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UNIVERSITY OF ALBERTA
FACULTY OF MEDICINE & DENTISTRY
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Critical Care SCN
Alberta Society of Intensive Care Physicians Research Symposium Abstracts

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On behalf of the Alberta Society of Intensive Care Physicians, I would like to welcome all the participants to this year's ASICP/CC SCN Research Symposium. Your hard work is so valuable for future advancement of Intensive Care in the province. Your ideas and findings are an important component of the Dr. Mark Heule Winter Meeting Educational program. I would like to thank you for all your efforts and your continued willingness to enrich our academic program by presenting here in Lake Louise! Good luck to you all.

Ken Parhar
President
ASICP

Welcome to the Annual ASICP/CCSCN Research Symposium! On behalf of the AHS Critical Care Strategic Clinical Network (CC SCN), we would like to welcome a broad spectrum of presenters, including multi-level learners, early career, and multi-disciplinary clinicians, who have been selected to present their exciting work at this year's symposium. This ASICP/CCSCN Research Symposium has grown into one of the highlights of the Annual Mark Heule ASICP Meeting at the Post Hotel in beautiful Lake Louise. We would also like to acknowledge the time and dedication to all the mentors and supervisors of this year's presenters without whose continuing support to our annual Research Symposium would not be possible. We look forward to hearing about the innovative work being done across Alberta.

Sean Bagshaw
Scientific Director CC SCN

Heat Shock Protein 27 as a mediator of disease pathogenesis in COVID-19 and Non-COVID Acute Respiratory Distress Syndrome

Chiu MH, O'Brien ER, Gershkovich B, Yu IL, Li J, McDonald B.

Background: Acute Respiratory Distress Syndrome (ARDS) is a common cause of hypoxemic respiratory failure in intensive care units that has increased dramatically as a result of the COVID-19 pandemic. In both COVID-19 and non-COVID ARDS, the pathogenesis of lung injury involves local (pulmonary) and systemic inflammation, leading to impaired gas exchange, requirement for mechanical ventilation, and a high risk of mortality. Heat Shock Protein 27 (HSP27) is a chaperone protein expressed in times of cell stress with roles in modulation of the NF-□B pathway. Recently, we recognized that HSP27 combines with anti-HSP27 antibodies to form an immune complex that downregulates inflammation in atherosclerotic cardiovascular disease. Given its important role as a modulator of inflammation, we sought to investigate the role of HSP27 and its associated auto-antibodies in ARDS caused by both SARS-CoV-2 and non-COVID etiologies.

Methods: A total of 68 patients admitted to the intensive care unit with ARDS requiring mechanical ventilation were enrolled in a prospective, observational study that included 22 non-COVID-19 and 46 COVID-19 patients. Blood plasma levels of HSP27, auto-antibody (AAB), and cytokine profiles were measured on days 1 and 3 after admission along with clinical outcome measures. Group comparisons were performed with Cox proportional hazard models.

Results: Patients with COVID-19 ARDS displayed higher levels of HSP27, and a higher ratio of HSP27:HSP27 AAB ($p<0.04$) on both day 1 and day 3 of ICU admission and was associated with a longer duration of mechanical ventilation and ICU length of stay ($p<0.004$). A proinflammatory cascade with higher levels of interleukin-10 (IL-10), IL-13, IL-6, MCP-1 and TNFα were seen in COVID ARDS. Stratification of COVID-19 ARDS patients based on HSP27 and HSP27:AAB ratios, it was found that higher HSP27 levels and HSP27:HPS27AAB ratio were associated with more severe systemic inflammation and hypoxemia.

Conclusion: In summary, increase in HSP27 compared to anti-HSP27 AAB during COVID-19 ARDS is associated with dysregulated systemic inflammation and worse clinical outcomes, and therefore may represent a potential therapeutic target against severe COVID-19 ARDS.

Emergency Cricothyrotomy Landmarking - Validating the Canadian Method of Cricothyroid Landmarking

Cowan S, Vadeanu C, Widder S.

Background
The feared scenario whereby a practitioner cannot intubate the airway coupled with the inability to oxygenate with supraglottic techniques represents a true life-threatening airway emergency. Many airway algorithms and guidelines recommend emergent surgical cricothyrotomy in failed airway scenarios. A variety of techniques for evaluating external neck anatomy for cricothyroid membrane (CTM) landmarking are described in the literature and these techniques demonstrate that acute care providers are, in fact, quite poor accurate landmark identification. One comparison study showed the accuracy of three landmarking techniques to be between 46-62%. The Canadian Method has been found to be successful in practice but has never been validated. The objective of our study is to determine the accuracy of the Canadian Method in identifying the CTM as compared to gold standard ultrasonography.

Methods
Using volunteer residents and staff from acute care specialties to perform baseline landmarking and landmarking using the Canadian Method to identify the cricothyroid membrane on neck volunteers with normal BMI, we aim to validate the accuracy of the Canadian Method of cricothyroid landmarking.
Using the literature quoted accuracy of 7mm (IQR 4-12mm), a minimum sample size of 28 participants was identified, with the literature supported standard of Identification of the CTM within 5mm of the ultrasound identified landmarks. 40 participants were set as a study target. Accuracy, measured as distance from the CTM in a vertical axis and deviation from midline were measured, in addition to incision length and time to completion.

Results
To date, 16 of 40 participants have been assessed. Average time to complete was similar between baseline and Canadian method procedures on interim analysis, 16.2 (5.3) seconds vs 17.2 (6.4) seconds (mean(SD)), and incision length 26.3 (9.5)mm vs 24.8 (5.3) mm long. Mean BMI of neck volunteers mean(SD) is 27.4 (1.3). Participants' experience varies from R1 to 6th year staff, and are all sampled from acute care specialties. Data collection is ongoing and will be complete for presentation. Interim analysis of our primary objective, deviation from CTM in the vertical and midline axis have been deferred to avoid collection biasing.

