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The Interaction of Vasopressin and Corticosteroids in Septic Shock: A Pilot Randomized Controlled Trial*

Gordon, Anthony C.; Mason, Alexina J.; Perkins, Gavin D.; More

- Objectives: **Vasopressin and corticosteroids** are both commonly used adjunctive therapies in septic shock. Retrospective analyses have suggested that there may be an interaction between these drugs, with higher circulating vasopressin levels and improved outcomes in patients treated with both vasopressin and corticosteroids. We aimed to test for an interaction between vasopressin and corticosteroids in septic shock.
- Design: Prospective open-label randomized controlled pilot trial.
- Setting: Four adult ICUs in London teaching hospitals.
- Patients: Sixty-one adult patients who had septic shock.
- Interventions: Initial vasopressin IV infusion titrated up to **0.06 U/min** and then IV **hydrocortisone (50 mg 6 hourly)** or **placebo**. Plasma vasopressin levels were measured at 6–12 and 24–36 hours after hydrocortisone/placebo administration.
- Measurements and Main Results: Thirty-one patients were allocated to vasopressin + hydrocortisone and 30 patients to vasopressin + placebo. The hydrocortisone group required a **shorter duration of vasopressin** therapy (3.1 d; 95% CI, 1.1–5.1; shorter in hydrocortisone group) and required a **lower total dose of vasopressin** (ratio, 0.47; 95% CI, 0.32–0.71) compared with the placebo group. Plasma vasopressin levels were **not higher** in the hydrocortisone group compared with the placebo group (64 pmol/L difference at 6- to 12-hour time point; 95% CI, –32 to 160 pmol/L). Early vasopressin use was well tolerated with only one serious adverse event possibly related to study drug administration reported. There were **no differences in mortality rates** (23% 28-day mortality in both groups) or organ failure assessments between the two treatment groups.
- Conclusions: Hydrocortisone spared vasopressin requirements, reduced duration, and reduced dose, when used together in the treatment of septic shock, but it did not alter plasma vasopressin levels. Further trials are needed to assess the clinical effectiveness of vasopressin as the initial vasopressor therapy with or without corticosteroids.

Arterial Catheters as a Source of Bloodstream Infection: A Systematic Review and Meta-Analysis*

O' Horo, John C.; Maki, Dennis G.; Krupp, Anna E.; More

- Objective: Catheter-related bloodstream infections are associated with significant costs and adverse consequences. Arterial catheters are commonly used in the critical care setting and are among the most heavily manipulated vascular access devices. We sought to evaluate the prevalence of arterial catheter-related bloodstream infection.
- Data Sources: PubMed, CinAHL, EMBASE, and Web of Science.
- Study Selection: Included studies reported prevalence rate of catheter-related bloodstream infection for arterial catheters **used for critical illness or postoperative monitoring**. For the purposes of this study, catheter-related bloodstream infection was defined as **positive blood culture collected from an arterial catheter and from the periphery with the same organism in a patient demonstrating systemic signs of sepsis**.
- Data Extraction: The study population, site of insertion, antiseptic preparation, catheter days, and prevalence of catheter-related bloodstream infection were abstracted. When data were not available, authors were contacted for further information.
- Data Synthesis: Forty-nine studies met criteria including 222 cases of arterial catheter-related bloodstream infection in 30,841 catheters. Pooled incidence was 3.40/1,000 catheters or 0.96/1,000 catheter days. Prevalence was considerably higher in the subgroup of studies that cultured all catheters (1.26/1,000 catheter days) compared with those studies that cultured only when the arterial catheter was suspected as the source for the catheter-related bloodstream infection (0.70/1,000 catheter days). Pooled data also found a significantly increased risk of infection for **femoral site** of insertion compared with **radial artery** for arterial catheter placement (relative risk, 1.93; 95% CI, 1.32–2.84; $p = 0.001$)
- Conclusions: Arterial catheters are an underrecognized cause of catheter-related bloodstream infection. Pooled incidence when catheters were systematically cultured and correlated to blood culture results indicated a substantial burden of arterial catheter-related bloodstream infection. Selection of a radial site over a femoral site will help reduce the risk of arterial catheter-related bloodstream infection. Future studies should evaluate technologies applied to preventing central venous catheter-related bloodstream infection to arterial catheters as well.

Early Multimodal Outcome Prediction After Cardiac Arrest in Patients Treated With Hypothermia*

Oddo, Mauro; Rossetti, Andrea O.

