6TH ANNUAL
MITCHELL P. FINK SCHOLAR DAY
ABSTRACTS

Celebrating the Scholarship of the
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CRITICAL CARE MEDICINE
ORAL PRESENTATIONS

Intensity of Ultrafiltration and Mortality in Critically Ill Patients with Acute Kidney Injury and Fluid Overload
   Balakumar V, Murugan R, Clermont G, Palevsky PM, Kellum J

Implementation and Evaluation of a Web-based Critical Care Curriculum Using a Mixed Media Approach
   Gidwani H, Rieker J, Moore J

Vasopressin Use for Hypotension in a Transplant Intensive Care Unit
   Kim CH, Huang D, Angus D, Cornman L, Kim H, Murugan R, Wallace DJ, Al-Khafaji A

A Gene Variant Analysis for Dysregulated Inflammatory Conditions in Septic Shock Patients with Features of Macrophage Activation Syndrome and Extreme Hyperferritinemia

CLINICAL RESEARCH

Multi-Drug Resistant Organism Sepsis in Pediatric Liver Transplant Recipients – A Burgeoning Problem
   Alcamo AM, Alessi LJ, Vehovic SN, Pang D, Bond G, Carcillo JA, Michaels M, Aneja RK

Cell-cycle Arrest Biomarkers [TIMP2]*[IGFBP7] for Risk Stratification of Acute Kidney Injury in Patients with Sepsis
   Fiorentino M, Keener C, Smith A, Kellum JA

Serial Evaluation of qSOFA Among Patients with Suspected Infection
   Kievlan DR, Zhang LA, Chang CC, Angus DC, Seymour CW

Identifying High-Risk Suspected Infection Patients Using Serial qSOFA Measurements and Group-Based Trajectory Modeling
   Kievlan DR, Zhang LA, Chang CC, Angus DC, Seymour CW

Effect of Targeted Anti-inflammatory Therapy on Mortality of Patients with Sepsis-induced Macrophage Activation Syndrome

SIRS is Prevalent in Early SAH and Associated with Worse GCS and Higher Mortality
   Reyes L, Seymou CW, Angus DC, Kaynar AM, Chou SH

SIRS is Prevalent in ICH and Associated with Mortality
   Reyes L, Seymou CW, Gidwani H, Angus DC, Kaynar AM, Chou SH,
The Triple Variable Index (TVI), a Novel Methodology Linking Real-time Patient Physiology to Postoperative Outcome

Identification of Sepsis Phenotypes Using Clustering Methods
   Xu Z

HEALTH SERVICES RESEARCH

Hospital-level Variation in Risk-adjusted Mortality for Pediatric Sepsis
   Ames SG, Davis BS, Carcillo JA, Angus DC, Kahn JM

Hospital Perceptions of Medicare’s Sepsis Quality Reporting Initiative
   Barbash IJ, Rak KJ, Kuza CC, Kahn JM

Focused Evaluation with Echo in New Onset Anuria and Oliguria in the Critically Ill Patient (FENA Trial)
   Freyer AJ, Yende SX, Schott CK

Provider Perceptions of Rounding Checklists in the Intensive Care Unit: A Quality Improvement Project
   Hallam BD, Kuza CC, Rak KJ, Fleck JC, Heuston MM, Saha D, Kahn JM

Evaluation of Enoxaparin for Venous Thromboembolism Prophylaxis for Trauma Patients
   Malik D, Hogue A, Loveranes M, Kautza B, Gunn S, Rosengart M

Rothman Index has Good Predictive Value for Mortality in a Large Academic Medical Center
   Pacheco C, Scholle C; Cua-Martin S; Lovasik D, Cochenour C, Simmons RL, Murugan R

Epidemiology of Hospitalizations with Sepsis in Children in the United States
   Prout A, Talisa VB, Mayr F, Chang CC, Yende S

Using an Inductive Approach to Create a Brief Survey of Practices, Barriers, and Facilitators Related to Interdisciplinary Family Meetings

QUALITY IMPROVEMENT & EDUCATION

Rectal Trumpet Associated Hemorrhage in the ICU: Report of a Quality Improvement Initiative
   Glass D, Huang DT, Dugum M, Chintamaneni P, Cua S, Saul M, Marsh W, Al-Khafaji A
Extubation Outcomes of Critically Ill Patients with Known Difficult Airways: A Quality Improvement Project

Adherence to Low Tidal Volume Ventilation in Pregnancy
    Paruchuri Y, Hauspurg A, Donadee C, Murugan R

Critical Care Fellows as Team Leaders of Rapid Response Teams: A Safety Evaluation in a Mature Rapid Response System

When ECMO Fails: A Critical Care Simulation for First Year Fellows
    Shafer K, Brackney C, Emlet L

Pilot Evaluation of Telemedicine Brain Death Examination
    Tahseen M, Glass D, Darby J, Shutter L, Neuro Critical Care group

The Critical Need in the Critical Care Fellowship Quality Improvement
    Thangudu P, Gunn S

Research for the Non-research Oriented Fellow; the MCCTP-MACRO Experience
    Thangudu P, Padmanabhan R, Huang DT

Quality Improvement: Assessment of Neuromuscular Blockade Use in Adults with Acute Respiratory Distress Syndrome
    Thangudu P, Donadee C, Groetzinger L, Rivosecchi R, Then J, Smithburger P, Gunn S

**TRANSLATIONAL RESEARCH**

Cytokine Response in Adult Severe Sepsis Patients with Features of Macrophage Activation Syndrome
    Anderko R, Jackson V, Peck Palmer O, Angus DC, Gomez H, Kellum J, Carcillo J

Reversal of Warburg Effect via Metabolic Reprogramming Decreases Sustained Inflammation and Improves Lifespan in a Drosophila Model of Surviving Sepsis
    Bakalov V, Reyes Uribe LI, Deshpande R, Stelmach M, Gelhaus Wendell S, Kaynar AM

A Systemic Review of Sepsis Induced Macrophage Activation Syndrome (MAS)

Increase in HSP27 in Pediatric Cardiopulmonary Bypass and its Relationship with AKI
    Gretchen C, Bayir H, Viegas M, Sharma M, Kim-Campbell N

▲ Back to top
Mechanisms for Sepsis-associated AKI Non-recovery
Li S, Frank A, Wen X. Kellum J

Modulation of IGFBP7 and TIMP2 Expression and Secretion by Clinically Relevant Insults In Vitro
Emlet DR, Morrisroe S, Frank A, Kellum J

Sublingual Microvascular and Tongue, Renal, and Hepatic Tissue Responsiveness to Resuscitation in a Porcine Model of Sepsis
Pool R, Haugaa H, Botero A, Escobar D, Maberry D; Tønnessen TI, Zuckerbraun BS, Pinsky MR, Gomez H

Pilot Study of Aquaporin-4 Inhibition on Cerebral Edema and Early Functional and Histological Outcome After Cardiac Arrest
Wallisch JS, Jha RM, Farr GW, McGuirk PR, Pelletier MF, Jackson TC, Kochanek PM, Manole MD

Serum Biomarker-based Models to Predict Intracranial Pressure in Pediatric Traumatic Brain Injury
Woods KS, Au AK, Kochanek PM, Bell MJ, Clark RSB
ORAL PRESENTATIONS

Intensity of Ultrafiltration and Mortality in Critically Ill Patients with Acute Kidney Injury and Fluid Overload

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Primary affiliation of lead author: Department of Critical Care Medicine, University of Pittsburgh

Level of training of first author: Fellow 1\textsuperscript{st} year

Abstract type: Original Research

Objective: Although fluid overload is independently associated with increased mortality in critically ill patients with acute kidney injury, the association between fluid removal (Ultrafiltration, UF) and mortality is unclear. Thus, we examined the association between intensity of ultrafiltration and risk-adjusted one-year mortality among critically ill patients with fluid overload and receiving renal replacement therapy (RRT).

Methods: We analyzed the High Density Intensive Care (HiDenIC-8) dataset, which includes adults admitted to UPMC ICUs between 2000 and 2008. AKI was defined according to KDIGO criteria and only patients with AKI and fluid overload ≥ 5% of body weight prior to initiation of RRT were included. UF intensity was calculated as volume removed per day from initiation of either continuous or intermittent RRT until end of ICU stay adjusted for patient hospital admission body weight as follows: high >25ml/kg/day; moderate ≤25 - >20ml/kg/day, and low ≤20ml/kg/day. We constructed a propensity score to account for indication bias for UF intensity using age, sex, body mass index, race, surgery, baseline estimated GFR, first RRT modality, pre-RRT fluid balance, duration of RRT, time to RRT initiation as well as risk factors measured in the first 24 hours of ICU admission such as APACHE-III score, vasopressor use, mechanical ventilation use, suspected sepsis and severity of hypotension. We examined Kaplan-Meir failure plots in the propensity-matched cohort and fitted multivariable logistic regression for mortality.

Results: Of 1,075 patients with ≥ 5% fluid overload and receiving RRT, the distribution of high, moderate and low intensity UF were 40.4\%(n=434), 15.2\%(n=166) and 44.2\%(n=475), respectively. The crude mortality was 59.4\%, 60.2\% and 69.7\%, respectively. After combining low and moderate intensity groups (n=322) and after propensity matching with high intensity group (n=322) in a 1:1 ratio, the high intensity UF groups had lower mortality compared with moderate and low intensity UF (56.5\% vs. 70.2\%, P<0.001; Figure 1). In the overall cohort, the mortality was lower in the high intensity UF group compared with low intensity UF (adjusted OR,
0.51, 95% CI, 0.35 - 0.73; P<0.001), whereas, there was no difference in mortality between moderate, compared with low intensity UF group (adjusted OR, 0.67; 95% CI, 0.42-1.05; P=0.08).

**Conclusions:** Higher intensity ultrafiltration of > 25mls/kg/day compared with low intensity ultrafiltration of < 20mls/kg/day is associated with lower one-year mortality in critically ill patients with fluid overload.

Figure 1

Kaplan Meier failure plots showing mortality over a 1-year period after the ICU admission between patients that received high intensity UF (>25ml/kg/day) versus combined low and moderate intensity UF (≤25ml/kg/day) in the propensity-score matched cohort.
Implementation and evaluation of a web-based Critical Care curriculum using a mixed media approach

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Abstract type: Educational Initiative

NEEDS STATEMENT / OBJECTIVES

Web-based teaching is widely used in medical education, however there is a paucity of literature comparing different online learning modalities. Such comparison may inform educators of more effective online teaching methods. In this before/after observational study, we evaluated the effectiveness of a web-based, mixed media Critical Care curriculum to improve cognitive performance in medical trainees. We also evaluated learner attitudes toward the curriculum and preferences regarding content delivery.

METHODS

We developed an online educational course teaching common evidence based medicine in intensive care that consisted of five modules containing video lectures, audio lectures and text based teaching for each module. Access the course was given to Internal Medicine residents and first year Critical Care Medicine fellows after completion of a survey of baseline characteristics. Participation was voluntary. Content delivery was through a commercially available online learning management system, which also allowed tracking of usage logs for each learner. A single group pre/post-test design was used to assess knowledge changes. Data on user satisfaction was also collected.

RESULTS

Sixty four percent (n=36) of invited participants completed the pre-course survey. Most of these participants (n=31) indicated a high level of comfort using online learning resources. At the interim analysis, 50% of invited participants (n=28) have been using the curriculum. Pre-course knowledge assessment test average = 65%. Results of the post-course knowledge assessment are pending. Using page views, assessment of preferred mode of content delivery (video lectures, audio lectures, text based) will be calculated.
CONCLUSIONS

This interim analysis demonstrates the ability to incorporate multiple media format choices into a single online curriculum. It also demonstrates the value of a computerized learning management system for collecting complex outcomes such as online activity. Our final analysis will include assessment of cognitive improvement, learner attitudes, and content delivery preferences for learners completing the curriculum.
Title: Vasopressin Use for Hypotension in a Transplant Intensive Care Unit

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Primary affiliation of first author: University of Pittsburgh Medical Center Presbyterian Hospital

Level of training of first author: Transplant ICU Unit-based Clinical Pharmacist

Abstract type: QI project

Learning objectives: The VASST trial showed no difference in mortality in patients who received norepinephrine alone compared to norepinephrine plus vasopressin. Despite this finding, low-dose vasopressin is often used as a second vasopressor with norepinephrine for hypotensive patients. Recently the price of vasopressin increased 10-fold in the United States. High cost and lack of robust evidence prompted initiating a quality improvement project aimed at reducing the use of vasopressin in a busy academic transplant intensive care unit (ICU).

Methods: We evaluated vasopressin use in an adult transplant ICU during two ten-month periods; from 9/1/2014 to 6/30/2015 and from 9/1/2015 to 6/30/2016. Between these periods, clinical faculty implemented a guideline that recommended adding vasopressin only when norepinephrine dose reached 1.5 mcg/kg/min or higher. Data from both pre-restriction and post-restriction periods was collected retrospectively using electronic medical and pharmacy records. We monitored vasopressin use, average daily census, risk-adjusted ICU mortality, risk-adjusted duration of mechanical ventilation, and risk-adjusted ICU length of stay. The project was approved by the local quality improvement review committee.