Conclusion
This analysis of accuracy in identifying the Canadian Method of cricothyroid membrane landmarks hopes to validate a method in use currently, and if found to be superior to other methods as reported in the literature, may improve successful cricothyroidotomy landmarking.

Methods for Determination of Optimal Positive End Expiratory Pressure: a scoping review

Edginton S, Kruger T, Stelfox HT, Brochard L, Gaudet J, Solverson K, Robertson HL, Zuege DJ, Fiest KM, Niven DJ, Bagshaw SM, Parhar KKS.

Background: Titration of positive end expiratory pressure (PEEP) is an important part of safe mechanical ventilation. Setting an appropriate PEEP can have many benefits including improved oxygenation and respiratory mechanics. Inadequate or excessive PEEP can have negative consequences such as barotrauma or atelectrauma. The method by which optimal PEEP is determined and titrated varies widely, and there is no consensus as to what defines optimal PEEP. Many methods for determining optimal PEEP have been assessed in clinical studies but only some have been tested by rigorous randomized trials. A clearly superior method of optimal PEEP determination has not been determined. To better understand the methods of determining optimal PEEP, we used scoping review methodology to identify the methods of optimal PEEP determination that have been described, and the contexts in which they have been studied.

Methods: This review was conducted according to the PRISMA Extension for Scoping Reviews and was registered using Open Science Framework (https://osf.io/atzqc). Inclusion and exclusion criteria were developed using the recommended Population, Concept, Context framework. Articles selected for inclusion were primary research studies involving hospitalized adults undergoing invasive mechanical ventilation for any reason. To be included, it was necessary for the article to evaluate a method of determining optimal PEEP and to measure a clinical or physiologic outcome associated with the setting of PEEP. The search was developed with an expert librarian. Databases searched included MEDLINE, EMBASE, Web of Science, CENTRAL, and Scopus. Articles published up until December 2021 were included. All titles and abstracts were screened independently by two authors for eligibility of full text review. Disagreements about inclusion were resolved through discussion or with a third reviewer.
Abstracted data included the method of PEEP determination, study setting, population, primary and secondary reported outcomes, study design, country or continent of origin, and funding source.

Results: The search identified 9,596 unique citations, among which 217 articles met inclusion criteria. A total of 18 different methods of determining optimal PEEP were described (Table 1). Studies were either in an intensive care unit (ICU) or operating room (OR). The two most common study designs included observational (n=143; 66%) and randomized controlled trials (RCTs) (n= 58; 27%). Among the RCTs, 11 different methods of PEEP titration were tested. The titration methods and the frequency with which they were studied changed over time (Figure 1). The majority of RCTs in the ICU had a clinical outcome as the primary endpoint (n=19; 53%), and most RCTs in the OR had physiologic measures as the primary endpoint (n=17; 77%). Among ICU RCTs, the most common clinical outcomes (primary or secondary) were ventilator-free days/duration of mechanical ventilation (n=28; 78%) and mortality (n=27; 75%). Among OR RCTs, the most common physiologic outcomes were oxygenation (n=12; 75%) and compliance (n=6; 38%).

Conclusion: Although 18 methods of determining optimal PEEP amongst mechanically ventilated patients were identified, only 11 have been tested with an RCT. The six most studied methods include best compliance, PEEP-FiO_2 tables, imaging-based, use of esophageal probe, oxygenation, and use of pressure-volume curves. The methods of PEEP titration studied have changed over time and have focussed on different outcomes. Studies

of PEEP in the ICU have focused on duration of mechanical ventilation and mortality in contrast to studies in the OR which have focused on physiological outcomes. Several methods remain untested and should be considered for future RCTs.

Developmental effects of neonatal sepsis on metabolic parameters in a preclinical model of late onset sepsis

Jahandideh F, Liu SN, Macala K, Bourque S.

Background: Neonatal late onset sepsis (LOS), defined as sepsis onset after 72h of life, is a leading cause of mortality in the neonatal intensive care unit. Neonatal sepsis occurs during a period of developmental plasticity, and thus may cause persistent changes that predispose survivors to health complications in later life. We hypothesized that neonatal LOS changes energy metabolism in sepsis survivors following fecal slurry (FS)-induced peritonitis.

Methods: At postnatal day 3, Sprague Dawley pups were injected with FS (1.0mg/g body weight) or 5% dextrose (vehicle), intraperitoneally. Pups received sustained release buprenorphine (0.5mg/kg) at the time of injection, subcutaneously (SC) for pain control. Antibiotics (Ampicillin 20mg/kg and Gentamicin 4mg/kg) and fluids were administered at 4h and 16h post-injection SC. Pup health was monitored for 24h; sick pups reaching humane endpoints were euthanized between 6 and 12h post-FS injection and classified as non-survivors. All surviving pups were euthanized at 24h post-injection. Blood glucose was measured at the time of euthanasia using a glucometer (n=16-26). Plasma was collected for measuring alanine aminotransferase (ALT) activity and insulin (n=12-17; ELISA) as well as L-lactate (n=16-19; colorimetric assay) levels. Liver was harvested and flash frozen for RT-qPCR (n=6-12). Data presented as mean ± SEM was analyzed by two-tailed student t-test.

