ability to navigate individual patient, family, social and system-wide realities to fully engage patients and families in clinical decision-making across a spectrum of modalities that include virtual, in-person, and hybrid communication. In an era where "personalized medicine" evokes the intricacies of an individual's genetic code, there remains an unfortunate gap in medical communication personalized to individual patient and family circumstances. Virtual communication has been increasingly utilized in various medical fields, but literature is scarce regarding best practices. In view of these challenges, our study's goal is to provide Pediatric Critical Care trainees with tools to navigate difficult medical discussions in various settings.

The study is divided into three phases with defined objectives : (a) explore the strategies utilized by expert clinicians when managing difficult conversations across diverse modalities; (b) use this data to create a simulation curriculum that invokes a spectrum of communication modalities (virtual, telephone, in-person, mixed) to impart critical communication skills that are adaptable and inclusive of the patient and family's context; (c) evaluate this novel simulation curriculum using observations and feedback from the participants and from communication assessment tools, for sustainable, iterative curriculum development[a].

Methods:
To gather data about strategies for difficult clinical communications in Pediatric Critical Care, we will ask expert clinicians in that field to participate in simulation scenarios that involve critical communication using diverse modalities (virtual meetings on *Teams* or *Zoom*, phone conversation (audio only), and in-person), to explore how clinicians adapt to each context. Their strategies and feedback will be gathered using a field guide and a semi-structured interview, and patient partners will be engaged for feedback regarding the strengths and pitfalls of different modalities with respect to sensitive and effective communication.

Following this preparatory work, learners will then practice in a simulation curriculum designed to incorporate a Preparation for Future Learning framework (Mylopoulos et al., 2016) including variability, experimentation in a safe environment, and feedback from different stakeholders. Variability will be reflected in the same diversity of modalities (virtual, phone, and in-person), a diversity of disease processes, and family contexts (including routine information updates, language barriers, family-provider disagreement, communicating a clinical deterioration, end-of-life care); active experimentation will take place in a safe environment (simulation with ability to ask for a personal time-out); and feedback will be solicited from different perspectives (standardized patients, facilitators, peers, patient partners, psychologist). A similar design has been invoked in another pediatric study seeking to instill an adaptive expertise (Kawamura et al., 2016).
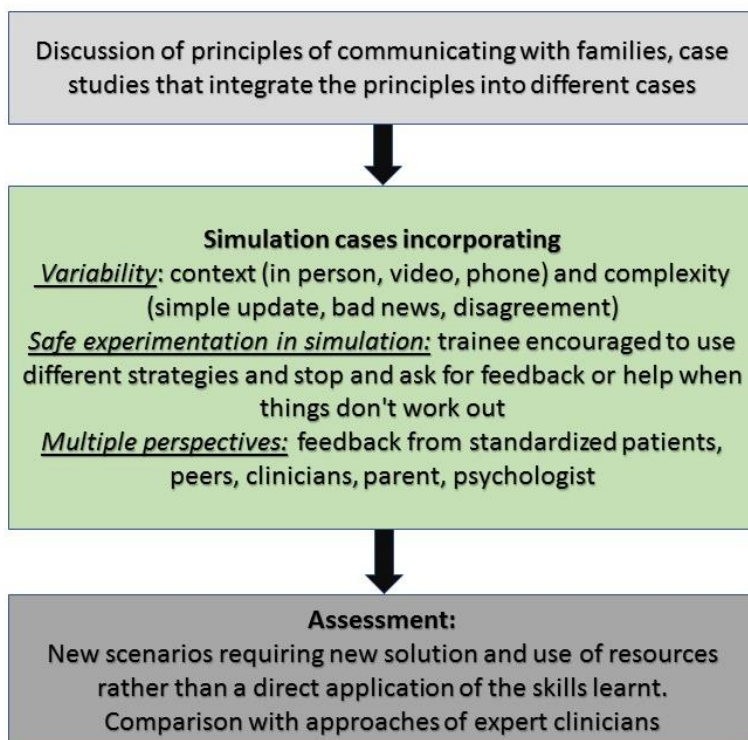
Assessment of learners in our simulation curriculum will be focused on the strategies trainees use to adapt to varied modalities and patient/family situations, especially (a) their use of resources such as colleagues or family members and (b) their flexibility of approach in comparison to the preliminary work with experts. This data will be collected using observations and interviews. In addition, we will assess trainees and experts (faculty with at least 5 years of experience) using published tools with validity evidence (Calhoun et al., 2009). The interviews with participants will allow us to also evaluate our curriculum for iterative changes.