Results: In the pre-restriction period, 181 of 1266 patients received a continuous vasopressin infusion. The average dose of norepinephrine when vasopressin was started was 0.2 mcg/kg/min. In the post-restriction period, 26 of 1066 patients received a continuous vasopressin infusion. During this period, the average dose of norepinephrine when vasopressin was added was 0.8 mcg/kg/min. After guideline implementation, we saved approximately $170,000 in charges attributable to vasopressin, representing a 90% reduction. No differences were found in the average daily census (17.4 vs 17.1 days), risk-adjusted ICU mortality (17.2% vs 14.4%), risk-adjusted duration of mechanical ventilation (3.9 vs 4.0 days), and ICU length of stay (2.9 vs 3.0 days) in the pre- and post-restriction periods respectively.

Conclusion: Implementing a vasopressin use guideline for hypotensive patients in Transplant ICU led to a significant reduction in vasopressin use and charges without significant differences in risk-adjusted clinical outcomes.
A gene variant analysis for dysregulated inflammatory conditions in septic shock patients with features of macrophage activation syndrome and extreme hyperferritinemia

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Introduction: We recently reported that septic shock patients with features of macrophage activation syndrome experienced a 50% reduction in mortality when treated with an anti-inflammatory biologic agent, interleukin 1β receptor antagonist protein. Methods: Of the 1341 adult patients enrolled in the ProCESS trial for septic shock, we selected the 6 patients with macrophage activation syndrome and the highest ferritin levels (mean 24,030.7 ng/ml, +/-SEM 7,411.1) for whole exome sequencing. Results/Discussion: All 6 subjects were found to have pathologic variants related to dysregulated inflammation, with 5 of 6 having conditions for which interleukin 1β receptor antagonist protein therapy is recommended (1 NLRP3 and 2 MEFV autosomal dominants, and 3 UNC13D autosomal recessives). Interestingly 3 of the 6 have conditions for which anti C5a monoclonal antibody is recommended (1 C3 and 2 CD46 autosomal dominants, and 1 CFHR5 autosomal dominant). Additional work investigating variant targeted precision medicine may benefit this septic shock subset with genetic evidence of dysregulated inflammation.
Multi-drug Resistant Organism Sepsis in Pediatric Liver Transplant Recipients – A Burgeoning Problem


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Type of Research: Original Research

Recent studies have noted an increased prevalence rate for pediatric severe sepsis to 7.7%, with mortality of 12%. However, there is a significant gap in knowledge about the impact of sepsis on immune-compromised solid organ transplant recipients. We aim to describe the characteristics of liver transplant (LTx) patients admitted with sepsis to the pediatric intensive care unit (PICU).

A retrospective descriptive analysis of all LTx recipients admitted to the PICU from Jan 2010 to July 2016 who met the International Consensus Conference criteria for pediatric sepsis. Multi-drug resistant organisms (MDROs) were defined as bacteria resistant to greater than one class of antimicrobial agents.

Of 161 LTx patients, 38 (23%) were admitted to PICU with sepsis, accounting for a total of 58 episodes. The most common reasons for LTx were biliary atresia (26%) and inborn errors of metabolism (26%). 35% received living-related LTx while the rest received deceased organ grafts. The mean age was 4.6 y (6 m – 24 y) and 55% were female. Almost one third of the 58 episodes met criteria for septic shock and 39% had multiple organ dysfunction syndrome. Approximately 52% of the patients required mechanical ventilation and 5% of the patients were placed on extracorporeal membrane oxygenation support. The primary sites of infection included blood (40%), respiratory tract (16%), peritonitis (14%). Culture results were documented as bacterial (68%), culture negative (13%), viral (7%), and fungal (2%). Of note, 50% of bacterial infections were due to MDROs, predominantly vancomycin resistant enterococcus and extend spectrum beta lactamase producers. No graft loss was attributable to sepsis. Mortality for this cohort was 5%.

MDRO infections in a septic pediatric transplant patient should be of high concern. Compared to the general PICU population, liver transplant recipients are more likely to be septic but have lower mortality despite infection with MDROs. Knowledge about local bacterial epidemiology should guide initial empiric antibiotic therapy. Future studies are needed to identify potential risk factors in this cohort, including immunosuppression management.
Figure 1.

Source of Infection

Bacterial - Total 68%

- Polymicrobial 9%
- Culture Neg 14%
- Fungal 2%
- Viral 7%

Bacterial - Non-MDRO 34%

Bacterial - MDRO 34%
Cell-cycle arrest biomarkers [TIMP2]*[IGFBP7] for risk stratification of acute kidney injury in patients with sepsis

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Abstract type: Original research

Objectives: Acute kidney injury (AKI) is associated with both short- and long-term adverse outcomes in septic patients. Standard criteria for AKI, like serum creatinine (sCr) and urine output (UO), are late and non-specific diagnostic tools. The aim of this study is to analyze the performance of cell cycle arrest biomarkers tissue inhibitor metalloproteinase-2 (TIMP2) and IGF-binding protein 7 (IGFBP-7) in addition to standard criteria for early prediction of severe sepsis-associated AKI.

Methods: We analyzed data from 1243 patients with septic shock enrolled in the ProCESS trial, for which biomarkers at admission and at 6 hour were available. TIMP2 and IGFBP-7 were measured and their product (Nephrocheck test) was combined with clinical parameters for AKI (sCr and UO). The primary endpoint is the development of severe AKI (KDIGO stage 3), renal replacement therapy (RRT) and death in the first 7 days of enrollment. We analyzed the frequency of the outcomes and the odds ratios (ORs) for each combination, compared to the reference combination (normal sCr, UO and [TIMP2]*[IGFBP-7] ≤0.3 ng/ml²/1000).

Results: We analyzed 732 patients with hour 0 data and 785 patients with available parameters at hour 6 (Figure 1). The percentage of patients with all the three parameters negative at hour 0 who achieved the endpoint was low (5.7%). Interestingly, this percentage was significantly higher in patients with no AKI by sCr and UO but [TIMP2]*[IGFBP-7] positive (16.2% vs 5.7%, p=0.02) and the odds of developing the endpoint was three times higher compared to the reference group (OR 3.03, 95%CI 1.27-7.22). Similarly, the percentage of patients with sCr negative, UO negative, and [TIMP2]*[IGFBP-7] negative at hour 6 who reached the endpoint was low (7%). However when only [TIMP2]*[IGFBP-7] negative at hour 6 who reached the endpoint was positive, this percentage was significantly higher (17.8% vs 7%, p<0.001) and the odds for the endpoint was similar to that for hour 0 data (OR 2.85, 95%CI 1.33-6.1).

Conclusions: Early assessment of [TIMP2]*[IGFBP-7] in the first 6 hours of admission in ICUs may significantly improve the ability to predict hard outcomes in apparently “asymptomatic” septic patients (normal sCr and UO).
Figure 1. Study population
Serial evaluation of qSOFA among patients with suspected infection

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INTRODUCTION/HYPOTHESIS
Sepsis-3 suggests the qSOFA score may be a prompt to consider sepsis among patients with suspected infection. We sought to determine the predictive validity of serial qSOFA measurements over time to identify patients at high risk for sepsis.

METHODS
We used electronic health records (EHR) criteria to identify all adults with suspected infection at nine hospitals in southwestern Pennsylvania in 2012. For each encounter, we determined the greatest qSOFA score during 6-hour epochs from the onset of suspected infection to 48 hours later. We used a multivariable logistic regression model accounting for age, gender, race, and comorbidity to predict the baseline risk of death during hospitalization, then determined the predictive validity of i) initial qSOFA (highest value during the first epoch), ii) the mean qSOFA over 48 hours, and iii.) maximum qSOFA at 24 and 48 hours. When studying each parameter's predictive validity for sepsis beyond the baseline model (i.e., discrimination using area under the receiver operating characteristic [AUROC] curve), we used in-hospital mortality as the primary outcome, as this is more common among encounters with sepsis than those without.

RESULTS
The final cohort included 37,591 encounters with suspected infection of whom 1,769 (4.7\%) died during hospitalization. Compared to encounters that survived, deaths had greater initial qSOFA scores (median 1 [IQR, 1-2] vs 0 [IQR, 0-1], \( p<0.01 \)). The initial qSOFA improved predictive validity compared to the baseline model (AUROC=0.79 [95\% CI, 0.78-0.80] vs 0.63 [95\% CI, 0.62-0.65], \( p<0.01 \)). Models with maximum qSOFA at 24 hours (AUROC=0.81 [95\% CI, 0.80-0.82]), maximum at 48 hours (AUROC=0.83 [95\% CI, 0.82-0.84]), and mean over 48 hours (AUROC=0.86 [95\% CI, 0.85-0.86]) further improved predictive validity (\( p<0.01 \)). These findings were consistent in analyses restricted to complete cases (N=14,075; 37\%) and non-ICU encounters (N=32,865; 87\%).

CONCLUSIONS
Among encounters with suspected infection, serial qSOFA measurements improved predictive validity for sepsis compared to initial qSOFA alone.
Identifying High-Risk Suspected Infection Patients Using Serial qSOFA Measurements and Group-Based Trajectory Modeling

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RATIONALE
Among patients with suspected infection, a single assessment of blood pressure, respiratory rate and mental status, known as qSOFA, may have good predictive validity as a clinical prompt for sepsis. We sought to identify the predictive validity of distinct qSOFA trajectories over the 48 hours after infection to distinguish patients at high risk for sepsis.

METHODS
We used electronic health record (EHR) data to identify all adults with suspected infection at nine hospitals in southwestern Pennsylvania in 2012. For each encounter, we determined the maximum qSOFA score during 6-hour epochs from the onset of suspected infection to 48 hours later. We used latent group-based trajectory modeling with zero-inflated Poisson distribution to identify distinct qSOFA trajectories and selected the best-performing model using the Bayesian information criterion. We determined the predictive validity of the initial qSOFA (highest value during the first epoch) versus qSOFA trajectory groups over 48 hours. When studying each parameter’s predictive validity for sepsis beyond the baseline model (i.e., discrimination using area under the receiver operating characteristic [AUROC] curve), we used in-hospital mortality as the primary outcome, as this is more common among encounters with sepsis than those without.

RESULTS
The final cohort included 37,591 encounters with suspected infection of whom 1,769 (4.7%) died during hospitalization. After multiple imputations for missing data, the best-performing trajectory model consisted of five qSOFA groups (Figure 1): i.) low (N=68,675; 36.5%), ii.) increasing (N=8,734; 4.7%), iii.) decreasing (N=55,106; 29.3%), iv.) moderate (N=40,119; 21.4%), and v.) high (N=15,321; 8.2%). The odds ratios for in-hospital mortality were greatest comparing moderate, high, and increasing qSOFA trajectories versus low or decreasing trajectories (Figure 1). The trajectory model improved predictive validity compared to the baseline model (AUROC=0.85 [95% CI, 0.85-0.85] vs 0.63 [95% CI, 0.63-0.63], p<0.01), and was greater than that of the model incorporating initial qSOFA alone (AUROC=0.79 [95% CI, 0.79-0.79], p<0.01).

CONCLUSIONS
Using group-based modeling, the qSOFA trajectory after suspected infection may improve predictive validity for patients likely to be septic compared to initial qSOFA alone.
Effect of targeted anti-inflammatory therapy on mortality of patients with sepsis-induced Macrophage Activation Syndrome

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1. Fellow, Dept. of Critical Care, University of Pittsburgh

Abstract Type: QI initiative

Statement of Need:

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, that has been recently shown to manifest in the form of distinct phenotypes. Sepsis induced Macrophage Activation Syndrome (sepsis/MAS) is of particular interest because mortality has been reported to be 3 times that of the general septic population. In our institution, patients with sepsis/MAS (from PROCESS dataset) compared to age matched septic controls had 90 day mortality of 61% vs 28% respectively, confirming reported data. Importantly, MAS is potentially susceptible to targeted anti-inflammatory therapies. In a post-hoc analysis of the Interleukin-1 Receptor Blockade in Sepsis trial, patients receiving IL-1β receptor antagonist (Anakinra) had a 30% decrease in mortality compared to placebo. In the absence of better data and an unacceptable high mortality, we designed a QI initiative to evaluate the impact of protocolized, targeted anti-inflammatory therapy on the mortality rate of patients with sepsis/MAS.

Methods:

We have created a Sepsis/MAS working group within the department of Critical Care Medicine that includes residents, PhD students, fellows, and faculty. Lead by Dr. John Kellum, Joseph Carcillo, Holt Murray and Hernando Gomez, we are developing several projects which includes this QI initiative assessing the effect of Anakinra and high dose steroids on sepsis/MAS mortality.

Results:

Adult patients with sepsis admitted to the ICU will be screened for inclusion and exclusion criteria, which are summarized in Table 1. Patients that fulfill Sepsis/MAS criteria will be treated as follows: Anakinra (5mg/kg/day divided in 4 doses, maximum 400 mg/day) plus methylprednisolone (500 mg IV daily x 3 days). If there is renal involvement and thrombocytopenia, the patients will also undergo plasmapheresis for 5 consecutive sessions. Our primary end point will be in-hospital mortality. Secondary outcomes will be 30 day mortality, and organ dysfunction.