Results: Plasma ALT activity was higher in septic survivors compared to their control littermates (71.0±20.0 vs 8.5±0.6nmol/min/mL, respectively, P=0.006). Plasma lactate was lower in survivors compared to controls (0.61±0.04mM vs. 0.80±0.04mM, P=0.002). While surviving pups had lower blood glucose (3.9±0.2mM) than controls (6.1±0.2mM, P<0.0001), no differences in insulin levels were observed (0.8±0.2 vs 0.4±0.1ng/mL in survivors and controls, respectively, P=0.09). mRNA expression of gluconeogenesis genes was differentially affected by sepsis; g6pc1 was upregulated 64±17% (P=0.006), while pyruvate carboxylase was downregulated by 62±3% (P<0.0001) in survivors. Furthermore, FS-induced peritonitis affected mRNA expression of glucose transporter in survivors; while heart glut4 mRNA expression was comparable between the two groups (P=0.19), liver glut2 and brain glut1 mRNA expressions were downregulated by 40±7% (P<0.0001) and upregulated 51±8% (P=0.01), respectively in the sepsis survivors compared to the controls.

Conclusions: Our data suggests the potential metabolic derangements in neonatal survivors following FS-induced peritonitis. Liver damage may be involved in the observed dysregulated glucose homeostasis, while β-cell dysfunction and changes in tissue glucose uptake may also be implicated. Current studies are underway to determine if these metabolic alterations are adaptive or maladaptive, and whether they persist into adulthood.

Follow-up Care of Critically Ill Patients with Acute Kidney Injury

Jeong R, Clarke A, James MT, Quinn RR, Ravani P, Bagshaw SM, Stelfox HT, Pannu N, Wald R, Harrison TG, Niven DJ, Lam NN.

Background: Acute kidney injury (AKI) occurs in more than half of critically ill patients and is associated with adverse outcomes. Chronic kidney damage can occur even when AKI seems to resolve, as serum creatinine measurements can be misleadingly low due to loss of muscle mass and hemodilution in the setting of critical illness. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI recommends evaluation at 3 months for AKI resolution, and new-onset or worsening of chronic kidney disease (CKD). Currently, the proportion of survivors of critical illness with AKI who receive follow-up care in line with guideline recommendations is unknown. In this study, we determine the proportion of patients receiving guideline recommended evaluation for CKD in survivors of critical illness and AKI.

Methods: We conducted a retrospective cohort study of patients admitted to the intensive care unit with AKI (defined as ≥50% or ≥26.5 μmol/L serum creatinine increase) from 2005-2018 in Alberta, Canada. The primary outcome was the cumulative incidence of an outpatient creatinine and urine protein measurement at 3 months of hospital discharge. Secondary outcomes included an outpatient creatinine or urine protein measurement, or an outpatient family physician or nephrologist visit at 3 months of discharge. We used non-parametric methods (Aalen-Johansen) to estimate the cumulative incidence functions of outcomes accounting for competing events of death and kidney replacement therapy (maintenance dialysis or kidney transplantation).

Results: There were 29,732 critically ill adult patients with AKI. The median age was 68 years (interquartile range [IQR] 57-77), 39% were female, and the median baseline estimated glomerular filtration rate was 72 mL/min/1.73 m^2 (IQR 53-90). The median length of ICU stay was 13 days (IQR 7- 24) and 50% received invasive mechanical ventilation. Overall, 70%, 18%, and 13% of patients experienced KDIGO stage 1, stage 2, and stage 3 AKI, respectively, and 5% received acute dialysis. Nephrology consultation occurred in 20% of the cohort. The cumulative incidence of having both an outpatient creatinine and urine protein measurement at 3 months of hospital discharge was 25% (95% confidence interval [CI] 25-26). At 3 months of discharge, 64% (95% CI 64-65) and 28% (95% CI 27- 28) of patients had an outpatient creatinine or urine protein measurement, respectively. The cumulative incidence of an outpatient visit to a family physician or nephrologist were 89% (95% CI 89-90) and 5% (95% CI 4-5), respectively.

Conclusions: Only 1 in 4 survivors of critical illness and AKI receive the recommended laboratory testing at 3 months of hospital discharge. Nephrology follow-up was rare, despite a third of the cohort having experienced KDIGO stage 2 or 3 AKI. Our findings illustrate an important gap in the transition of care for survivors of critical illness and AKI. Better recognition of the long-term implications of AKI and effective communication between patient providers during transitions of care may advance the follow-up care of critically ill patients with AKI. Further research is needed to determine if post-AKI care can improve long-term outcomes for survivors of critical illness and AKI.

The Impact of a 3-Tiered Model of Nursing Redeployment During the COVID-19 Pandemic: A Cross-Sectional Mixed Methods Study

Kissel K, Filipek C, Folz E, Jenkins J.

Background: The high volumes of critically ill patients during the COVID-19 pandemic resulted in extreme system pressures. Nurses were redeployed to intensive care units (ICUs) to support surges in patient volume. Worldwide, various redeployment models were used to support the rapid expansion of ICUs, however little is known about how to best support nurses during redeployment or the impact of a tiered model of care on nursing staff. Our aim was to explore the local impacts of a 3-tiered nursing model on nurses working in ICUs during the COVID-19 pandemic.

Methods: This study utilized a mixed method, cross-sectional design. A survey developed by Lauck et al. (2022) was adapted to explore the experience of nurses working in 4 adult ICUs, in one urban city in Alberta, during the 3rd or 4th pandemic wave. The survey evaluated nursing experiences within a 3-tiered model of care, layered within the contexts of expedited ICU orientations and redeployment. The Copenhagen Burnout Inventory (CBI) was used to measure burnout at time of survey. Outcomes were analyzed using descriptive statistics.

Results: We analyzed 191 surveys (59 ICU and 132 redeployed nurses). Several themes were explored in the survey examining impacts on both ICU, team leads, and redeployed nurses. The majority of team leads reported ability to lead teams effectively (85%). Amongst redeployed nurses, team leads and secondary nurses reported highest disagreement regarding clear role expectations. Only 45% of all redeployed nurses reported receiving adequate education to perform role. Redeployed roles identified their highest need being additional orientation and educational supports. Forty-seven percent of nurses had not received support for burn-out, self-care, and/or moral distress. Burnout scores were highest among team leads and ICU nurses. Across all roles, support from colleagues was the most cited aid to success. Flexible scheduling and advanced redeployment notice was recommended by many nurses, with some indicating they had less than 24 hours' notice prior to redeployment. Redeployed nurses without prior ICU experience stated they would have benefited from education and support for traumatic situations witnessed in the ICU. Three nurses (2%) reported needing medical or stress leave as a result of redeployment to ICU.