- Objectives: Therapeutic hypothermia and pharmacological sedation may influence outcome prediction after cardiac arrest. The use of a multimodal approach, including clinical examination, electroencephalography, somatosensory-evoked potentials, and serum neuron-specific enolase, is recommended; however, no study examined the comparative performance of these predictors or addressed their optimal combination.
- Design: Prospective cohort study.
- Setting: Adult ICU of an academic hospital.
- Patients: One hundred thirty-four consecutive adults treated with therapeutic hypothermia after cardiac arrest.
- Measurements and Main Results: Variables related to the cardiac arrest (cardiac rhythm, time to return of spontaneous circulation), clinical examination (brainstem reflexes and myoclonus), electroencephalography reactivity during therapeutic hypothermia, somatosensory-evoked potentials, and serum neuron-specific enolase. Models to predict clinical outcome at 3 months (assessed using the Cerebral Performance Categories: 5 = death; 3–5 = poor recovery) were evaluated using **ordinal logistic regressions** and **receiving operator characteristic curves**. Seventy-two patients (54%) had a poor outcome (of whom, 62 died), and 62 had a good outcome. Multivariable ordinal logistic regression identified **absence of electroencephalography reactivity** ($p < 0.001$), **incomplete recovery of brainstem reflexes in normothermia** ($p = 0.013$), and **neuron-specific enolase higher than 33 $\mu\text{g/L}$** ($p = 0.029$), but not somatosensory-evoked potentials, as independent predictors of poor outcome. The combination of clinical examination, electroencephalography reactivity, and neuron-specific enolase yielded the best predictive performance (receiving operator characteristic areas: 0.89 for mortality and 0.88 for poor outcome), with 100% positive predictive value. Addition of somatosensory-evoked potentials to this model did not improve prognostic accuracy.
- Conclusions: Combination of clinical examination, electroencephalography reactivity, and serum neuron-specific enolase offers the best outcome predictive performance for prognostication of early postanoxic coma, whereas somatosensory-evoked potentials do not add any complementary information. Although prognostication of poor outcome seems excellent, future studies are needed to further improve prediction of good prognosis, which still remains inaccurate.

Optimal Range of Global End-Diastolic Volume for Fluid Management After Aneurysmal Subarachnoid Hemorrhage: A Multicenter Prospective Cohort Study*

Tagami, Takashi; Kuwamoto, Kentaro; Watanabe, Akihiro; More

- Objectives: Limited evidence supports the use of hemodynamic variables that correlate with delayed cerebral ischemia or pulmonary edema after aneurysmal subarachnoid hemorrhage. The aim of this study was to identify those hemodynamic variables that are associated with **delayed cerebral ischemia** and **pulmonary edema** after subarachnoid hemorrhage.
- Design: A multicenter prospective cohort study.
- Setting: Nine university hospitals in Japan.
- Patients: A total of 180 patients with aneurysmal subarachnoid hemorrhage.
- Interventions: None.
- Measurements and Main Results: Patients were prospectively monitored using a **transpulmonary thermodilution system** in the 14 days following subarachnoid hemorrhage. Delayed cerebral ischemia was developed in 35 patients (19.4%) and severe pulmonary edema was developed in 47 patients (26.1%). Using the **Cox proportional hazards model**, the mean global end-diastolic volume index (normal range, 680–800 mL/m²) was the independent factor associated with the occurrence of delayed cerebral ischemia (hazard ratio, 0.74; 95% CI, 0.60–0.93; p = 0.008). Significant differences in global end-diastolic volume index were detected between the delayed cerebral ischemia and non–delayed cerebral ischemia groups (783 ± 25 mL/m² vs 870 ± 14 mL/m²; p = 0.007). The global end-diastolic volume index threshold that best correlated with delayed cerebral ischemia was **less than 822 mL/m²**, as determined by receiver operating characteristic curves. Analysis of the Cox proportional hazards model indicated that the mean global end-diastolic volume index was the independent factor that associated with the occurrence of **pulmonary edema** (hazard ratio, 1.31; 95% CI, 1.02–1.71; p = 0.03). Furthermore, a significant positive correlation was identified between global end-diastolic volume index and extravascular lung water (r = 0.46; p < 0.001). The global end-diastolic volume index threshold that best correlated with severe pulmonary edema was greater than **921 mL/m²**.
- Conclusions: Our findings suggest that global end-diastolic volume index impacts both delayed cerebral ischemia and pulmonary edema after subarachnoid hemorrhage. Maintaining global end-diastolic volume index slightly above normal levels has promise as a fluid management goal during the treatment of subarachnoid hemorrhage.