Conclusion:

Sepsis-induced MAS occurs in about 6.4% of septic patients, and thus we expect to enroll 10-20 patients in the course of 2-3 years in our ICUs.
Inclusion Criteria

Serum ferritin > 2,000 ng/ml and 3 out of the following:

1. Bicytopenia with two of the following:
   a. Absolute Neutrophil Count < 1,000,
   b. Platelets < 100,000/mm³,
   c. Hemoglobin < 9 mg/dl

2. Fasting triglyceride > 265 mg/dL

3. Splenomegaly

4. ALT OR AST > 120 IU/L (or > 2x upper limit of normal)

5. Fever with temp ≥ 101° F

6. Fibrinogen < 1.5 g/L (150 mg/dl) or INR > 1.5 or d-dimer > 500 ng/ml

Exclusion Criteria

- Evidence of malignancy
- Known diagnosis of rheumatological disease including but not limited to rheumatoid arthritis, SLE, SJIA etc.
- Known EBV viremia by PCR at time of screening (positive serologies are not an exclusion; results of EBV testing will not be necessary for enrollment, but may be ordered as part of the standard of care assessment to guide future management as results become available)
- Previous treatment for the current MAS episode with corticosteroids, anakinra, tocilizumab, anti-TNF therapy or cyclosporine
- Family history of familial HLH
- History of Hemochromatosis

| Table 1 |
Figure 1. Mean qSOFA score for each trajectory group among 37,591 encounters in the 48 hours after suspected infection. qSOFA trajectory groups are: low (black), moderate (pink), high (red), decreasing (grey), and increasing (blue). Inset are odds ratios for in-hospital mortality for each group category compared to referent (low qSOFA group), adjusted for baseline factors.
Title: SIRS is Prevalent in Early SAH and Associated with Worse GCS and Higher Mortality
Abstract type: Original Research

Authors: Laura Reyes¹, MD; Christopher Seymour, MD, MSc; Derek C. Angus, MD, MPH; A. Murat Kaynar, MD, MPH; Sherry H-Y. Chou, MD, MMSc.
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Fever, tachypnea, tachycardia, and leukocytosis are well-known systemic manifestations of subarachnoid hemorrhage (SAH). We hypothesize that systemic inflammatory response syndrome (SIRS) is common in SAH and represent higher disease severity and worse outcome.

Using ICD code 430, we retrospectively identified all SAH patients admitted to a 12-hospital medical system from 2010-2012 through electronic medical record and collected clinical data. We examined each component of SIRS criteria in first 96 hrs, suspected infection defined as the combination of antibiotics initiation and body fluid cultures obtained within a pre-specified time frame. Logistic regression modeling is used to examine the relationship between initial Glasgow Coma Scale (GCS) and SIRS, and SIRS and in-hospital mortality.

The study cohort had 720 subjects with a mean age of 61 years and 60% female. In-hospital mortality was 17.08%. Within 96 hrs of admission, 68% of the entire SAH cohort met SIRS criteria. However, only 38.9% of the cohort met criteria for suspected infection. Within the first 96 hrs, up to 24% patients had temperature >38 or <36°C, 45% had heart rate>90/min, 53% had respiratory rate>20/min, and 45 % had WBC >12K/uL or <4K/uL. Presence of SIRS is associated with worse GCS on presentation (OR=0.84. p=0.02) and younger age (OR =-0.012 p=0.000). Older age, GCS on presentation, and number of SIRS criteria met within first 96 hrs (OR =1.43, p=0.05) are all independently associated with increased in-hospital mortality.

SIRS is highly prevalent within the first 96 hrs of SAH. Higher SAH severity
represented by lower GCS on initial presentation is associated with higher odds for developing SIRS within the first 96 hrs. Younger age is also associated with higher odds for early SIRS in SAH, criteria, possibly due to a more robust inflammatory response. SIRS within 96 hrs is an independent risk factor in-hospital SAH mortality. Further studies are necessary to determine the pathophysiology of SIRS in SAH and its role in SAH mortality.
Fever, tachypnea, tachycardia, and leukocytosis are common systemic symptoms of primary intracerebral hemorrhage (ICH) and may be secondary to primary central nervous system injury or extra-cerebral etiologies. We hypothesize that SIRS physiology is prevalent in ICH and may be associated with worse outcome.

Using ICD code 431, we retrospectively identified all ICH patients admitted to a 12-hospital medical system (University of Pittsburgh Medical Center) from 2010-2012 through electronic medical record and collected clinical data. We examined each component of SIRS criteria in first 96 hrs, incidence of suspected infection defined as the combination of antibiotics initiation and body fluid cultures obtained within a pre-specified time frame, in-hospital mortality, and hospital length of stay. Logistic regression modeling is used to examine the relationship between initial Glasgow Coma Scale (GCS) and SIRS, and SIRS and in-hospital mortality.

Study cohort consisted of 2,650 subjects with mean age 67.9 years and 50% were female. In-hospital mortality was 20.2%. Within 96 hrs of admission, up to 25% patients had temp >38 or <36°C, up to 40% had heart rate >90/min, 46% had respiratory rate >20/min, and 41 % had WBC >12K/uL or <4K/uL. Within 96 hrs of admission, 71.25% of total cohort met SIRS criteria, but only 32.1% of the total cohort met criteria for suspected infection throughout their entire hospital stay. After adjusting for age and GCS on presentation, meeting SIRS criteria within 96 hrs of admission is independently associated with increased odds for in-hospital death (OR =1.28, p=0.009) as well as increased hospital length of stay. Number of positive SIRS criteria present is negatively associated with age (OR = -0.006,
SIRS is highly prevalent within the ICH patient population and is associated with increased in-hospital mortality with longer hospital length of stay. Younger patients are more likely to manifest SIRS, presumably due to a more robust inflammatory response. Further studies are necessary no determine the etiology of SIRS and its association to mortality in ICH patients.
Title
The Triple Variable Index (TVI), a novel methodology linking real-time patient physiology to postoperative outcome

Authors
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Abstract-Original research
Health care systems generate a tremendous volume of data for the patient populations they treat. As data volume grows, novel approaches are required to better understand the underlying complexity related to patient outcomes. Here, we introduce a profiling system called the Triple Variable Index (TVI) that objectively captures physiologic status in real-time using intraoperative monitoring data (Figure 1). TVI patterns are driven by the intrinsic properties of the input data and do not require threshold cutoffs used by other data methods. Surgical patients, independent of preoperative status or type of surgery performed, exhibit one of three TVI patterns, each representing a distinct physiologic state characterized by a host of patient and procedure-specific factors. Patterns reflect essential components of human physiology including organ system regulation and homeostasis, patient specificity, risk of developing disease, and death following surgery. Overall, TVI profiling represents a novel platform of analysis to better understand the translation of patient risk into postoperative outcome.

Figure 1: 2000 sampled TVI profiles following K-means cluster analysis where k clusters=5. White in the heatmap represents periods of monitoring where TVI could not be calculated because 1) monitoring was not taking place or 2) MAP, MAC, BIS values were not concurrently measured.
Title: Identification of sepsis phenotypes using clustering methods

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Abstract type: original research

Abstract

Objectives: Sepsis is a high risk and life-threatening syndrome caused by the body’s overwhelming inflammatory response to infection. Traditionally, sepsis has been considered as one syndrome with clinical presentations varying only by severity. However, recent data has challenged this paradigm, and has suggested that sepsis probably encompasses multiple phenotypes. In this study, we focused on exploring diverse patterns of sepsis in a cohort of critically ill patients, in order to better understand different response and further design targeted treatment on specific phenotypes.

Methods: We used the HiDenIC-8 dataset, which includes all patients admitted to the intensive care unit (ICU) in Presbyterian hospital from 2000-2008 (n=46655). From this dataset, we selected a cohort of patients with “suspected sepsis” defined as those patients that had prescriptions of antibiotics and orders for blood cultures (n=3267). We based our clustering models on ICU admission demographic, clinical, and laboratory data. Several clustering methods were applied including consensus k-means clustering, consensus hierarchical clustering, and tight clustering. To assess the clinical relevance of the resulting clusters, we analyzed the association of each cluster with outcomes including organ dysfunction at 72 hours, ICU and hospital mortalities.
Results: Comparing different clustering methods, we found the number of clusters and the patterns describing these clusters are very similar. We found 7 clusters of patients which demonstrated significant differences between each other, and were associated with subsequent clinical characteristics showing the clinical value of the identified clusters (Figure 1).

Conclusions: Unsupervised clustering techniques based on frequently collected demographic, clinical, and physiologic data, can be used to interrogate the structure of a large database, and derive distinct and biologically sound clusters of patients with suspected sepsis.

Figure 1. Comparison of mortality in ICU and hospital per cluster among different methods.

Note: Method 1 referring to consensus k-means clustering; Method 2 referring to consensus hierarchical clustering; Method 3 referring to tight clustering.
HEALTH SERVICES RESEARCH

Hospital-Level Variation in Risk-Adjusted Mortality for Pediatric Sepsis

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Department of Critical Care, University of Pittsburgh, Pittsburgh, PA (Pediatric Critical Care Fellow)

Original Research

Objectives: Understanding variation in the quality of care of pediatric sepsis across hospitals may provide insight into strategies to improve outcomes. We sought to develop a risk-adjustment model to benchmark sepsis mortality across hospitals.

Methods: We performed a retrospective cohort study using 2011-2013 Pennsylvania hospital discharge data linked to the Pennsylvania vital status records. We included patients ≤19 years old with sepsis using validated ICD-9-CM diagnosis and procedure codes. We excluded hospitals admitting <10 eligible patients per year and selected a random encounter per patient to avoid interdependence of observations. We constructed a de novo risk-adjustment model using patient demographics, pediatric complex chronic conditions, organ-failures on admission, admission source and infection types, with mortality by 30-days of admission or at any time during hospitalization as the dependent variable. We then used hierarchical logistic regression to calculate annual hospital-specific risk-standardized mortality rates.

Results: We identified 9013 cases of pediatric sepsis in 153 acute care hospitals. Once excluding low volume hospitals and repeat patient visits, we analyzed 6512 patients at 25 hospitals. The overall unadjusted mortality rate was 6.4% (range across all hospitals: 1.5% to 10.4%). The median number of pediatric sepsis cases per hospital was 67 (range across all hospitals: 34-1858). The hierarchical logistic regression model for 30-day risk-adjusted mortality showed good discrimination (C-statistic = 0.80) and calibration (slope and intercept of calibration plot: 0.94 and -0.01 respectively). However, the hospital specific risk-adjusted mortality rates calculated from this model varied minimally, ranging from 6.2 to 7.0%.

Conclusions: The use of risk-adjusted 30-day mortality rates as a hospital quality measure in pediatric sepsis is not useful due to low volume of pediatric sepsis cases in majority of hospitals. Novel metrics to evaluate pediatric sepsis care quality are needed.
Hospital Perceptions of Medicare’s Sepsis Quality Reporting Initiative

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Original Research Abstract

Objectives
In October 2015 the United States Centers for Medicare & Medicaid Services began requiring that US hospitals report on their compliance with a treatment bundle for patients with sepsis—a program known as “SEP-1”. Understanding how hospitals perceived and responded to SEP-1 is a critical first step in evaluating the program’s impact on sepsis treatment and outcomes.

Methods
We conducted semi-structured telephone interviews with hospital quality officers from a stratified random sample of non-federal hospitals in the United States, sampling hospitals based on size, teaching status and ownership. The interview script addressed four domains: structure and nature of the hospitals’ sepsis quality improvement initiatives before and after the Medicare reporting program; reception of the hospital responses by clinical staff; the approach to data abstraction and reporting; and overall impressions of the program’s impact. The interviews were recorded, transcribed, and coded for content. Interviews and analysis proceeded concurrently until thematic saturation was achieved.

Results
We completed 29 interviews before achieving thematic saturation. Hospitals reported a variety of actions in response to SEP-1, including efforts to collect data, improve sepsis diagnosis and treatment, and manage clinicians’ attitudes toward SEP-1 (Table). These efforts required dedicated resources to meet the program’s requirements for treatment and documentation. Although most respondents felt that SEP-1 was likely to improve sepsis outcomes, they also described revisions that could improve its effectiveness, including providing hospitals with additional flexibility to focus on treatment processes most directly associated with improved patient outcomes and aligning the measures sepsis definitions with current clinical definitions.