Conclusions: Recommendations for future surge planning should target key areas including role selection and education/support. Interventions protective of staff well-being, including mitigators of burnout, are requiring during and post pandemic surges.

Material Deprivation and Pediatric Intensive Care Unit (PICU) admission and outcomes in Alberta

Lee LA, Black J, King JA, Fiest KM, Doig C.

Background: Socioeconomic deprivation (SED) is associated with worse health outcomes. Critically ill adults with greater deprivation have increased severity of illness on hospital admission, higher mortality, higher readmission rates and more long-term disability. Data in pediatric critical care shows increased rates of PICU admission for those with greater SED, but no relationship between SED and PICU outcomes. Given the differential effect of SED on health by country, it is essential to understand it in a Canadian context. The primary objective of this study is to describe the distribution of SED for children admitted to a PICU in Alberta. The secondary objectives are to determine the association between SED and PICU outcomes (hospital mortality, PICU LOS and hospital LOS).

Methods: This was a retrospective study using administrative data. PICU records were extracted from the Discharge Abstract Database (DAD) and SED information from the Pampalon database. Dissemination areas within the Pampalon database were matched deterministically to each participant based on the full, six-digit postal code provided in the DAD record. We included children admitted to a PICU in Alberta between 1/1/2011 and 12/31/2021 (Figure 1). The main exposure variable was the Pampalon material deprivation index (PMDI), a validated SED measure calculated based on dissemination areas and national census data, available from Statistics Canada. It is derived from education, employment, and income and classifies levels of SED into 5 quintiles with quintile 1 (Q1) being the least deprived and quintile 5 (Q5) being the most deprived. Outcome measures included hospital mortality (%), PICU LOS (hours) and hospital LOS (days) as extracted from the DAD. Covariates included sex, age, rural status, type of admission (e.g., emergent vs. elective) and source of admission (e.g., inpatient unit vs. emergency department) as extracted from the DAD. Patient demographics, admission characteristics and outcomes were described. Proportions of deprivation within PICUs were compared to the general Alberta population with a two-sample test of proportions. Logistic (mortality) and negative binomial (LOS) regression models were fit to examine the association between SED and each outcome while assessing for modification and confounding by covariates. Statistical significance was set at $p < 0.05$.

Results: In total, 18,449 records were extracted, 7,995 were excluded for the following reasons: non- Alberta resident (n=2,313), missing postal code (n=7), missing PMDI (n=29), inability to assign PMDI due to inadequate census data (n=640), subsequent PICU admission (n=3809), and admitted during washout period (n=1,197). A total of 10, 454 children were included with a median age of 2 years (IQR, 0-9 years). The overall proportion of mortality was 3.0%, the median ICU LOS was 41.3 hours (IQR, 23.8-81.3), and median hospital LOS was 3 days (IQR, 3-11). In contrast to the Alberta population (20.0% per quintile), 26.7% of children admitted to a PICU reside in the most deprived quintile ($p<0.001$), while 15.8% reside in the least deprived quintile ($p<0.001$). Proportion of mortality was the lowest for Q1 (2.3%) and highest for Q4 and Q5 (3.6% and 3.3%). Median ICU LOS ($p=0.71$) and hospital LOS ($p=0.23$) were similar across quintiles. Children from Q4 and Q5 had 1.59 (95%CI: 1.15- 2.18) and 1.47 (95%CI: 1.09-1.98) times higher odds of mortality than those in the combined first and second quintiles, respectively. No difference in PICU length of stay between quintiles was observed ($p=0.20$). Children residing in Q5 had an estimated 19.5% (95%CI: 9.8%-30%) longer hospital stay ($p<0.001$) than those residing in Q1. This effect decreased with increasing age.

Conclusions: Children who reside in the most deprived neighborhoods are overrepresented in Alberta PICUs, have increased odds of mortality, and an increased duration of hospital stay

when compared to children residing in the least deprived neighborhoods. This is consistent across urban and rural residences. Further research aimed at minimizing the negative impacts of these social determinants of health are essential for improving the health of Alberta's most vulnerable children.

Does pain optimisation impact delirium outcomes in critically ill patients? A systematic review and meta-analysis of randomised controlled trials

Leong AY, Burry L, Fiest KM, Doig C, Niven DJ.

Background*:* Delirium and pain are experienced in up to 45% and 80% of intensive care unit (ICU) patients, respectively. Delirium and uncontrolled pain have short- and long-term consequences, including: longer ICU and hospital lengths of stay, cognitive impairment, impaired wound healing and mental health problems. We performed a systematic review and meta-analysis of studies examining the relationship between pain or pain medications (two exposures) with delirium (outcome) incidence, duration, and severity among adults admitted to ICUs. In this study, we report the subgroup analysis of randomised controlled trials.

Methods: *Study design:* Systematic review with meta-analysis. The review protocol was registered on PROSPERO (ID: CRD42022367715). MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of controlled trials, and a review of recent conference abstracts were searched without restriction from inception to 1 October 2022. *Setting and Population:* Studies were included if they were: 1) randomised controlled design; 2) in adult humans in the ICU; 3) reported a measure of pain, pain medications, and delirium. Studies were excluded if they reported: 1) alcohol withdrawal delirium or delirium tremens; and 2) emergence delirium. There was no language restriction. *Measures and Analytic Procedures:* Covidence software was used to screen titles and abstracts of studies in duplicate. Data was extracted in duplicate using a data extraction tool on Microsoft Excel. Risk of bias was assessed with the Risk of Bias 2 tool. Dichotomous estimates were pooled using random effects meta-analysis. Studies were analysed for time-varying and unmeasured confounding.