Leukocyte Infiltration and Activation of the **NLRP3 Inflammasome** in White Adipose Tissue Following Thermal Injury*

Stanojcic, Mile; Chen, Peter; Harrison, Rachael A.; More

- **Objectives** Severe thermal injury is associated with extreme and prolonged inflammatory and hypermetabolic responses, resulting in significant catabolism that delays recovery or even leads to multiple organ failure and death. Burned patients exhibit many symptoms of stress-induced diabetes, including hyperglycemia, hyperinsulinemia, and hyperlipidemia. Recently, the **nucleotide-binding domain, leucine-rich family (NLR), pyrin-containing 3 (NLRP3) inflammasome** has received much attention as the sensor of endogenous “danger signals” and mediator of “sterile inflammation” in type II diabetes. Therefore, we investigated whether the NLRP3 inflammasome is activated in the adipose tissue of burned patients, as we hypothesize that, similar to the scenario observed in chronic diabetes, the cytokines produced by the inflammasome mediate insulin resistance and metabolic dysfunction.
- **Design** Prospective cohort study.
- **Setting** Ross Tilley Burn Centre & Sunnybrook Research Institute.
- **Patients** We enrolled 76 patients with burn sizes ranging from 1% to 70% total body surface area. All severely burned patients exhibited burn-induced insulin resistance and hyperglycemia.
- **Interventions** None.
- **Measurements and Main Results:** We examined the adipose tissue of control and burned patients and found, via **flow cytometry and gene expression studies**, increased infiltration of leukocytes—especially **macrophages**—and evidence of inflammasome **priming and activation**. Furthermore, we observed increased levels of **interleukin-1 β** in the plasma of burned patients when compared to controls.
- **Conclusions:** In summary, our study is the first to show activation of the inflammasome in burned humans, and our results provide impetus for further investigation of the role of the inflammasome in burn-induced hypermetabolism and, potentially, developing novel therapies targeting this protein complex for the treatment of stress-induced diabetes.

Prospective Study of Vitamin D Status at Initiation of Care in Critically Ill Surgical Patients and Risk of 90-Day Mortality*

Quraishi, Sadeq A.; Bittner, Edward A.; Blum, Livnat; More

- Objectives: 1) To characterize vitamin D status at initiation of critical care in surgical ICU patients and 2) to determine whether this vitamin D status is associated with the risk of prolonged hospital length of stay, 90-day readmission, and 90-day mortality.
- Design: Prospective cohort study.
- Setting: A teaching hospital in Boston, MA.
- Patients: Hundred surgical ICU patients.
- Interventions: None.
- Measurements and Main Results: Mean (\pm sd) serum total 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were 17 ± 8 ng/mL and 32 ± 19 pg/mL, respectively. Mean calculated bioavailable 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were 2.5 ± 2.0 ng/mL and 6.6 ± 5.3 pg/mL, respectively. Receiver-operating characteristic curve analysis demonstrated that all of four vitamin D measures predicted the three clinical outcomes; total 25-hydroxyvitamin D was not inferior to the other measures. Median (interquartile range) hospital length of stay was 11 days (8–19 d). Poisson regression analysis, adjusted for biologically plausible covariates, demonstrated an association of total 25-hydroxyvitamin D with hospital length of stay (incident rate ratio per 1 ng/mL, 0.98; 95% CI, 0.97–0.98). The 90-day readmission and mortality rates were 24% and 22%, respectively. Even after adjustment for biologically plausible covariates, there remained significant associations of total 25-hydroxyvitamin D with readmission (odds ratio per 1 ng/mL, 0.84; 95% CI, 0.74–0.95) and mortality (odds ratio per 1 ng/mL, 0.84; 95% CI, 0.73–0.97).
- Conclusions: Serum **25-hydroxyvitamin D levels** within 24 hours of ICU admission may identify patients at high risk for prolonged hospitalization, readmission, and mortality. Randomized trials are needed to assess whether vitamin D supplementation can improve these clinically relevant outcomes in surgical ICU patients.

Stress Hyperlactatemia Modifies the Relationship Between Stress Hyperglycemia and Outcome: A Retrospective Observational Study*