Conclusions
Hospitals are responding to the SEP-1 program with varying intensity, but in ways that consistently require dedicated resources. Optimizing the effectiveness of the SEP-1 program may require revisions that provide hospitals the flexibility to focus on treatment processes with the most direct impact on patient-centered outcomes.
Table. Range of Hospital Responses to SEP-1

<table>
<thead>
<tr>
<th>Domain of Response</th>
<th>Range of Responses</th>
<th>Barriers and Challenges</th>
<th>Representative Quotations</th>
</tr>
</thead>
</table>
| Efforts to Collect Data | -use of third-party vendors  
-employing in-house abstractors | -time and money  
-coding variation  
-heavy reliance on clinical documentation | “It’s such a horrendous and time consuming abstraction process.” |
| Efforts to coordinate hospital responses | -development of multi-stakeholder committees  
-employing dedicated staff and sepsis coordinators | -requires multiple moving parts  
-human resources  
-iterative revision/refinement | “We had a little bit of stumbling issues when we first started that group, as far as assuring that we had the right people at the table. And we have representatives now from critical care, emergency room, administrative support, and our quality folks as well as bedside nurses.” |
| Efforts to Improve Sepsis Diagnosis | -electronic sepsis alerts  
-manual screening for sepsis | -resource requirements  
-alert fatigue | “We’re building [an alert] into the electronic system that we’ve had for some time (and we’re continuing this), is certain vital sign changes go directly to our MET teams that will come and look at people that may have those issues; sepsis or something similar.” |
| Efforts to Improve Sepsis Treatment | -sepsis treatment protocols  
-structured order sets | -resistance to protocolized care—  
“cookbook medicine”  
-different needs in different places | “Well some of them said it was ‘cookbook medicine.’ That they’re trying to tell us how to practice when they don’t know the patient.” |
| Efforts to Manage Clinicians’ Attitudes | -local clinician champions  
-show clinicians the data  
-infusion of new individuals/culture  
-top-down support from administration | -lack of buy-in; particularly around documentation  
-hierarchy (within clinical medicine and QI infrastructure) | “…even though I can tell them what their opportunities for improvement are, if the physician tells them the same thing, they hear it. I'm just a nurse...”  
“I'm very fortunate in the physician champion in the emergency department is very engaged. And then has engaged some of the nursing leadership there.” |
Focused Evaluation with echo in New onset Anuria and oliguria in the critically ill patient (FENA Trial)

Abhishek J Freyer, MD 1 Sachin X. Yende 2,3, MD, MS and Christopher K. Schott, MD, MS, RDMS, FACEP 2,4

1 Department of Critical Care, University of Pittsburgh and University of Pittsburgh Medical Center (UPMC)
2 VA Pittsburgh Health Care Systems
3 Associate Professor, Department of Critical Care Medicine, University of Pittsburgh and University of Pittsburgh Medical Center (UPMC)
4 Assistant Professor, Department of Critical Care Medicine and Emergency Medicine, University of Pittsburgh and University of Pittsburgh Medical Center (UPMC)

Background:
Oliguria is a common and multifactorial reflection of organ dysfunction in the acutely-ill patient. Restoring adequate urine output is dependent on accurate identification of pathology. Ultrasonography allows for rapid bedside assessment of organ function. Yet, to date, no standardized protocol has been studied to assess oliguria. Here, we describe a protocol to assess the causes of oliguria using focused ultrasonography.

Methods:
This quality improvement project uses five previously validated ultrasound windows to evaluate the cause of oliguria. The standardized sequence has been designed to allow for rapid determination of post-renal, pre-renal and intra-renal causes of oliguria. This protocol is taught to critical care faculty and fellows at a single center. The ultrasound images are already used low urine output in our surgical ICU patients, and we will obtain these windows in a medical ICU setting blinded to and compared with current patient standard of care.

Results:
Comparative statistics have been performed on the diagnosis of oliguria derived from these windows with current standard of care testing and clinical course with reporting of the time for acquisition, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for this ultrasound based sequence. To present, 17 patients have been enrolled. Average time to complete this protocol is 13 minutes. The sensitivity, specificity, PPV and NPV were 100% each, for pre-renal (cardio-renal) and post-renal (retention) etiology, with more variation seen for intra-renal (ATN) or pre-renal (intra-vascular volume depletion) causes. Patient enrollment is still ongoing.

Conclusion:
Ultrasound is an increasingly available bedside tool to quickly assess the acutely ill patient. Oliguria is a prominent issue in this population with multifactorial causes. Current windows have already been validated for low urine output. Treatment is guided by the appropriate identification of underlying pathology. A protocol for ultrasound-based assessment of oliguria may aid in the real-time diagnosis and targeted treatment.
FIGURE 1: Ultrasound Protocol Approach to the Patient with Oliguria

1. Bladder
   Scan Bladder in transverse plane
   Is there urine in the bladder? Yes → Post renal obstruction
   No → Next

2. Right Kidney
   Scan in Longitudinal and transverse planes
   Is there evidence of hydronephrosis? Yes → Obstruction
   No → Next

3. Left Kidney
   Scan in Longitudinal and transverse planes
   Is there evidence of hydronephrosis? Yes → Obstruction
   No → Next

4. Heart
   Subxiphoid or parasternal long axis
   How is the LV gross contracting?
   Decreased Contractility → Pre-renal (cardio-renal syndrome)
   Preserved contractility
   Hypocontractility

5. Inferior vena cava
   Assess gross size and respiratory variation
   Plethoric with little resp variation → Intra-renal etiology
   Plethoric with little resp variation
   Pale with little resp variation
   Small with large resp variation → Pre-renal (Obstructive shock)

No other noted findings from above

Intra-renal etiology

* Obstruction: consider stone, obstructed ureter, etc.
** Spontaneously breathing patient, gross calcification
*** Intra-renal (causes): ATN, AMI, CIN, etc.
**** Consider massive PE, Tension Pneumothorax

Back to top
Provider Perceptions of Rounding Checklists in the Intensive Care Unit: a Quality Improvement Project

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3. UPMC Health System, Pittsburgh, Pennsylvania, USA

Objectives: Rounding checklists are increasingly common in the intensive care unit (ICU).

However, effectiveness studies have shown conflicting results. We sought to understand ICU providers’ perceptions of checklists as well as barriers and facilitators to effective utilization of checklists during daily rounds.

Methods: We performed a qualitative study in 32 ICUs within 14 hospitals in the United States.

Data collection methods included direct observation of daily rounds and semi-structured interviews with ICU providers. Observations and interviews were thematically coded for a priori-determined themes and emergent content.

Results: We conducted 89 interviews and performed 114 hours of observation. Among study ICUs, 12 (37.5%) used checklists and 20 (62.5%) did not. Participants described the purpose of rounding checklists as tools to standardize care and improve communication by initiating discussion about evidence-based practice. Checklists were perceived as helpful when they were targeted to the ICU’s specific patient population and as unhelpful when they were overly
generic. Barriers to effective use included lack of time, lack of accountability, and resistance to use by one or more rounding team members. Strategies to overcome those barriers include fostering buy-in, ensuring that the checklist is relevant to the ICU and all checklist items are relevant to the team’s daily practice, and using them consistently day in and day out.

**Conclusions:** Our results provide insights about why checklists frequently fail to improve outcomes and offer a framework for effective checklist implementation through greater feedback and accountability.
**Title:** Evaluation of Enoxaparin for Venous Thromboembolism Prophylaxis for Trauma Patients

**Authors:** Danish Malik, MD, Ashleigh Hogue, PharmD, Melissa Loveranes DO, Benjamin Kautza, MD, Scott Gunn, MD, Matthew Rosengart MD

**Primary Affiliation of Authors:** Danish Malik, MD – Critical Care Medicine Fellow, Ashleigh Hogue, PharmD – 6FG Clinical Pharmacist, Melissa Loveranes, DO – Trauma/Surgical Critical Care Fellow

**Abstract Type:** QI Project

**Objectives:**
The purpose of this quality improvement project is to evaluate the efficacy and safety of anti-Xa guided dosing strategies of enoxaparin for venous thromboembolism prophylaxis (VTE) in trauma patients. Our goal is to improve upon prescribing practices of enoxaparin used for VTE prophylaxis as well as to evaluate safety and efficacy when utilizing anti-Xa levels to achieve prophylactic dosing.

**Methods:** All patients admitted to the Surgical Trauma ICU will be evaluated. Patients will be identified for inclusion when treating clinicians initiate prophylactic enoxaparin for venous thromboembolism prophylaxis. Enoxaparin will be ordered at BID dosing intervals. Anti-Xa trough levels to be drawn prior to the 4th enoxaparin administration at current dose. Anti-Xa target range is 0.1-0.2 IU/ml. Dose adjustments are made based on trough levels, and dose adjustments are made accordingly. Trough levels will be ordered via the electronic order system with monitoring and guidance from the Surgical Trauma ICU unit-based pharmacist. Nurses, APPs, and physicians will be educated on trough ordering and subsequent dose adjustment methods. Outcomes measured are demonstrated in Table 1.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age</th>
<th>Body Mass Index</th>
<th>Injury severity score</th>
<th>SCR</th>
<th>Time to 1st prophylactic dose</th>
<th>Dose Required to Achieve Target AntiXa Level (mg/kg)</th>
<th>Trough Anti Xa Level(s)</th>
<th>VTE</th>
<th>Bleeding</th>
<th>Platelets</th>
</tr>
</thead>
</table>

**Table 1.** Enoxaparin for VTE prophylaxis data grid.

**Results/Conclusions:** This project is ongoing. Results and conclusions pending completion of the project.
Rothman Index has Good Predictive Value for Mortality in a Large Academic Medical Center

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University of Pittsburgh Medical Center, Pittsburgh, PA

Introduction: The Rothman Index (RI) is a severity of illness score designed for early detection of patients who are clinically deteriorating in a hospital setting. The RI is unique in that it incorporates 26 different variables including vital signs, laboratory data and nursing assessments that are continually updated in the electronic medical record.

Study Objectives: To examine the predictive value of RI for serious adverse events for patients admitted to the floor.

Methods: We analyzed a large dataset of patients admitted to a tertiary care academic medical center from March 2014 – December 2014, excluding those who were directly admitted to the ICU. We examined predictive value of first RI obtained in the first 24 hours of hospital admission for rapid response team calls including crisis (Condition C); cardiac or pulmonary arrest (Condition A); ICU transfer; or hospital mortality, using Receiver Operating Characteristic Curve (ROC) Analysis.

Results: Of 24,060 patients admitted to the floor, 3.02% had Condition C, 0.17% Condition A, 12.28% were transferred to ICU, and 1.39% died. The RI value was lower among patients with the events compared to those without (Table 1). The First RI value had a good predictive value for hospital mortality and modest predictive value for other events. The combined predictive value of the first RI for all events were only modest (ROC, 0.7387, 95%CI, 0.7283 – 0.7491).

Conclusion: Among patients hospitalized to a large academic medical center, the first RI had a good predictive value for mortality and modest predictive value for crisis, cardiopulmonary arrest and ICU transfer.

Table 1:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Mean (SD) for patients with event</th>
<th>Mean (SD) for patients without event</th>
<th>ROC (95%CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition C</td>
<td>59.5 (19.6)</td>
<td>73.2 (16.8)</td>
<td>0.714 (0.695-0.733)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Condition A</td>
<td>56.2 (23.1)</td>
<td>72.8 (17.1)</td>
<td>0.723 (0.646-0.801)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICU transfer</td>
<td>55.9 (24.2)</td>
<td>75.1 (14.3)</td>
<td>0.736 (0.727-0.749)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>42.5 (25.0)</td>
<td>73.2 (76.5)</td>
<td>0.841 (0.817-0.865)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Title: Epidemiology of Hospitalizations with Sepsis in Children in the United States

Andrew Prout MD, MPH, Victor B. Talisa MS, Florian Mayr MD, MPH, Chung-Chou H. Chang Ph.D., Sachin Yende MD, MS

First author affiliation: Department of Critical Care Medicine, University of Pittsburgh.

Abstract type: Original research

Introduction/Hypothesis

Contemporary estimates of the national incidence of sepsis and mortality among children in the United States are not available. We hypothesized that the incidence of sepsis has increased and the hospital mortality has decreased compared to prior studies. We also explored risk factors for mortality.

Methods

We analyzed the 2013 Nationwide Readmissions Database, a multistate dataset that included 49% of all hospital admissions in the US. We analyzed patients <19 years old with a hospital admission with sepsis identified by ICD-9 CM codes. We estimated national incidence using weights included in the database and hospital mortality in the cohort and within predefined subgroups. We used a mixed effect logistic regression model to explore risk factors associated with hospital mortality for non-neonatal patients.

Results

Of the 1,227,931 pediatric admissions, 19,048 admissions, representing 16,815 unique patients, were hospitalized with sepsis. A majority (69.6%) had at least one underlying chronic disease. Estimated national incidence was 0.90 cases per 1000 per year, with an estimated 71,375 cases nationally per year. The incidence was highest in the neonatal age group and declined afterwards, with a slight increase in the adolescent age group. Hospital mortality was 4.5% overall, and was 1.1% for previously healthy patients and 6.0% for patients with any chronic disease. Most chronic diseases were associated with increased mortality, especially neurologic or neuromuscular conditions (OR 3.4), cardiovascular conditions (OR 2.8), and oncologic conditions (OR 2.0). Although patients at children’s hospitals had a higher acute and chronic burden of illness with a higher risk of mortality during their hospitalizations, no difference in overall mortality was noted between childrens’ hospitals and other hospitals.

Conclusions

Compared to prior studies, the incidence of sepsis hospitalizations in children has remained stable but hospital mortality has declined over the past ten years. Two out of three children admitted with sepsis have at least one chronic disease and these patients have increased hospital mortality.
Figure: Case fatality by age groups among previously healthy and chronically ill patients
**Title:** Using an Inductive Approach to Create a Brief Survey of Practices, Barriers, and Facilitators Related to Interdisciplinary Family Meetings

**Authors:** Jennifer B. Seaman, PhD RN; Robert Arnold MD; Kimberly J. Rak PhD MPH MA; Marci L. Nilsen, PhD RN; Amanda Argenas, MA; Anne-Marie Shields, MSN; Douglas B. White, MD MAS.