Results: Ten studies were included in the systematic review, of which four were meta-analysed. Among these articles, four were in the USA and two were set in China. The most commonly described ICU setting was general (n=4), followed by mixed medical or surgical (n=3). There was little consistency in the reporting of pain or pain medications and its relation to delirium. A qualitative risk of bias analysis indicated that six studies had high risk of bias. In patients exposed to pain medications, compared to those unexposed to pain medications, the risk of developing delirium was 0.49 (95%CI 0.20 – 1.17, p = 0.08). Only three studies controlled for known confounding and one study performed time-varying analysis. E-values, a measure of unmeasured confounding, ranged from 1.00 to 4.76.

Conclusions: Our meta-analysis of RCTs suggest that no relationship exists between pain medications and delirium. In contrast, prior literature suggested a potential protective effect of pain medications on the development of delirium in the critically ill. While critical care guidelines indicate that pain optimisation is imperative for delirium management, the results from our review suggest that these teachings may be based on conflicting data. The results of our review should be interpreted as support for the need for additional, more rigorous studies to examine the true nature of the relationship between pain and pain medications as potential risk factors for delirium.

Non-steroidal anti-inflammatories for pain control in the critically ill patients: a systematic review and meta-analysis

Ma CH, Tworek K, Kung JY, Kilcommons S, Wheeler K, Parker A, Senaratne J, Macintyre E, Sligl W, Karvellas C, Zampieri FG, Kutsogiannis DJ, Basmaji J, Lewis K, Rewa OG, Rochwerg B, Bagshaw SM, Lau VI.

Background: Opioids are part of usual critical care analgesia and sedation. However, concerns remain regarding adequate analgesia in the critical care setting and excess opioid use leading to dependency after hospital discharge. Therefore, we conducted a systematic review and meta-analysis to evaluate the safety and opioid-sparing effects of non-steroidal anti-inflammatories (NSAIDs) in the critically ill adult population.

Methods: We conducted a systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, trial registries, Google Scholar, and relevant systematic reviews. We identified randomized control trials (RCTs) that compared NSAIDs to opioids for systemic analgesia. Our primary outcome was total opioid utilization. Secondary outcomes were reductions in pain scores, duration of mechanical ventilation, ICU length of stay, and delirium. Additional outcomes explored were hospital length of stay, mortality (ICU and hospital), adverse events. We pooled data and presented results in mean difference for continuous outcomes and relative risk for dichotomous outcomes with 95% confidence intervals (CIs). We evaluated studies with the Cochrane Collaboration Risk of Bias 2 tool and the overall certainty of the evidence with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework.

Results: We included 15 RCTs (n=1621 patients) in our meta-analysis which demonstrated that the addition of an NSAID as adjunctive analgesia reduced 24-hour oral morphine equivalent consumption by
-21.4 mg (95% CI: -30.95 to -11.81, p<0.0001, low-to-moderate certainty) and reduced pain scores (measured by visual analogue scale) by -6.1 mm (95% CI: -12.2 to 0.06, p=0.05, very low certainty). In addition, the duration of mechanical ventilation with the NSAID group was decreased by -1.6 hours (95% CI: -2.7 to -0.4, p=0.007, very low certainty); however, no statistical difference in ICU length of stay was observed (-2.1 hours, 95% CI -6.1 to 2.0, p=0.31, very low certainty). Blood loss after 24 hours was reduced in the NSAID group by -32.7 mL (95% CI -42.3 to -23.0, p<0.00001, moderate certainty), although unclear of clinical significance. Other adverse outcomes were variably reported in the evaluated citations (e.g. acute kidney injury and gastrointestinal bleeding), which precluded analysis.

Conclusion: In critically ill adult patients, NSAIDs significantly reduce opioid use and modestly reduce pain. Further research is required to characterize the prevalence of NSAID-related adverse outcomes.

Methods to monitor and evaluate safe Neuromuscular Blockade use in patients with Hypoxemic Respiratory Failure and Acute Respiratory Distress Syndrome: A scoping review

Morton S, Irwin A, Kissel K, Jewers D, Dhillon P, Morrissey J, Loroff N, Knight G, Cashen D, Parhar KKS.

Background: Neuromuscular blocking agents (NMBAs) are an important therapy in managing moderate to severe acute respiratory distress syndrome (ARDS); however, the current evidence does not support a clear consensus on the most effective way to monitor NMBA administration in this patient population.
Variations in NMBA monitoring practices may affect provider, patient, or resource outcomes. The aim of the scoping review was to describe the methods used to monitor the effectiveness of NMBAs, the outcomes associated with these monitoring strategies, and the different study designs used to assess these strategies. This will provide clarity and guide clinical practice for NMBA monitoring for clinicians using this therapy in patients with moderate to severe ARDS.

Methods: The population of interest was adults undergoing invasive mechanical ventilation in a critical care setting who received NMBAs and had ARDS or hypoxemic respiratory failure. The primary concept was to describe the strategies used to monitor the effectiveness of NMBA. The context was not limited based on geography, culture, or gender. The scoping review was prepared following the framework initially proposed by Arksey and O'Malley with updates from Levac and most recently updated by the Joanna Briggs Institute. The scoping review protocol is registered in Open Science Framework. Based on the inclusion and exclusion criteria, a comprehensive literature search was conducted in three bibliographic databases – MEDLINE (Ovid), Embase (Ovid), and CINAHL (EBSCO). The full text of 387 publications were independently reviewed by two team members to determine if inclusion criteria was met. Disagreement was resolved by discussion with two other team members. The full-text assessment identified eight relevant studies. Data were extracted and an analysis was completed to synthesize the results.