Results and conclusions:
The project is ongoing. We expect that the initial exploratory phase of our study will unveil practical communication strategies invoked across a diversity of modalities by experienced clinicians to undertake difficult conversations. We anticipate that our novel simulation curriculum will drive substantive change in Pediatric Critical Care trainees' approach to sensitive communication with patients and families at their most vulnerable moments. Our program represents a unique effort to instill adaptability, flexibility, and innovative solutions across the spectrum of existing and future communication modalities. Importantly, the barriers to healthcare access unmasked by this pandemic will persist beyond COVID-19, and our project is intended to create an habitual awareness of the impact of the social determinants of health upon pediatric critical communication and to instill an impetus to overcome these barriers. Our intention is to implement this curriculum within our training program, and to disseminate our project through medical education workshops.

[a]*Appendix 1 : Communication simulation curriculum flow*

Appendix 1 : Communication simulation curriculum flow

Discussion of principles of communicating with families, case studies that integrate the principles into different cases

Simulation cases incorporating
Variability: context (in person, video, phone) and complexity (simple update, bad news, disagreement)
Safe experimentation in simulation: trainee encouraged to use different strategies and stop and ask for feedback or help when things don't work out
Multiple perspectives: feedback from standardized patients, peers, clinicians, parent, psychologist

Assessment:
New scenarios requiring new solution and use of resources rather than a direct application of the skills learnt.
Comparison with approaches of expert clinicians

SEPARATION FROM MECHANICAL VENTILATION AND SURVIVAL AFTER SPINAL CORD INJURY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction & Objective: Prolonged need for mechanical ventilation (MV) greatly impacts life expectancy and quality of life of patients after spinal cord injury (SCI). Outcomes related to weaning from MV have not been systematically assessed. We aimed to evaluate the probability of weaning success, duration of MV and mortality and their predictors in mechanically ventilated adult patients after SCI.

Methods: We searched six databases from inception until January 2020 for observational studies and randomized-controlled trials (RCTs) enrolling adult patients (≥16 years) with SCI from any cause requiring MV. We screened studies and extracted data independently and in duplicate. Synthetic results are reported as meta-analytic means and proportions, based on random effects models. The study is registered with PROSPERO (CRD42020156788).

Results: Thirty-six studies (8492 patients, mean age 42.5), including 35 retrospective cohort studies and 1 RCT, were selected. Cervical lesions were predominant (6689 patients had cervical lesions only, 1726 in association with other levels' lesions). Twenty-two studies were conducted in Intensive Care Units (ICUs), 14 in rehabilitative settings.

In ICU, the mean time from injury to hospitalization was 7.5 h [95% confidence interval, 6.6 – 8.5], mean duration of MV 27.8 days [20.1 – 35.4], probability of weaning success 63.1% [45.2 – 77.9] and mortality 7.7% [5.1 – 11.4]. Patients hospitalized in rehabilitation centres had a greater number of patients with high-level cervical lesions, were at 39.9 days [28.6 – 51.3] from injury and were ventilated for a mean total of 96.5 days [65.1 – 127.8]: 82.3% [69.6–90.4] of them were successfully weaned, while mortality in rehabilitation was 0.8% [0-18.5].

Conclusion: Although our study highlights the lack of uniform definition of weaning success, of clear factors associated with weaning outcomes, and of high-level evidence to guide optimal weaning in patients with SCI it shows that around two thirds of MV patients can be weaned in ICU after SCI. A substantial gain in weaning success can be obtained during rehabilitation, with additional duration of stay but minimal increase in mortality.

THE UTILITY OF THE RAPID SHALLOW BREATHING INDEX IN PREDICTING SUCCESSFUL EXTUBATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction & Objective: Clinicians use several measures to ascertain whether individual patients will tolerate liberation from mechanical ventilation. The rapid shallow breathing index (RSBI) is the most commonly measured index to screen invasively ventilated patients to decide who should proceed to an SBT, and to predict extubation success. We sought to summarize and synthesize the literature regarding how clinicians use the RSBI among different patient populations, timing of measurement, thresholds utilized, and ability to predict successful extubation.