**Primary affiliation of first author:** University of Pittsburgh, School of Medicine, Department of Critical Care Medicine, CRISMA Center

**Abstract type:** original research

**Objectives:** Interdisciplinary family meetings (IDFMs) are a key component of patient and family-centered ICU care; and while recommended best practice is to hold an IDFM early in the ICU stay, adherence to this recommendation is low. To understand the factors underlying poor adherence, we inductively developed an electronic survey for ICU directors and nurse managers about barriers, facilitators and care processes related to the conduct of IDFMs.

**Methods:** This work is the second step in a two-phased approach, based in implementation science theory. In our prior study, we used in-depth semi-structured interviews with diverse ICU clinicians to elicit the full range of practices, barriers, and facilitators related to IDFMs; analysis yielded a matrix of clinician-, unit- and hospital-level barriers and facilitators, as well as future intervention ideas. We formulated questions to validate barriers and facilitators at each level and additional questions to test attitudes towards potential intervention components. We incorporated branching logic to minimize burden and maximize relevance to the respondent (Figure 1).

**Figure 1—Process of Inductive Survey Development**
Results: The survey contains a variable-length section with items pertaining to key domains about IDFMs followed by a demographic form. By way of example: one theme among unit-level barriers was the lack of a written protocol for holding IDFMs. We devised corresponding survey questions: Is there a protocol for IDFMs; if so, is an IDFM indicated based on clinical criteria (severity of illness, anticipated functional impairment, etc.); and is an IDFM required within a specific timeframe (24/48/72 hours of admission)? An emergent idea for future interventions was the use of preemptive scheduling for IDFMs, an idea we test using Likert-scaled responses (strongly agree to strongly disagree). We also include items to test participant attitudes (using similar responses) towards IDFMs—for example: “Family meetings should be held only after it’s clear that a decision needs to be made about goals of care”.

Conclusions: This inductive methodology facilitated the development of a brief survey targeting the full range barriers and facilitators expressed by clinicians.
Rectal Trumpet Associated Hemorrhage in the ICU: Report of a Quality Improvement Initiative

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First author is a critical care fellow

Abstract:

Objective: The rectal trumpet is a nasopharyngeal airway connected to a drainage system inserted into the rectum of a patient to manage fecal incontinence. No published data exists on adverse events caused by the use of a rectal trumpet. The object of this study was to determine the incident rate of rectal trumpet associated hemorrhage per rectal trumpet treated patient in our specialty transplant intensive care unit (TICU).

Design: Retrospective chart review of a single specialty ICU.
Setting: TICU at an academic medical center.

Patients: All patients admitted to the TICU between January 1, 2014 and May 31, 2016

Interventions: None

Measurements and Main Results: 3933 patients were admitted to the TICU during the study period. Of these, we estimate that approximately 400 were treated with a rectal trumpet. We found 3 possible and 9 probable cases of rectal trumpet associated hemorrhage for a total of 12 cases—an incident rate of 3% per rectal trumpet treated patient. All of these patients underwent invasive procedures for hemostasis. They received a mean of 4.9 units of packed red blood cells and 9 of them experienced hypotension. 8 out of the 9 probable rectal trumpet associated hemorrhage patients experienced hemorrhage only after greater than 7 days of treatment with a rectal trumpet. Following this initiative, RT use was banned in our TICU. Comparing the three months preceding to the three months following the initiation of the RT ban, there were no significant differences in the incidence of sacral decubitus pressure ulcers diagnosed in the TICU.

Conclusions: The use of rectal trumpets can cause hemorrhage with clinically significant consequences. Following this initiative, their use was banned in our TICU.
Extubation Outcomes of Critically Ill Patients with Known Difficult Airways

A Quality Improvement Project

Christopher Johnson*, M.D., Rachel Hadler, M.D., Hernando Gomez Danies, M.D., Joseph Darby, M.D., A. Murat Kaynar, M.D. and Dennis Phillips, D.O.

*Anesthesiology Critical Care Fellow, University of Pittsburgh Medical Center

Objectives

Although there is ample literature on the management of patients at risk for difficult intubation, the course of patients with known difficult airways following extubation is largely unknown. Identifying patients with difficult airways who are likely to fail extubation would allow the presence of skilled airway managers at the time of extubation. The objectives of this quality improvement project were to determine the frequency of failed extubation in patients with known difficult airways and to identify predictors of failed extubation.

Methods

The electronic record was queried to identify adult patients who had difficult intubation added to their problem lists during an encounter at Presbyterian (PUH) between January 1, 2009 and June 30, 2016. A retrospective chart review was conducted to abstract data including age, body mass index, difficult airway team involvement, duration of intubation, location of extubation trial, in-hospital mortality and whether re-intubation or surgical airway was required.

Results

The search yielded 43 patients, of which six required re-intubation and one required a cricothyrotomy. Although none of the patients who failed extubation died during attempts to re-secure the airway, two died during their hospitalization compared to none who were successfully extubated. Duration of intubation was at least one day for five of the seven patients who failed. Only 17 of the 36 patients successfully extubated were intubated for more than one day. All failed extubations for which the time of extubation was documented occurred after noon. All but one failure occurred at least one day after extubation.

Conclusions

Over 15% of patients with known difficult airways at PUH fail extubation. Patients intubated for more than one day are at greater risk. All patients with known difficult airways should be extubated in the morning. As most patients with known difficult airways who fail extubation require re-intubation more than one day later, alerting the difficult airway team at the time of extubation is unlikely to change outcome. The delay before failure does, however, suggest the importance of documenting an extubation plan for future providers.
Title: Adherence to Low Tidal Volume Ventilation in Pregnancy

Authors: Yasaswi Paruchuri, MD; Alisse Hauspurg, MD; Chenell Donadee, MD; Raghavan Murugan, MD, MS, FRCP

Affiliations of First Author: UPMC Magee Women's Hospital

Level of Training: PGY2 Resident in Obstetrics and Gynecology

Abstract Type: QI project

Objectives:
Management of Acute Respiratory Distress Syndrome (ARDS) changed in 2000, after a landmark study showed that low-tidal volume ventilation decreased mortality. ARDS occurs more frequently in pregnancy and in studies of the 2009 influenza epidemic, 18.8% of hospitalized pregnant patients required mechanical ventilation. Pregnant women are clearly at increased risk of respiratory morbidity but changes in respiratory physiology during pregnancy and concern about fetal-acid base status and oxygenation may interfere with low tidal volume strategy. Case reports and consensus statements support low tidal volume ventilation in pregnancy, however pregnant women are often excluded from larger trials. This study sought to assess the feasibility of low tidal volume ventilation in pregnant patients.

Methods:
This is a retrospective cohort study of pregnant women, mechanically ventilated for > 24 hours between Jan. 2012 and Feb. 2017 at Magee Women's Hospital. Women were identified through a ventilated patient database, collected as part of a quality improvement project. Data collected included age, average tidal volume per day of ventilation, gestational age and primary diagnosis. Low tidal volume ventilation was defined as tidal volume ≤ 8 mL/kg of ideal body weight.

Results:
We included 3552 data points from 681 non-pregnant patients and 136 data points from 33 pregnant patients in pregnancy. The average daily tidal volume for the non-pregnant cohort was 7.27 ml/kg (SD 1.55) and 7.66 ml/kg (SD 1.22) in the pregnant cohort.

Overall, compliance with low tidal volume in pregnancy was high, ranging from 63% (2015) to 100% (in 2013) with one outlying 35% (2016). This is similar to the non-pregnant cohort compliance, which ranged from 57% (2014) to 79% (2016). When stratified by gestational age, 73% of patients in the third trimester achieved low tidal volume compared to 93% in first trimester and 45% in the second trimester.
Conclusions:
Low tidal volume was achieved in pregnant patients across gestational ages, and should be promoted despite perceived barriers in pregnancy physiology. Additional studies are needed to evaluate maternal and fetal outcomes with low tidal volume ventilation.

References:


Critical Care Fellows as Team Leaders of Rapid Response Teams: A Safety Evaluation in a Mature Rapid Response System

Debjit Saha, Ryan Lapointe, Joseph Darby, Raghavan Murugan, Ali Al-Khafaji, Richard Simmons, Lillian Emlet

Abstract Category - Quality Innovations

Objectives:
Rapid response teams (RRT) vary in structure between institutions, with differences in the number of team responders and differences on whether an intensivist, nurse, hospitalist, or advanced practice providers serve as team leader. The RRT at the University of Pittsburgh Medical Center (UPMC) was modified from an attending intensivist-led to a Critical Care fellow-led team to manage all responses to crisis (Condition C). Condition A (cardiopulmonary arrest) responses remained unchanged with both the fellow and attending intensivist responding. The objective of this study was to evaluate if there was an impact with this change in team leader by examining the frequency of repeated RRT events on the same patient after implementation of the modified system.

Methods:
All Condition C calls between July to September of 2015 (attending intensivist-led RRT) were compared with that of July to September of 2016 (critical care fellow-led RRT). We examined the total number of repeat calls for Condition C/A activation for the same patient within 6, 12, and 24 hours. Categorical variables were expressed as percentages and compared with χ² of Fisher exact test as appropriate. Analysis was done using Stata® v13 (StataCorp LP, College Station, TX)

Results:
Our total number of RRT events for the three months period in 2015 was 192 and 161 in 2016. Table 1 shows the frequency of Repeat RRT Events (RREs), along with a breakdown of the number of RRE at 6, 12, and 24 hours. The total number of repeat events for 2015 was 65, with 30 that were called less than 24 hours, of which 12 were less than 6 hours, 13 were between 6 to 12 hours, and 5 were between 12 to 24 hours. For 2016 there were a total of 65 repeat RREs, with 19 that were called less than 24 hours, of which 10 were less than 6 hours, 7 were between 6 to 12 hours, and 2 were between 12 to 24 hours. There was no statistical difference in the number of RREs in any of our subgroups.

Discussion:
In a large academic medical center with an established rapid response system, implementation of a fellow-led RRT was not associated with an increased frequency of repeated RRT events. For a majority of Condition C, the fellow trainee as team leader does not result in an increase of repeat RRT activations for patients who are triaged to remain at same location on floor.
Table 1:

<table>
<thead>
<tr>
<th>Variable</th>
<th>2015</th>
<th>2016</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Repeat RREs (N)</strong></td>
<td>65</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Total RRE within 24 hrs</td>
<td>30 (46.2)</td>
<td>19 (29.2)</td>
<td>0.047</td>
</tr>
<tr>
<td>Less Than 6hrs</td>
<td>12 (18.5)</td>
<td>10 (15.4)</td>
<td>0.64</td>
</tr>
<tr>
<td>Less Than 12hrs, but Greater Than 6hrs</td>
<td>13 (20.0)</td>
<td>7 (10.8)</td>
<td>0.145</td>
</tr>
<tr>
<td>Repeated RREs Less than 24hrs, Greater than 12 hrs</td>
<td>2 (3.08)</td>
<td>5 (7.69)</td>
<td>0.44</td>
</tr>
<tr>
<td>Repeated RREs Greater Than 24hrs</td>
<td>35 (53.8)</td>
<td>46 (70.8)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Numbers expressed as n (%)  
† p-values represent chi-squared tests or Fisher exact tests where appropriate  
* values significant at 5%
“When ECMO Fails: A Critical Care Simulation for First Year Fellows “

Author: Krystle Shafer MD, Christopher Brackney MD, Lilian Emlet MD, MS, FACEP

Primary affiliation of the first author: UPMC
Level of Training of first author: Fellow
Abstract Type: educational initiative

Objective: University of Pittsburgh Medical Center has a well-established, high volume, and reputable ECMO program and requires all critical care medicine fellows of all specialties to rotate within this unit. Currently, preparation includes an introductory manual to read prior to the rotation and also a three-hour lecture series, but despite this education fellows still struggle with the recognition, identification, and treatment of common ECMO complications. This simulation series intends to reinforce this knowledge.

Methods: Three first-year critical care fellows will be placed together as a simulation team and will manage three separate simulation scenarios. In each simulation the fellows will rotate their team leader, allowing each fellow a chance to lead the team. Each individual scenario will span over a forty-minute period, with 15 minutes utilized for the simulation and 25 minutes utilized for the debriefing session, which will be performed immediately at the conclusion of the scenario. The simulation will use an actual ECMO circuit, which will be set-up in a closed loop circuit thus allowing for a high fidelity environment. The simulation topics include the following scenarios: bleeding from cannulation site resulting in hypovolemia and leg hematoma requiring surgical evacuation, pericardial tamponade, and hypoxemia due to both a pneumothorax and cannula recirculation. Major critical actions focus on identifying and diagnosing the above complications, developing an appropriate differential diagnosis, and implementing the appropriate treatment plan. Participants will be provided with a quiz prior to and at the conclusion of the simulation, which test their ECMO knowledge in board review fashion and also will be provided with a feedback survey to be completed at the conclusion of the course.

Results: This simulation is schedule to be performed in April-May, 2017.