Results: The evidence associated with monitoring strategies and the effectiveness of NMBAs in patients with ARDS remains unclear. Of the eight studies, only one was an RCT. NMBA dosing and monitoring strategies varied significantly, which makes comparison difficult. Peripheral nerve stimulation with a train-of-four (TOF) monitor was the most commonly reported monitoring strategy. Location and goals for TOF monitoring varied amongst the studies. Clinical assessment was also reported as an adjunct or comparator to TOF and as an independent monitoring strategy. Out of the six studies that assessed clinical variables, ventilator dyssynchrony was most commonly described. End-tidal CO2 was not reported as a monitoring strategy used to guide NMBA administration or monitoring. Patient, provider and resource outcomes varied. No significant differences were observed between administration and/or monitoring strategies and mortality, length of stay, or duration of mechanical ventilation. A guided dosing strategy was used in seven studies. A decrease in the amount of NMBA administered was associated with this strategy. Despite this finding, impacts on patient-related outcomes within these studies remain unclear.

Conclusions: Evidence in support of a method to monitor the effectiveness of NMBA in patients with ARDS is sparse and represents a gap in the literature. This work has implications for future research and the development of guidance for critical care clinicians in administering and monitoring NMBAs.

Community Intensive Care Unit Recruitment to Improve Research Efficiency: ICU Community Modeling and Artificial Intelligence to Improve Efficiency (ICU-CoMMA)

Quigley N, Bagshaw SM, Lau VI.

Background: In Canada, critical care research has traditionally been conducted in academic hospital intensive care units (ICUs) affiliated with universities. Although efforts have been made to increase clinical research engagement amongst community hospital ICUs, many community hospitals have significant barriers to participation as they lack dedicated research infrastructure, funding, and access to crucially important research coordinators. Increasing community ICUs participation (which represents two-thirds of ICU capacity in Canada) in large multi-center trials may enhance recruitment, shorten the time for completion of clinical trials, and improve the generalizability and quality of evidence. Moreover, this will further accelerate knowledge translation and implementation. Strategies to facilitate community ICU involvement in research have been identified. Amongst them, incorporating artificial intelligence (AI) automation to perform basic research tasks could reduce research costs, making participation in research more feasible and less burdensome in both community and academic ICUs.

Objectives: To identify community ICU patients that could be screened for and enrolled in large multi- center trials and quantify the potential opportunity associated with greater community ICU participation. We aimed to describe the number of additional eligible patients available for recruitment in community ICUs, and how this would impact time to completion of large multi-center trials.

Methods: We performed a decision-tree analysis using *Alberta Health Services* (AHS) IT databases (eCritical, TRACER, DIMR) to quantify the effects of community ICU recruitment. We first identified 10 landmark multi-center critical care trials suitable for community ICUs and extracted data on patient recruitment and study completion from screening and eligibility to completed data collection. We retrospectively analyzed patients admitted to Alberta ICUs from January 1 to December 31, 2018 and identified those who could have been considered for the chosen landmark trials based on their clinical characteristics and management strategies. Using decision tree analysis, we described the number of Alberta ICU patients, both in community and academic settings, that could have been eligible for participation in landmark trials. We further estimated the differences in time to completion with the inclusion of community ICU patients.

Results: 10,157 adult patients were admitted to Alberta ICUs in 2018. Amongst those, 5,650 (55.6%) were in academic centers and 4,507 (44.4%) were in community hospitals. An estimated 6,486 patients could have been screened and additional 1,555 patients potentially eligible for the landmark trials. Community ICU patients would have accounted for 40.0% of those and their inclusion would have led to a 64% increase in the number of patients potential enrolled (from 948 to 1555). Inclusion of community ICU patients would have decreased the mean time to completion of trials from an estimated 2.8 years with academic ICU patients only to 1.6 years (43% reduction in duration).

Conclusion: The inclusion of eligible patients admitted to community ICUs in multi-center clinical trials can accelerate recruitment and reduce time to trial completion.

Impact of frailty on long-term quality of life in patients undergoing cardiac surgery

Schroyens M, Bagshaw SM, Norris CM, Rolfson DB, Meyer SR, Stelfox HT, Zibdawi MA, Montgomery CL.

Background: Frailty is associated with a risk of worse outcomes and higher health services use in adult patients undergoing cardiac surgery. However, there is limited data on the impact of frailty on long-term postoperative quality of life. In this study the primary aim was to assess the impact of baseline frailty status on health-related quality of life (HRQL) at 12 months following cardiac surgery.

Methods: This prospective cohort study included patients aged 50 years and older who underwent non- emergent cardiac surgery between November 2011 and March 2014 in the two adult cardiac surgery programs in Alberta, Canada. Frailty was defined as a Clinical Frailty Scale (CFS) score of 5 or greater. HRQL was assessed using the EuroQol 5-domain 3-level (EQ-5D) and Short Form-12 (SF-12) surveys in person pre-operatively and by telephone at 6 months and at 12 months following surgery. Other details collected were patient socio-demographics, comorbidities, surgery details, cardiac surgery risk scores, adverse events and discharge disposition.

Results: The cohort (529 patients) mean (SD) age was 67 (9) years. 25.9% were female and the pre- operative prevalence of frailty was 9.6%. Patients with frailty were older (median [IQR] age 75 [65-80] v. 67 [60-73], $p<0.001$) and had higher EuroSCORE II (8 [6-9] v. 5 [3-7], $p<0.001$). SF-12 physical component score increased from baseline to 12-months in frail (27.5 [9.4] to 38.2 [11.9], $p<0.001$) and non-frail patients (37.0 [11.4] to 47.3 [9.9], $p<0.001$). Mental component score in patients with frailty was similar (47.7 [12.0] to 52.2 [10.4], $p=0.29$) and increased in non-frail (51.8 [10.7] to 54.9 [8.5], $p<0.001$). Mean (SD) EQ-5D VAS increased in frail (46.2 [18.9] to 60.3 [21.6], $p<0.001$) and non-frail (60.2 [20.2] to 76.6 [15.4], $p<0.001$).