Kaukonen, Kirsi-Maija; Bailey, Michael; Egi, Moritoki; More

- Objective: To study the effect of stress hyperlactatemia on the association between stress hyperglycemia and mortality.
- Design: Retrospective cross-sectional observation study.
- Setting: Three ICUs using arterial blood gases with simultaneous glucose and lactate measurements during ICU stay.
- Patients: Cohort of 7,925 consecutive critically ill patients.
- Interventions: None.
- Measurements and Main Results: We analyzed 152,349 simultaneous measurements of glucose and lactate. We performed multivariable analysis to study the association of different metrics of glucose and lactate with hospital mortality. On day 1, first ($p = 0.013$), highest ($p = 0.001$), mean ($p = 0.019$), and time-weighted mean ($p = 0.010$) glucose levels were associated with increased mortality. A similar, but stronger, association was seen for corresponding lactate metrics ($p < 0.0001$ for all). However, once glucose and lactate metrics were entered into the multivariable logistic regression model simultaneously, all measures of glycemia ceased to be significantly associated with hospital mortality regardless of the metrics being used (first, highest, mean, time-weighted; $p > 0.05$ for all), whereas all lactate metrics remained associated with mortality ($p < 0.0001$ for all). In patients with at least one episode of moderate hypoglycemia (glucose ≤ 3.9 mmol/L), glucose metrics were not associated with mortality when studied separately ($p > 0.05$ for all), whereas lactate was ($p < 0.05$ for all), but when incorporated into a model simultaneously, highest glucose on day 1 was associated with mortality ($p < 0.05$), but not other glucose metrics ($p > 0.05$), whereas all lactate metrics remained associated with mortality ($p < 0.05$ for all).
- Conclusions: Stress hyperlactatemia modifies the relationship between hyperglycemia and mortality. There is no independent association between hyperglycemia and mortality once lactate levels are considered.

C1 Esterase Inhibitor Activity in Amniotic Fluid Embolism*

Tamura, Naoaki; Kimura, Satoshi; Farhana, Mustari; More

- Objectives Amniotic fluid embolism exhibits activation of the complement system and the kallikrein-kinin and coagulofibrinolytic systems. C1 esterase inhibitor is a major inhibitor of C1 esterase and can inhibit plasma kallikrein and also factors XIIa and XIa. Its activity has been shown to be significantly lower in pregnancy and labor than in the nonpregnant state. The purpose of this study was to determine C1 esterase inhibitor activity levels in amniotic fluid embolism.
- Design Retrospective study.
- Setting A single university-based center.
- Patients One hundred six cases with amniotic fluid embolism in a total of 194 singleton pregnant women between January 2010 and December 2011.
- Interventions None.
- Measurements and Main Results One hundred six cases of amniotic fluid embolism had applied to the Japan amniotic fluid embolism registration center in Hamamatsu University School of Medicine between January 2010 and December 2011. In amniotic fluid embolism cases, 85 cases were nonfatal and 21 cases were fatal. Eighty-eight women who delivered without amniotic fluid embolism were regarded as a control. C1 esterase inhibitor activity levels were significantly lower in amniotic fluid embolism patients ($30.0\% \pm 1.8\%$) than in control women ($62.0\% \pm 2.0\%$) ($p < 0.0001$). C1 esterase inhibitor activity levels in fatal amniotic fluid embolism cases ($22.5\% \pm 3.4\%$) were significantly lower than those in nonfatal amniotic fluid embolism cases ($32.0\% \pm 2.1\%$) ($p < 0.05$).
- Conclusions: These results demonstrated that **low C1 esterase inhibitor activity levels** were closely associated with the pathogenesis of amniotic fluid embolism suggesting that C1 esterase inhibitor activity levels have potential as a prognosis factor of amniotic fluid embolism.

Traumatic Injury, Early Gene Expression, and Gram-Negative Bacteremia*

Thompson, Callie M.; Park, Chin H.; Maier, Ronald V.; More

- Objectives: Bacteremic trauma victims have a higher risk of death than their nonbacteremic counterparts. The role that altered immunity plays in the development of bacteremia is unknown. Using an existing dataset, we sought to determine if differences in **early postinjury immune-related gene expression** are associated with subsequent Gram-negative bacteremia.
- Design: Retrospective cohort study, a secondary analysis of the **Glue Grant database**.
- Setting: Seven level I trauma centers across the United States.
- Subjects: Severely injured blunt trauma patients.
- Interventions: None.
- Measurements and Main Results: Total leukocyte gene expression was compared between the subjects in whom Gram-negative bacteremia developed and those in whom it did not develop. We observed that Gram-negative bacteremia was an independent risk factor for death (odds ratio, 1.86; $p = 0.015$). We then compared gene expression at 12 and 96 hours after injury in **10 subjects** in whom subsequently Gram-negative bacteremia developed matched to **26 subjects** in whom it did not develop. At 12 hours, expression of 64 probes differed more than or equal to 1.5-fold; none represented genes related to innate or adaptive immunity. By 96 hours, 102 probes were differentially expressed with 20 representing 15 innate or adaptive immunity genes, including **down-regulation of IL1B** and **up-regulation of IL1R2**, reflecting suppression of innate immunity in Gram-negative bacteremia subjects. We also observed down-regulation of adaptive immune genes in the Gram-negative bacteremia subjects.
- Conclusions: By 96 hours after injury, there are differences in leukocyte gene expression associated with the development of Gram-negative bacteremia, reflecting suppression of both innate and adaptive immunity. Gram-negative bacteremia after trauma is, in part, consequence of host immunity failure and may not be completely preventable by standard infection-control techniques.