Conclusion: We expect that adding simulation to an established program of reading and lecture will improve the ability of early critical care fellows to recognize, identify, and treat ECMO complications.
Title:
Pilot evaluation of telemedicine brain death examination.

Authors:
Muhammad Tahseen MD, Daniel Glass MD, Joseph M. Darby MD, Lori Shutter and Neuro Critical Care group.

Primary affiliation of first author:
Department of Critical Care Medicine, University of Pittsburgh School of Medicine

Level of training of first authors:
Fellow

Abstract type:
QI project
**Introduction:**
Clinicians with the knowledge and skills necessary to perform the brain death examination necessary to declare death by neurological criteria are easily available in large academic medical centers, they may not be physically available in smaller hospitals. Telemedicine technologies now allow the physical examination, including a detailed neurological examination, to be performed reliably. These systems might allow experts to complete a remote brain death examinations when local experts are unavailable.

**Objectives:**
We sought to determine whether telemedicine technology could be employed to determine death by neurological criteria remotely.

**Methods:**
We enrolled a convenience sample of patients with catastrophic brain injury at UPMC Presbyterian Hospital and performed a standard brain death examinations and apnea testing. A remote attending neurocritical care physician familiar with brain death testing used a mobile telemedicine cart equipped with an HD camera and Polycom Vidya software to direct a bedside examiner. Evidence based guidelines for the determination of brain death in adults was used including motor response, brainstem reflexes, pupil size with reactivity and apnea test.

**Results:**
In the pilot phase of this observational study eight patients were enrolled. Remote brain death testing was successfully completed in all cases. Both the bedside and remote examiners recorded same findings when observing baseline physiological data, heart rate response to atropine, motor activity, spinal reflexes, brainstem reflexes and respiratory efforts during apnea test. Remote examiner recorded different measurement of pupillary size and reactivity to light in only two cases but was able to confirm the non-reactivity and accurate size with the help of Neuroptics pupillometer. Both the local and remote examiners independently concluded that the exam findings were consistent with brain death in each case.

**Conclusion:**
Our results confirm the feasibility of remote brain death examination facilitated by telemedicine technology. Future work will enroll additional patients to allow formal hypothesis testing, and enroll patients with severe coma but no brain death to confirm sufficient sensitivity of the remote exam to detect subtle signs of life.

**REFERENCES**
The Critical Need in the Critical Care Fellowship Quality Improvement

Authors: Pavan Thangudu MD, Scott Gunn MD
Primary Author Affiliation: UPMC Critical Care Fellow
Abstract Category: Educational Initiative

Statement of Need: The American College of Graduate Medical Education (ACGME) mandates that all trainees participate in quality improvement (QI) projects prior to graduation. Historically, most fellows attempt single-ICU projects with a limited scope of impact and little support from the health system. This meta QI project (quality improvement aimed at improving quality improvement) attempted to couple the adult critical care medicine (CCM) fellows to ongoing, system-wide QI projects to further enrich the QI experience of the CCM fellows and create a sustainable pathway for annual participation in system-wide QI projects that have meaningful outcomes for health system and the backing of the System ICU Performance and Operations Committee as well as the Wolff Center for Patient Safety and Quality Improvement.

Methods: We queried the System ICU Performance and Operations Committee to develop a list of ongoing QI projects. We then sent questionnaire to each of the QI project leaders asking the following questions:
1. Project Name
2. Team Members
3. Project Description
4. Approximate number of hours of work expected per week

We summarized this data and shared it with the CCM fellows. The estimated number of hours per week provided by the project leaders determined how many fellows could join each project. Conclusion: The CCM fellow QI experience has unrealized educational opportunity. This initiative resulted in the review of over 50 system-wide and individual ICU QI projects. All 19 CCM fellows were successfully paired to an active QI project. This initiative was a first step in establishing a pathway for sustained fellowship participation, contribution, and training through ongoing QI initiatives. There remains work to be done to explore the optimal educational experience for adult CCM fellows based upon feedback from fellows, their mentors, and QI project leaders. The next phase of our project will be determining whether this initiative should be continued and if so, how it might be improved.
Research for the non-research oriented Fellow; the MCCTP-MACRO experience

Pavan Thangudu MD, Raj Padmanabhan MD, David T. Huang MD, MPH

Primary Author Affiliation: UPMC Critical Care Medicine Fellow
Category: Educational Initiative

Statement of Need: The Multidisciplinary Critical Care Training Program (MCCTP) currently offers 3 tracks of development: The T32 Research, Clinical Leadership and Education tracks. UPMC Critical Care Medicine is an international leader in clinical research. For fellows interested in clinical research but not in a career of grant writing and papers, there were no avenues for involvement. This initiative had 2 aims 1) To equip fellows with skills to become site principal investigators (PI) and 2) to expose Fellows to the processes and intricacies of patient enrollment into clinical trials. Methods: We (PT, RP) first met with the MACRO director (DTH) to discuss our goals. We completed CITI training and chose to become site co-investigators on the ROSE trial (Reevaluation Of Systemic Early neuromuscular blockade). We reviewed the protocol, methodology paper and MACRO informed consent manual. We then participated in screening patients and observed research informed consent discussions with families. We then lead these discussions ourselves with supervision, and received feedback on our performance. We learned nuances of ROSE protocol implementation at the bedside: titration of sedation and ventilator settings, hemodynamic effects, and communication with the clinical team. We also evaluated research protocols for implementation feasibility by reviewing protocols submitted to MACRO. All research activities were conducted with respect to Fellows’ schedules. Results: We (PT, RP) enrolled 6 patients independently within 5 months of this initiative and participated in daily patient screenings. An unexpected benefit was deeper understanding of the decades-old debate on how the conceptual model of ARDS informs both clinical care and research. Conclusions: There is opportunity within the MCCTP to enrich the Fellow experience and increase research exposure of non-research oriented fellows. Such investment would empower Fellows to become involved in research in their future careers and serve as site PIs. Our recommendation is this initiative be implemented and expanded in ensuing years for interested fellows.

Title 125 character max
Abstract 2200 max
Quality Improvement: Assessment of Neuromuscular Blockade Use in Adults with Acute Respiratory Distress Syndrome

Authors: Pavan Thangudu MD, Chenell Donadee MD, Lara Groetzinger PharmD BCCCP, Ryan Rivosecchi PharmD BCCCP, Janine Then PharmD BCCCP, Pamela Smithburger PharmD BCCCP, Scott Gunn MD

Statement of Need: Across UPMC intensive care units (ICUs) there is a wide variation in practice when using neuromuscular blockade (NMB) for patients with severe acute respiratory distress syndrome (ARDS). Our quality improvement project aimed to: 1) assess current NMB practice in ICUs at Presbyterian and Montefiore University Hospitals, Mercy and Magee-Womens Hospital and 2) develop a model for potential standard practice. Methods: We convened a multidisciplinary group of intensivists and critical care pharmacists for this project. First, we conducted a retrospective review of NMB use in patients with severe ARDS in 12 ICUs at 4 hospitals. Next, we reviewed the literature on NMB in ARDS and surveyed ICU directors, intensivists, and critical care pharmacists on potential protocols. We then iteratively developed 2 protocols and presented them to the ICU directors. Using their input, we arrived at a single protocol. Finally, we projected cost data for the protocol based on patients receiving NMB from 2016. Results: Our retrospective review confirmed our initial suspicion of a wide variation in practice patterns (Table 1). Median length of NMB was 2 days with a range of 1.3-3.9 days. We found disagreement amongst intensivists and pharmacists regarding best practices for sedation and NMB. The greatest consensus was with the ACURASYS trial’s fixed-dose regimen. The total cost for cisatracurium in fiscal year 2016 at UPMC Presbyterian University Hospital was approximately $285,000 (Figure 1). Adoption of this protocol would result in a total cost of approximately $1.4 million over the course of 1 year (Figure 1). Conclusions: The protocol underwent 2 iterations of the PDSA cycles for refinement. The financial cost of protocol implementation coupled with a lack of large, multi-center randomized control trials demonstrating a conclusive mortality benefit to cisatracurium infusion lead us to two conclusions. First, there is insufficient evidence to adopt a protocol. Second, we should participate in generating that evidence, hence our participation in the ARDSNet trial, Reevaluation Of Systemic Early Neuromuscular Blockade (NCT02509078).

<table>
<thead>
<tr>
<th>ICU</th>
<th>Trauma</th>
<th>MICU</th>
<th>TICU</th>
<th>NICU</th>
<th>CTICU/SICU</th>
<th>CCU</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Patients</td>
<td>34</td>
<td>25</td>
<td>22</td>
<td>13</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Duration in days, median (IQR)</td>
<td>2 (1.3-3.9)</td>
<td>2.1 (1.4-3.6)</td>
<td>2.1 (1.4-2.6)</td>
<td>2.5 (1.4-3.1)</td>
<td>2.7 (1.4-2.8)</td>
<td>2.1 (1.3-3)</td>
</tr>
</tbody>
</table>

Figure 1
Stop NMB

Once there is ventilator dyssynchrony or patient movement, then assess Riker

Riker 1?

Yes

Sedation Adequate

No

Titrato to Riker 3

Titrato Sedation to Riker 1

Bolus 15mg of Cisatracurium

Continuous Infusion of Cisatracurium (be dosing addendum for 48h)

At next 8000 or 24h, Perform NMB & Sedation Interruption Assessment

PEEP ≥10 and FiO2 ≥60%

Discontinue NMB & titrate to Riker 4

---

**Cost of NMB for FY16**

~285,000

**Projected Cost of Nimbex @ 37.5mg/hr for 48h**

$1,349,264

**Cost of Cis @ 2mcg/kg/min for 48h**

$337,316

FY16 based off of 98 patients at Presby
Cytokine response in adult severe sepsis patients with features of macrophage activation syndrome

Renee Anderko1; Vanessa Jackson; Octavia Peck Palmer, PhD; Derek Angus, MD, MPH; Hernando Gomez, MD, MPH; John Kellum, MD; Joseph Carcillo, MD

1Staff Researcher/MS Student, Department of Critical Care Medicine, University of Pittsburgh

Abstract Type: Original Research

Objectives Shakoory et al. performed a post hoc analysis of a randomized clinical trial of anakinra, an IL-1 receptor antagonist1, and reported that severe sepsis patients with features of macrophage activation syndrome (MAS), defined by concurrent hepatobiliary dysfunction and disseminated intravascular coagulation, represented 5.6% of the severe sepsis population. Anakinra, in comparison with placebo, reduced 28-day mortality (34.6% vs 64.7%; \( p < 0.05 \)) in a subset of patients with features of MAS1. Thus, we hypothesized that the Protocolized Care for Early Septic Shock (ProCESS) trial2 would contain a similar proportion of septic patients with features of MAS and a similar mortality rate and that MAS patients would have elevated circulating biomarkers related to macrophage activation.

Methods We selected all patients with features of MAS and age-matched controls without features of MAS from the ProCESS trial. Ferritin, IL-18, IL-1\( \beta \) and IFN-\( \gamma \) concentrations were measured in plasma samples collected on day 1. Mortality was assessed at hospital discharge and at 90 days. MAS patients were further stratified according to ferritin levels. A threshold of 1200 ng/ml was established based on the upper limit of the 95% confidence interval for the mean ferritin concentration in MAS survivors.

Results Of the 1341 ProCESS subjects, 82 exhibited features of MAS (6.1%). In-hospital and 90-day mortality rates were higher in MAS than non-MAS patients (42.7% vs 9.8% and 61.0% vs 28.1%; \( p < 0.05 \)). MAS subjects also showed higher ferritin, IL-18 and IL-1\( \beta \) concentrations (\( p < 0.05 \)). Nearly 27% of septic patients with features of MAS had ferritin levels >1200 ng/ml. These patients had the highest in-hospital (63.6%) and 90-day (72.7%) mortalities, as well as higher IL-18, IL-1\( \beta \) and IFN-\( \gamma \) concentrations compared to septic patients without MAS (\( p < 0.05 \)).
Reversal of Warburg effect via metabolic reprogramming decreases sustained inflammation and improves lifespan in a Drosophila model of surviving sepsis.

Veli Bakalov, MD, Laura Isabel Reyes Uribe, MD, Rahul Deshpande, PhD, Michael J. Stelmach, Stacy Gelhaus Wendell, PhD, A. Murat Kaynar, MD, MPH

First Authors: Veli Bakalov, MD, Laura Isabel Reyes Uribe, MD
Primary affiliation of first author: Department of Critical Care Medicine, University of Pittsburgh School of Medicine
Level of training of first authors: visiting research scholar
Abstract type: original research

Abstract

Objectives. In addition to high mortality rates in discharged patients as compared to the matched cohort, sepsis survivors continue to experience long-term complications, such as accelerated cardiovascular and neuro-cognitive decline, new infections, cancer, and metabolic disturbances. One of the possible explanations of long-term complications in sepsis survivors is sustained inflammation. During sepsis, innate immune cells shift their metabolic balance in favour of aerobic glycolysis over oxidative phosphorylation (Warburg effect) producing excessive amounts of lactate. Recent work suggests a link between a metabolic shift (aerobic glycolysis) and proinflammatory state in infection as well as cancer. Pyruvate dehydrogenase (PDH) is a key regulatory metabolic enzyme linking glycolysis to the citric acid cycle as well as lipogenesis and its activity is crucial in lactate metabolism. In the current study, we hypothesized that metabolic reprogramming of glycolysis (reversal of Warburg effect) through chemical and genetic manipulation of pyruvate dehydrogenase (PDH) regulates sustained inflammation and associated mortality in sepsis survivors. We tested our hypothesis in a Drosophila melanogaster model of surviving sepsis by promoting PDH activity with dichloroacetic acid (DCA).