Conclusion: HRQL was more impaired in patients with frailty at baseline although incremental improvement in HRQL was reported in frail and non-frail patients over 12-months post-operatively. Recognizing the risk to HRQL among patients with frailty pre-operatively requires further exploration to identify potential interventions to optimize outcomes.

Development and Pilot Testing of the Critical Care Pain Observation Tool for Families (CPOT-Fam)

Shahid A, Sept BG, Owen VS, Johnstone C, Paramalingam R, Moss SJ, Soo A, Brundin-Mather R, Krewulak KD, Gélinas C, Fiest KM, Stelfox HT.

Background: Many intensive care unit (ICU) patients are non-communicative and cannot self-report pain. For these patients, family members or close friends may be able to assist in pain assessment. Engaging families in pain assessment could facilitate timely pain recognition and improve satisfaction with care. We aimed to 1) adapt a pain assessment tool for family use, and 2) pilot test the tool to determine feasibility and acceptability.

Methods: A working group of patient-partners and critical care experts (physicians, nurses, researchers) used a deliberative process to iteratively refine the Critical Care Pain Observation tool (used by ICU nurses) for family use (creating the CPOT-Fam). The CPOT-Fam was pre-clinically tested with a convenience sample of individuals who used it to score sample cases representing ICU patients experiencing pain. The tool was then revised based on feedback received from participants. Clinical pilot testing was performed by collecting simultaneous pain assessments from interested families and nurses for a given ICU patient. The primary outcome was the degree of agreement between CPOT-Fam and CPOT scores, determined using weighted kappa statistic (κ). Open-ended feedback on the CPOT-Fam was collected from families and nurses to inform further revisions of the tool, if needed.

Results: The CPOT-Fam was designed using the original CPOT dimensions evaluating facial expression, body movements, compliance with ventilator (if intubated) or vocalization (if not intubated), and muscle tension. During pre-clinical testing, participants (n=32) found the CPOT-Fam to be "informative" but "not visual enough". In response, the CPOT-Fam was restructured into an illustration- based flow sheet **(Figure 1)**. Participant recruitment for CPOT-Fam pilot testing is ongoing. Of the twenty-one family caregivers approached to participate in the study so far, (n=19; 90%) have consented. Results to date (n=19) show moderate (defined as 0.41-0.60) to substantial (defined as 0.61-0.80) agreement between family and nurse pain scores (CPOT-Fam vs. CPOT). Agreement is highest for the ventilator compliance/vocalization dimension (*How is the patient breathing* OR *Is the patient making any sounds*; κ = 0.61; 63% agreement) and lowest for the muscle tension dimension (*The patient's muscles appear to be..*; κ = 0.45; 63% agreement). Most families (n=16; 84%) report the CPOT-Fam to be "easy-to- use" and do not suggest further changes. Most (n=13; 68%) nurses find the CPOT- Fam to be a tool with "good illustrations and wording" that is "suitable for family use". A minority of nurses (n=3; 16%) have stated the CPOT-Fam may be unsuitable as families "do not need another thing to do" in the already stressful ICU circumstances.

Conclusion: Pilot testing suggests that family assessments of patient pain using the CPOT-Fam have moderate agreement with bedside nursing assessments using the CPOT. There may be a role for family caregivers to contribute to patient pain assessments in the ICU.

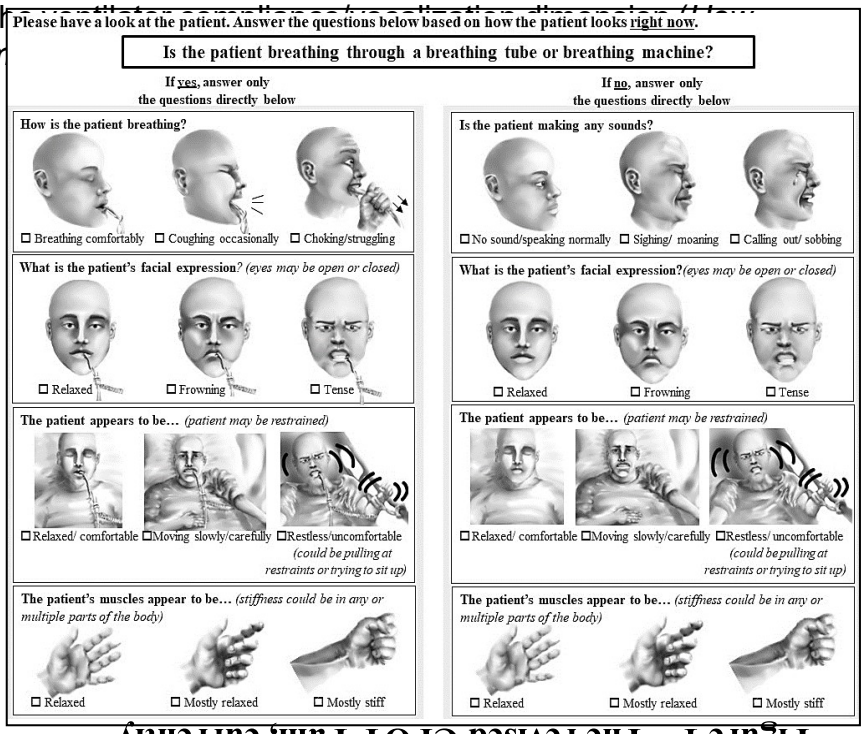

Figure 1 – The revised CPOT-Fam, currently

Reducing the Use of Sedatives and Analgesics in Critical Care (ROSA), Sturgeon Pilot Site

Slemko J, Dirks C, Rewa O, Widder S, Harris J, Parker A.