Methods: We searched six databases from inception through September 2019 and selected studies reporting the accuracy of RSBI in the prediction of successful extubation. We extracted study data and assessed quality independently and in duplicate. We computed pooled sensitivities, specificities, and diagnostic odds ratios (DOR) and depicted pooled estimates graphically using forest plots. Separate generalized linear mixed effects models were fitted on sensitivities, specificities, and DOR (without covariate adjustment) to construct corresponding 95% clopper-person confidence intervals (CIs) to compute the I-squared index for study heterogeneity. We assessed overall certainty of evidence for pooled diagnostic effect estimates for the primarily analysis using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.

Results: We included 48 studies involving RSBI measurements on 10,946 patients. Pooled sensitivity for RSBI <105 in predicting extubation success was moderate [0.83 (95% CI 0.78 – 0.87), moderate certainty], while specificity was poor [0.58 (95% CI 0.49 – 0.66), moderate certainty) with diagnostic odd's ratio of (DOR) 5.91 [(95% CI 4.09 – 8.52)]. RSBI thresholds

of <80 or 80-105 yielded similar sensitivity, specificity, and DOR. These findings were consistent across multiple subgroup analyses including timing and technique of RSBI measurement, ICU patient demographics (age, specialty ICU, COPD), and sensitivity analysis restricted to low risk of bias studies. reflecting different patient characteristics and operational differences in RSBI measurement.

Conclusion: As a stand-alone test, the RSBI has moderate sensitivity and poor specificity for predicting extubation success, possibly reflecting different patient characteristics and operational differences. Future research should evaluate its role as a permissive criterion to undergo an SBT for patients who are at intermediate pre-test probability of passing an SBT, rather than for predicting extubation success.

Protocol registration (CRD42020149196) April 2020

This study was unfunded

Table 1 – Summary estimates of the performance of RSBI <80, 80-105, and any <105 for the prediction of successful extubation

RSBI	Number of patients	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Diagnostic Odds Ratio (95% CI)	GRADE
<80	7993	0.84 (0.75 to 0.90)	0.62 (0.53 to 0.70)	7.43 (4.17 to 13.21)	⊕⊕◯◯ LOW
80-105	2953	0.83 (0.77 to 0.88)	0.54 (0.42 to 0.67)	5.30 (3.15 to 8.92)	⊕⊕⊕◯ MODERATE
Any <105	10946	0.83 (0.78 to 0.87)	0.58 (0.49 to 0.66)	5.90 (4.09 to 8.52)	⊕⊕⊕◯ MODERATE

RSBI = Rapid Shallow Breathing Index, CI = Confidence Interval, GRADE = Grading of Recommendations, Assessments, Development and Evaluation

Title: HAEMATOPOIETIC STEM CELL TRANSPLANT AND ECMO: WHERE TO GO NEXT? A SCOPING REVIEW.

S Watad [1], Y Chopra [2], Q Mahood [3], D Wall [2], E Gilfoyle [1], AM Guerguerian [1]

Introduction

Patients undergoing hematopoietic stem cell transplant (HSCT) are at risk for severe pulmonary complications requiring ICU level support. With improvement in overall long term outcome following HSCT, there is renewed interest in offering ECMO to select patients who require more intensive respiratory support to manage acute transplant-related toxicities. The aim of this report is to summarize a scoping review of the literature published on ECMO use in adults and pediatrics.

Methods:

The literature search conducted in Medline, Embase, and the Cochrane Central Register of Controlled Trials. Search terms fell into two broad concepts: (1) adult and pediatric populations who had received bone marrow transplants, and (2) who were supported with ECMO from 1998-2021. The searches were limited to English language and publication years 2000 to October 2020.

Results:

Thirty publications were identified between, 10 in adults and 20 in pediatrics. There was a combination of registry-based reports, case series and case reports. The majority of pediatric patients who were treated with ECMO were supported by VA ECMO whereas adults supported mostly by VV ECMO. Among pediatrics, the exposure to ECMO was early following HSCT, whereas in adults, ECMO was used months following transplant. The survival rates reported ranged from 0% to 50%; with a trend to improved survival rates in more recent publications.

Conclusion:

There is limited published evidence available to inform decision making about ECMO in HSCT. There is a trend towards improved survival in the more recent reports. With the advances in HSCT protocols, there is an urgent need to understand which patient subgroup may benefit from ECMO as a bridge to recovery with novel therapy delivery. Patients who have severe pulmonary toxicity with cytokine-release syndrome following CAR-T present a new patient population that may be considered. Given the extensive registries available in both domains, there may be a role for merging registries to undertake comparative registry-based studies or trials.

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