Methods. We used a model of percutaneous infection with Staphylococcus aureus in D. melanogaster to mimic sepsis. In addition to linezolid, flies received DCA 0.5 mg/ml in diet immediately after infection for one week. We determined inflammatory gene expression, anti-microbial peptides with quantitative real-time polymerase chain reaction (qRT-PCR) 24h and 1 week after inoculation with bacteria. We determined metabolic changes 1 week after infection using LC-electrospray ionization Mass Spectrometry. Kaplan-Meyer survival analysis was performed using GraphPad Pad 6. Metaboanalyst was used to implement the data analysis.

Results. When we treated flies with DCA alone for 24 hours without antibiotic treatment, DCA treatment did not change outcome of acute sepsis survival (Figure 1A). Sepsis survived flies treated with DCA for 1 week demonstrated improved lifespan compared to sepsis survived flies on regular diet (Figure 1B). We studied the role of DCA on the expression pattern of AMPs. When treated with DCA for 7 days and linezolid for first 24 hours, DCA-treated sepsis surviving flies had decreased expression of Drosomycin, Cecropin A, and Metchnikowin compared to the flies treated with linezolid alone (Figure 1C). Flies surviving sepsis on regular diet demonstrated increased amount of lactate and accumulation of TCA metabolites compared to sham and unmanipulated. When treated with DCA, levels of lactate and TCA metabolites (pyruvate, acetate, citrate/isocitrate, and fumarate) normalized and were similar to sham and unmanipulated groups (Figure 1D).

Conclusions. Our results suggest a role for metabolic reprogramming of the innate immune system as a therapeutic tool to improve outcomes in sepsis survivors through normalization of metabolic pathways and regulation of sustained inflammation through possibly epigenetic regulation. This disease model will facilitate exploration of various spatial and temporal interventions to lifespan and healthspan outcomes.
A Systemic Review of Sepsis Induced Macrophage Activation Syndrome (MAS)

Chandrasekaran N, MD; Mahmood S, MBBS; Anderko R; Murray H, MD; Carcillo J, MD; Kellum J, MD; Gomez H, MD, MPH

Objective: Macrophage Activation Syndrome (MAS) is a lethal, pro-inflammatory disorder of uncontrolled immune activation that can be triggered by sepsis and has been reported to increase sepsis mortality 3-fold. However, data in adults is lacking; thus, we conducted a systematic review of the literature to understand the impact of sepsis induced MAS (sepsis/MAS) on mortality, outcomes and potential therapies.

Methods: We reviewed citations from EMBASE, Cochrane Central Register of Controlled Trials Library database and MEDLINE from January 1, 2001 to February 1, 2017. We included studies of adult (>18 years) patients with sepsis, defined by the 2001 international sepsis definition conference, and MAS criteria (5 of 9 criteria). We excluded studies that included patients with MAS in the context of rheumatological disorders, family history of hemophagocytic lymphohistiocytosis or malignancy. We limited articles to randomized controlled trials, case reports, prospective cohort studies, case-controlled studies, case series, and case reports.

Results: We found a total of 3,118 articles. We excluded 1,222 articles for being duplicates, 1,079 for including patients with underlying rheumatologic conditions, malignancies or less than 18 years of age. We excluded 800 articles because they did not report on mortality, organ dysfunction, or treatment. Seventeen more articles were excluded after further assessment for reporting on patients with rheumatologic disorders and malignancies. We included a total of 9 articles. The results are presented in table 1.

Conclusion: There is very little evidence on the prevalence, outcome, and potential therapeutic interventions in adult sepsis induced MAS. The bulk of the evidence comes from case reports and short case series. The most informative evidence was found on a post-hoc analysis of a randomized controlled trial, which demonstrated a mortality incidence of 6% and a beneficial effect of treatment with the IL-1β receptor antagonist Anakinra.
Table 1

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Mortality</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arslan et al (2)</td>
<td>1</td>
<td>Female</td>
<td>51</td>
<td>Toxoplasmosis with MAS</td>
<td>Prednisolone 2mg/kg/day x 10 days, then 1g/day x 3 days, IVIG 0.5/kg/day x 4 days</td>
<td>Patient passed</td>
<td></td>
</tr>
<tr>
<td>Kumar et al (3)</td>
<td>1</td>
<td>Male</td>
<td>63</td>
<td>Human Ehrlichiosis with MAS</td>
<td>Doxycycline + methylprednisolone 1g/day x 3 days and Anakinra 100mg 2x/day x 2 days, then 100mg daily x 5 weeks</td>
<td>Patient did well</td>
<td>No permanent organ failure</td>
</tr>
<tr>
<td>Eirin et al (4)</td>
<td>1</td>
<td>Male</td>
<td>37</td>
<td>CMV + MAS</td>
<td>Prednisone 60mg/day, etoposide, cyclosporine 75mg/daily</td>
<td></td>
<td>'Histiocytic glomerulopathy’ found on kidney biopsy</td>
</tr>
<tr>
<td>Esmaili et al (5)</td>
<td>1</td>
<td>Male</td>
<td>39</td>
<td>Renal transplant patient + MAS</td>
<td>IVIG, and 2 liter/day therapeutic plasma exchange (TPE) with fresh frozen plasma replacement</td>
<td>Patient did well</td>
<td>Kidney biopsy Thrombotic microangiopathy</td>
</tr>
<tr>
<td>Bihl et al (6)</td>
<td>3</td>
<td>Patient 1: Female; Patient 2: Male; Patient 3: Male</td>
<td>Pt 1: 50; Pt 2: 63; Pt 3: 76</td>
<td>Patient 1: Sepsis MOF Patient 2: HCV + MAS Patient 3: necrotizing glomerulonephritis with ANCA negative small vessel vasculitis</td>
<td>Patient 1: failed IVIG + corticosteroid therapy; tried etoposide and anti-TNF alpha treatment Patient 2: IVIG Patient 3: IVIG+ steroids</td>
<td>Patient 1: did well; Patient 2: passed after findings of NHL; Patient 3: passed</td>
<td>Patient 1: underwent liver transplant (2/2 cirrhosis from MAS); All 3 patients: destructive cholangitis with one proceeding to ductopenia and cirrhosis</td>
</tr>
<tr>
<td>Study</td>
<td>Patient ID</td>
<td>Gender</td>
<td>Age</td>
<td>Presentation</td>
<td>Treatment Details</td>
<td>Outcome/Details</td>
<td></td>
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<td>-------------------------------</td>
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<td>-----</td>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>John et al (7)</td>
<td>1</td>
<td>Male</td>
<td>28</td>
<td>Fever of unknown origin + MAS with Acinetobacter Baumannii</td>
<td>Prednisolone 1mg/kg + cyclosporine 5mg/kg + colistin 2.5mg/kg/day + polymixin 15,000 IU/kg</td>
<td>Patient did well</td>
<td></td>
</tr>
<tr>
<td>Muta et al (8)</td>
<td>1</td>
<td>Female</td>
<td>26</td>
<td>Sepsis + MAS</td>
<td>Steroid pulse therapy with dexamethasone; Transient administration of cyclosporin A on the third hospital day had no effect</td>
<td>Patient passed</td>
<td>Autopsy: enlarged liver weighing 1650 g and swollen spleen weighing 140 g</td>
</tr>
<tr>
<td>Mercado et al (9)</td>
<td>1</td>
<td>Male</td>
<td>69</td>
<td>Septic Shock + MAS</td>
<td>Steroid treatment was started without changes in cytopenias or cytologic findings. Thus, etoposide and cyclosporine</td>
<td>Patient passed</td>
<td></td>
</tr>
<tr>
<td>Shakoory et al (10)</td>
<td>763</td>
<td>Males and Females</td>
<td>18+</td>
<td>Septic Shock + MAS</td>
<td>Anakinra</td>
<td>28 day mortality: 64.7% in patients who did not receive Anakinra; 34.6% mortality in patients with Anakinra</td>
<td></td>
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</table>


Increase in HSP27 in pediatric cardiopulmonary bypass and its relationship with AKI
Catherine Gretchen, MD¹ (Fellow); Hulya Bayir, MD¹; Melita Viegas, MD²; Mahesh Sharma, MD²; Nahmah Kim-Campbell, MD¹ (Mentor)

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Original Research

Objective: Pediatric cardiopulmonary bypass (CPB) has been associated with morbidity such as AKI. The mechanism is unclear and may include ischemia/reperfusion (I/R) injury and inflammation. Heat shock proteins (HSPs) are proteins that respond to cellular stress and have been shown to modulate apoptotic pathways and have anti-inflammatory actions. Specifically, an increase in HSP27, a small HSP (27kda), was shown to be protective against AKI in animal models of I/R. Our objectives are first, to examine the change in plasma concentrations of HSP27 during the pediatric cardiopulmonary bypass, and secondly, to examine the relationship of these changes with the incidence of AKI.

Methods: This is an observational pilot study of pediatric patients, 0-18 years old, undergoing CPB during corrective operations of congenital heart disease. Plasma samples were obtained at 4 time points during their course: baseline, at the end of CPB (EndCPB), 2 hours after reperfusion (2hREP), and 24 hours after reperfusion (24hREP). Patient demographic and laboratory data were collected from the electronic medical record. Patients were given the diagnosis of AKI based on KDIGO classification. Plasma HSP27 concentrations were obtained using commercially available ELISA.

Results: We examined 25 CPB patients. In this cohort, 11/25 (44%) met criteria for AKI using the KDIGO classification. HSP27 protein concentrations (ng/mL) increased during CPB and was decreased from baseline at 24hREP (3.1 vs. 4.063 vs. 1.6 for baseline, EndCPB, and 24hREP, respectively, p<0.05). In patients without AKI, there was an increase from baseline by the end of CPB (3.16 vs. 4.58, p<0.05). In the patients with AKI, there was an increase in HSP27 by 2hREP (2.21 vs. 3.2, p<0.05). When comparing patients with and without AKI, there was a significant difference between HSP27 concentrations at End CPB as well as 24hREP.

Fig. 1:
Conclusions: In pediatric CPB, there is change in plasma HSP27 concentrations. In those patients that do not develop AKI, this peak occurs earlier than those that develop AKI. This may be a useful target to affect the development of AKI and warrants further study in a larger patient population.
Original research

Mechanisms for sepsis-associated AKI non-recovery

Shengnan Li, MD., visiting scholar, Alicia Frank, Xiaoyan Wen, MD., PHD., John A. Kellum, MD.

Union hospital, Tongji Medical College, Huazhong University of Science & Technology.

**Background:** AKI is common in ICU, associated with both short-term and long-term mortality. As one of the common contributing factors for development of AKI, sepsis is associated with 26-50% of all AKI cases. Despite its importance, the mechanisms of sepsis-associated AKI (SA-AKI) and post-AKI recovery are not well-understood. The aim of this study is to establish a rodent model of SA-AKI with progression to chronic disease, and to explore quantitative short-term readouts. Our ultimate goals are to understand underlying mechanisms, and to provide potential targets for therapy.

**Methods:** Balb/c mice were subject to cecal ligation and puncture surgery. For survival assessment, animals were divided into 6 groups: sham, CLP1(1p-21G), CLP2(2p-21G), CLP3(2p-25G), CLP4(3p-21G) and CLP5(3p-25G) according to puncture number and needle size. After surgery, mice were observed each day for 14 days. Kaplan-Meier curves were constructed and analyzed by log-rank test. Blood for serum creatinine (sCr) was collected at 48h after surgery. In addition, kidneys for HE staining or Q-PCR were harvested at 72h or 14 days after surgery. Pair-wise comparisons between groups were analyzed by t-test. For all analyses, P < 0.05 was taken as significant.

**Results:** Survival rate for sham and CLP on day-14 for groups 1-5 were 100%, 35%, 25%, 35%, 0%, 10%, respectively. CLP3(2p-25G) had a 30% survival rate, significantly different from sham animals and thus was chosen to pursue additional testing. sCr in CLP3(2p-25G) increased by 60% 48h after surgery, P < 0.05 but recovered to baseline by 7-day. Morphological changes at 72h were characterized by brush border loss, tubular cells degeneration and sloughed. At 14 days mRNA expression of COL 1a1, Plod2, FSP1, Ki67 and CDKN1A in CLP mice were significantly increased compared to sham (P < 0.05). COL 1a1, Plod2 and FSP1 are fibrotic markers, while Ki67 and CDKN1A represent proliferation. At 14 days fibrosis and cell death were found on histologic examination in CLP animals but not sham animals.

**Conclusion:** In CLP induced SA-AKI mice model, morphologic damage, such as fibrosis were present even though serum markers completely recovered to baseline level. Our study establishes a model to study potential pathways for inhibiting or reversing fibrosis in the setting of SA-AKI.
Modulation of IGFBP7 and TIMP2 Expression and Secretion by Clinically Relevant Insults In Vitro.