Background: Excess use of sedative and analgesic infusions prolongs mechanical ventilation and increases intensive care unit (ICU) length of stay (LOS). This leads to complications which can contribute to morbidity and mortality in addition to extended ICU LOS and use of resources. Choosing Wisely Canada recommends to not "prolong mechanical ventilation by over-use of sedatives and bedrest" as well as "don't continue invasive mechanical ventilation without a daily assessment for the patient's ability to breathe spontaneously using coordinated spontaneous breathing and awakening trials."[1] ROSA is a quality improvement (QI) initiative for the Edmonton zone to reduce the use of sedative and analgesic infusions in the ICU. The Sturgeon Community Hospital (SCH) serves as the pilot site for this initiative, and learnings will be used to drive the successful implementation at other ICU sites.

Methods: The aim is to reduce the use of sedative and analgesic infusions in the first 7 days of ICU admission by 35% over 12 months. QI tools were used to identify causes and potential opportunities for improvement at the zone and SCH level. A standardized, evidence and multidisciplinary stakeholder informed analgesia and sedation guideline was developed for the zone, which includes a spontaneous awakening trial (SAT) protocol. These have been implemented at SCH with regular audits and transparent sharing of results via report cards and a unit dashboard accessible to all. Data collected includes outcome measures (cumulative duration and total dose of infusions, with specific emphasis on midazolam), process measures (SAT completion rate and Richmond Agitation Sedation Scale ordering) and balancing measures (unplanned extubation and unplanned central line removal).

Results: At baseline (January to August 2022), the SCH ICU had a total of 7.4 infusion hours per day in all patients, and 13.1 infusion hours per day in ever mechanically ventilated patients. The majority of infusion hours were accounted for by propofol and opiates. Multidisciplinary meetings were held to elucidate feedback on continuous infusion use in the SCH ICU. It was identified that a high patient acuity, delirium and agitation, prescriber preference and staffing shortages were contributors to infusion use. Early interventions included multidisciplinary education and use of the guideline, daily SATs, and the bedside audit tool. One month into implementation, SATs by infused patient day have improved from 4% to 21%. Daily RASS ordering compliance is 82%. Outcome and balancing measure data for SCH will be available by January 2023.

Conclusions: Implementation of the ROSA initiative is underway in the SCH ICU, which has provided learnings for optimization of future scale and spread at other sites in the Edmonton Zone planned for 2023.

Neonatal Sepsis and the Long-term Cardiovascular and Metabolic Effects

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Background: Neonatal sepsis is a dysregulated host response to pathogens occurring in very young infants. It affects 4 to 22 newborns per 1000 live births globally[1] and is a significant cause of mortality worldwide. In addition, survivors may suffer from long-term morbidity including cardiovascular and metabolic dysfunction. However, some long-term aspects of this septic developmental insult have yet to be explored. Using an established model of neonatal sepsis in Sprague Dawley rats, we sought to examine the long-term cardiovascular and metabolic effects of neonatal sepsis in adulthood.

Methods: We induced sepsis via intraperitoneal injection of fecal slurry (0.1mg/kg) at 3 days of age; controls received saline. SR buprenorphine was administered subcutaneously (SC) to all animals (0.5mg/kg) at the time of fecal slurry injection for pain management. The animals were assessed using our novel neonatal Rat Sepsis Score (nRSS) 4 hours post injection and then every 8 hours for 24 hours. Ampicillin (20mg/kg, SC, every 12 hours) and gentamicin (4mg/kg, SC, every 24 hours) were administered starting 4 hours post sepsis induction. Saline was administered SC for a total volume of 5mL/kg/day of fluids. At 6 months of age, surviving pups underwent investigations including cardiac echocardiography and blood pressure measurement via tail-cuff plethysmography, waist circumference and crown-rump length measurements, body composition by ECHO-MRI, as well as glucose tolerance tests (GTT) and insulin tolerance tests (ITT). Prior to GTTs, rats underwent a 16 hour fast, and blood glucose was measured at baseline, and then at 15, 30, 60, 90 and 120 minutes following glucose administration (2g/kg by oral gavage). ITTs were performed after a 4 hour fast and blood glucose measurements were performed at the same time intervals following injection of insulin (1 unit/kg, SC). All data sets were analyzed by two-way ANOVA with Sidak post-hoc test.

Results: All non-surviving pups were identified and euthanized between 6 to 12 hours post-fecal slurry injection; no mortalities were observed beyond 12 hours post-fecal slurry injection. Cardiac echocardiography revealed sex specific differences between groups, with female survivors having higher cardiac output (CO) than controls ($p=0.0375$), whereas male survivors had lower CO and stroke volume (SV) compared to respective controls ($p=0.0466$, $p=0.0482$ respectively). Other echocardiographic findings yielded no significant differences between groups, however factors including intraventricular relaxation/contraction time and left ventricular diastolic diameter followed similar trends. Blood pressure and metabolic investigations yielded comparable results between groups.

Conclusions: At six months of age, no apparent differences in metabolic function were identified between septic and control animals. However, significant sex differences in cardiovascular function were observed. Given their young age, it is conceivable that cardiovascular function will worsen, and differences will be exacerbated over time. Similarly, underlying metabolic dysfunction may manifest with increasing age. Consequently, we will continue to monitor survivors for cardiovascular and metabolic changes at 12 and 18 months of age. We anticipate further cardiovascular and metabolic changes will develop and elucidate the long-term developmental effects of neonatal sepsis.