David R. Emlet, PhD., Seth Morrisroe B.S., Alicia Frank B.S., John A Kellum, MD.

Center for Critical Care Nephrology, CRISMA, Department of Critical Care Medicine, University of Pittsburgh School of Medicine.

Presenting Author: Research Technician II

Abstract Type: Original Research

Objectives: Our group has recently identified variable constitutive expression and secretion of the AKI biomarkers Insulin-Like Growth Factor Binding Protein 7 (IGFBP7) and Tissue Inhibitor of Metalloproteinases-2 (TIMP2) in model systems of primary human kidney proximal and distal tubule epithelial cells in vitro. In this study, we utilized these systems to assess potential modulation of these biomarkers by clinically relevant insults, mimicking ischemia-reperfusion injury and hemoglobin or myoglobin release induced by trauma and/or surgery.

Methods: Primary human kidney tubule epithelial cells of proximal and distal tubule origin were immunoaffinity isolated from cortical cell cultures with antibodies directed against Aminopeptidase N (APN) and Mucin-1 (MUC-1) respectively, using the Dyanbead pan-mouse IgG system. Isolated proximal and distal tubule cells were cultured on transwell permeable supports in serum-free media to form monolayers. For insult testing, monolayer cells were subjected to oxygen-nutrient deprivation or treatment with hemoglobin or myoglobin. Cell lysates and conditioned media were assessed for IGFBP7 and TIMP2 levels, initiation of an inflammatory response, and cell death.

Results: Oxygen-nutrient deprivation demonstrated that deprivation suppressed the secretion of both biomarkers, and reperfusion caused an early and transient burst of secretion of both biomarkers. Both nutrient alone and oxygen-nutrient deprivation elicited an inflammatory response, but only oxygen-nutrient deprivation elicited measurable death. In the model of trauma/surgery, both hemoglobin and myoglobin also elicited an early burst of secretion of both markers, but there was variability in the inflammatory response, and only hemoglobin demonstrated measurable death.

Conclusions: Together, these data show that IGFBP7 and TIMP2 are indeed modulated by various clinically relevant kidney insults, and that different insults affect these molecules in different ways. This in vitro system will be a useful tool to further investigate the potential role of these markers in the etiology of AKI.
Sublingual microvascular and tongue, renal, and hepatic tissue responsiveness to resuscitation in a porcine model of sepsis

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¹University of Pittsburgh Medical Center, Department of Anesthesiology
Resident, PGY4
Original research

Objectives:
We hypothesized that sublingual (SL) microcirculatory parameters 1. Can predict microvascular response to resuscitation during sepsis; and 2. Are associated with tissue level lactate, lactate/pyruvate ratio (L/P) and tissue to blood lactate gradient (T-BLac).

Methods:
Lipopolysaccharide (LPS) was administered to 23 anesthetized Yorkshire-Durock pigs for 45 minutes. Thirteen animals received late (90 min after LPS) and 10 early (immediately after LPS) resuscitation. Five animals per group had available data for this opportunistic study. Sublingual microcirculatory parameters (microvascular flow index (MFI) and perfused vessel density (PVD)) were collected. Tissue level lactate and pyruvate were measured using microdialysis catheters inserted in the liver, kidney and tongue at baseline and pre-/post-resuscitation (Pre-R, Post-R). Resuscitation was driven by MAP and SvO2 targets, with SVV for fluid responsiveness. Data are shown in median (interquartile range).

Results:
Pre-R MFI correlated with Post-R MFI (r²=0.562, p=0.008). Microvascular ‘responsive’ animals (i.e. increase in MFI>50% or any increase in PVD) had lower Pre-R MFI and PVD (Fig 1). The presence of Pre-R systemic hyperlactatemia did not predict microvascular fluid responsiveness (p=0.05) as defined by an increase MFI>50%. A higher Pre-R MFI (>2.5) was associated with lower SLT-BLac (-0.42 (0.74) vs. 3.49 (0.34), p=0.008). An increased Post-R renal T-BLac was associated with a lower Pre-R MFI (p=0.06). Post-R PVD was directly associated with Post-R L/P in the liver (p=0.04).

Conclusions:
Pre-R MFI and PVD were associated with Post-R microvascular changes, but not Pre-R systemic lactate levels. Pre-R MFI and PVD may predict Post-R microvascular responsiveness. Pre- and Post-R sublingual MFI and PVD were associated with local metabolic changes in the tongue as well as in the kidney and the liver.

Figure 1:
Pilot study of aquaporin-4 inhibition on cerebral edema and early functional and histological outcome after cardiac arrest

Jessica S. Wallisch MD1,3, Ruchira M. Jha MD1,2, George W. Farr PhD4, Paul R. McGuirk PhD4, Marc F. Pelletier PhD4, Travis C. Jackson PhD1,3, Patrick M. Kochanek MD1-3, Mioara D. Manole MD2,3

Departments of 1Critical Care Medicine and 2Pediatrics, Children’s Hospital of Pittsburgh of UPMC, 3Safar Center for Resuscitation Research, 4Aeromics, Inc, Cleveland, OH

Objectives:
Cerebral edema after cardiac arrest (CA) is associated with poor outcomes. Cerebral edema and Aquaporin-4 (AQP4) expression appear to be linked in asphyxial CA, and AQP4 knockout mice exhibit reduced edema, ICP and neuronal loss vs wild-type in models of global ischemia. We hypothesized that selective inhibition of the AQP4 channel with AER-271 would reduce cerebral edema and improve outcomes in pediatric rat asphyxial CA.

Methods:
Post-natal day 17 Sprague-Dawley rats (n=6/group) were anesthetized, intubated, mechanically ventilated, and had venous and arterial catheters placed. Monitored rats were given vecuronium and disconnected from the ventilator, resulting in CA. Ventilation was re-initiated at 9 min and epinephrine and sodium bicarbonate were given with rapid manual chest compressions until return of spontaneous circulation (ROSC). Rats were randomized to AER-271 (initiated at ROSC, dosing by pharmacokinetic studies), vehicle (Tris base in saline, identical volume/time points), or naïve/sham groups and were sacrificed at 3, 6, or 24 h post-CA for cerebral wet-dry-weight analysis. Functional outcome was evaluated (Neurologic Deficit Score at 3, 24, 48, and 72 h post-CA) and 72 h histology performed (hippocampal CA1 neuronal death by H&E and Fluorojade; inflammation by Iba1 staining).

Results:
AER-271 was well tolerated with no difference in hemodynamics, time to ROSC, or lab values by group. Treatment with AER-271 ameliorated early edema and attenuated the early neurologic deficit at 3 h. Rats who received AER-271 showed 50% reductions in both neuronal death (by fluorojade and H&E) and in the microglial response assessed in CA1 hippocampus at 72h compared to vehicle. This exploratory report shows that the AQP4 targeting drug AER-271 produces rapid beneficial effects on brain edema and neurological outcome after CA and suggests an enduring attenuation of neuronal death and neuroinflammation.
Conclusions:
In this pilot study, treatment with AER-271 after pediatric rat asphyxial CA reduced early edema and had trends toward improved functional and histological outcome, supporting a definitive trial of AER-271 in our developmental model of CA in rats.  

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### Cerebral Edema by % brain water

<table>
<thead>
<tr>
<th></th>
<th>Naïve/Sham</th>
<th>Vehicle</th>
<th>AER-271</th>
<th>One-way ANOVA</th>
<th>Bonferroni correction p&lt;0.0167</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 h post-CA</td>
<td>82.95 ±0.17</td>
<td>83.87 ±0.08</td>
<td>83.28 ±0.05</td>
<td>&lt;0.0001</td>
<td>AER-271 vs Vehicle, Vehicle vs Naïve</td>
</tr>
<tr>
<td>6 h post-CA</td>
<td>82.95 ±0.17</td>
<td>83.20 ±0.08</td>
<td>83.23 ±0.09</td>
<td>0.36</td>
<td>None</td>
</tr>
<tr>
<td>24 h post-CA</td>
<td>82.95 ±0.17</td>
<td>83.16 ±0.09</td>
<td>83.21 ±0.13</td>
<td>0.46</td>
<td>None</td>
</tr>
</tbody>
</table>

### Neurologic Deficit Score

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Vehicle</th>
<th>AER-271</th>
<th>One-way ANOVA</th>
<th>Bonferroni correction p&lt;0.0167</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 h post-CA</td>
<td>0.83 ±0.83</td>
<td>335.83 ±29.33</td>
<td>261.67 ±20.56</td>
<td>&lt;0.0001</td>
<td>AER-271 vs Sham, Vehicle vs Sham</td>
</tr>
<tr>
<td>24 h post-CA</td>
<td>0.00 ±0.00</td>
<td>18.00 ±4.64</td>
<td>20.00 ±4.47</td>
<td>0.002</td>
<td>AER-271 vs Sham, Vehicle vs Sham</td>
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<tr>
<td>48 h post-CA</td>
<td>0.00 ±0.00</td>
<td>12.00 ±4.90</td>
<td>11.67 ±3.07</td>
<td>0.02</td>
<td>AER-271 vs Sham</td>
</tr>
<tr>
<td>72 h post-CA</td>
<td>0.00 ±0.00</td>
<td>10.00 ±4.18</td>
<td>9.17 ±2.71</td>
<td>0.03</td>
<td>AER-271 vs Sham</td>
</tr>
</tbody>
</table>

### 72 h Hippocampus CA1 Histology (cells/0.1mm)

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Vehicle</th>
<th>AER-271</th>
<th>One-way ANOVA</th>
<th>Bonferroni correction p&lt;0.0167</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorochrome +</td>
<td>0.08 ±0.03</td>
<td>15.38 ±4.20</td>
<td>7.79 ±4.30</td>
<td>0.02</td>
<td>Vehicle vs Sham</td>
</tr>
<tr>
<td>Neuronal Death H&amp;E</td>
<td>0.03 ±0.01</td>
<td>8.07 ±2.28</td>
<td>4.60±2.39</td>
<td>0.03</td>
<td>Vehicle vs Sham</td>
</tr>
<tr>
<td>Iba1 +</td>
<td>89.29 ±8.80</td>
<td>785.71 ±155.10</td>
<td>384.52 ±114.22</td>
<td>0.0016</td>
<td>Vehicle vs Sham</td>
</tr>
</tbody>
</table>
Serum biomarker-based models to predict intracranial pressure in pediatric traumatic brain injury

Kendra S. Woods, MD, Alicia K. Au, MD, Patrick M. Kochanek, MD, Michael J. Bell, MD, Robert S. B. Clark, MD

First author: Children’s Hospital of Pittsburgh of UPMC, Pediatric Critical Care Medicine; PGY6 Fellow

Abstract type: original research

Objectives:

Intracranial pressure (ICP) monitoring and treatment are mainstays of neurocritical care. To-date, detection of intracranial hypertension is either invasive or inferred from clinical and/or radiological examination. Well-validated serum biomarkers of somatic organs are useful in assessing function. However, while brain-related biomarkers have shown some utility in assessing damage to the brain from initial insults, the relationship between these biomarkers and immediate clinical disturbances of function has not been demonstrated. We hypothesized that increased ICP could be estimated from clinical variables and serum brain biomarker levels.

Methods:

Serum glial fibrillary acidic protein (GFAP; astrocyte biomarker) and neuron specific enolase (NSE) levels and time-synched hourly ICP measurements obtained as part of an IRB-approved clinical trial (NCT01322009) were used to generate models estimating ICP. All patients had severe TBI (Glasgow coma scale score ≤ 8) and invasive ICP monitors. Time after injury, age, patient sex, GFAP, NSE, and maximal ICP±12 h of blood draw (maxICP) were used for multivariate linear regression analysis.

Results:

The dataset consisted of 55 serum samples from 13 children (9 male, 4 female) aged 8.8±5.1 y obtained 8-90 h after TBI. GFAP concentration was 4.3±12.3 ng/ml and NSE was 3.4±5.7 ng/ml (mean±SD). Linear models predicting maxICP include:

\[
\text{maxICP}_{24h} = 28.817 + (0.0158 \times \text{time of sample h}) + (0.650 \times \text{GFAP}_{\text{ng/ml}}) - (0.228 \times \text{NSE}_{\text{ng/ml}}) - (0.980 \times \text{age}_{\text{y}}) - (0.549 \times \text{sex}_{M2_F1}); \quad r^2=0.366, P<0.001
\]

and, using only statistically significant variables:

\[
\text{maxICP}_{24h} = 25.172 + (0.620 \times \text{GFAP}_{\text{ng/ml}}) + (0.0308 \times \text{time of sample h}) - (0.853 \times \text{age}_{\text{y}}); \quad r^2=0.351, P<0.001
\]

Conclusions:

In this pediatric TBI dataset, serum GFAP and patient age can be used to predict maxICP within a 24 h period surrounding the time the sample was obtained. Refinement using other clinical variables, additional serum brain biomarkers, independent datasets, and more sophisticated mathematical modeling may culminate in a minimally invasive method for estimating intracranial pressure to be validated prospectively. Support NS069247 and U01 NS081041