A Better Understanding of Why Murine Models of Trauma Do Not Recapitulate the Human Syndrome*

Gentile, Lori F.; Nacionales, Dina C.; Lopez, M. Cecilia; More

- **Objective:** Genomic analyses from blood leukocytes have concluded that mouse injury poorly reflects human trauma at the leukocyte transcriptome. Concerns have focused on the modest severity of murine injury models, differences in murine compared with human age, dissimilar circulating leukocyte populations between species, and whether similar signaling pathways are involved. We sought to examine whether the transcriptomic response to severe trauma in mice could be explained by these extrinsic factors, by utilizing an increasing severity of murine trauma and shock in young and aged mice over time, and by examining the response in isolated neutrophil populations.
- **Design:** Preclinical controlled in vivo laboratory study and retrospective cohort study.
- **Setting:** Laboratory of Inflammation Biology and Surgical Science and multi-institution level 1 trauma centers.
- **Subjects:** Six- to 10-week-old and 20- to 24-month-old C57BL/6 (B6) mice and two cohorts of 167 and 244 severely traumatized (Injury Severity Score > 15) adult (> 18 yr) patients.
- **Interventions:** Mice underwent one of two severity polytrauma models of injury. Total blood leukocyte and neutrophil samples were collected.
- **Measurements and Main Results:** Fold expression changes in leukocyte and neutrophil genome-wide expression analyses between healthy and injured mice ($p < 0.001$) were compared with human total and enriched blood leukocyte expression analyses of severe trauma patients at 0.5, 1, 4, 7, 14, and 28 days after injury (**Glue Grant trauma-related database**). We found that increasing the severity of the murine trauma model only modestly improved the correlation in the transcriptomic response with humans, whereas the age of the mice did not. In addition, the genome-wide response to blood neutrophils (rather than total WBC) was also not well correlated between humans and mice. However, the expression of many individual gene families was much more strongly correlated after injury in mice and humans.
- **Conclusions:** **Although** overall transcriptomic association remained weak even after adjusting for the severity of injury, age of the animals, timing, and individual leukocyte populations, there were individual signaling pathways and ontogenies that were **strongly correlated** between mice and humans. These genes are involved in early inflammation and innate/adaptive immunity.

Conservative Oxygen Therapy in Mechanically Ventilated Patients: A Pilot Before-and-After Trial*

Suzuki, Satoshi; Eastwood, Glenn M.; Glassford, Neil J.; More

- Objectives: To assess the feasibility and safety of a conservative approach to oxygen therapy in mechanically ventilated ICU patients.
- Design: Pilot prospective before-and-after study.
- Setting: A 22-bed multidisciplinary ICU of a tertiary care hospital in Australia.
- Patients: A total of 105 adult (18 years old or older) patients required mechanical ventilation for more than 48 hours: 51 patients during the “conventional” before period and 54 after a change to “conservative” oxygen therapy.
- Interventions: Implementation of a conservative approach to oxygen therapy (target Spo₂ of 90–92%).
- Measurements and Main Results: We collected 3,169 datasets on 799 mechanical ventilation days. During conservative oxygen therapy the median time-weighted average Spo₂ on mechanical ventilation was **95.5%** (interquartile range, 94.0–97.3) versus 98.4% (97.3–99.1) ($p < 0.001$) during conventional therapy. The median Pao₂ was 83 torr (71–94) versus 107 torr (94–131) ($p < 0.001$) with a change to a median Fio₂ of 0.27 (0.24–0.30) versus 0.40 (0.35–0.44) ($p < 0.001$). Conservative oxygen therapy decreased the median total amount of oxygen delivered during mechanical ventilation by about two thirds (15,580 L [8,263–29,351 L] vs 5,122 L [1,837–10,499 L]; $p < 0.001$). The evolution of the Pao₂/Fio₂ ratio was similar during the two periods, and there were no difference in any other biochemical or clinical outcomes.
- Conclusions: Conservative oxygen therapy in mechanically ventilated ICU patients was feasible and free of adverse biochemical, physiological, or clinical outcomes while allowing a marked decrease in excess oxygen exposure. Our study supports the safety and feasibility of future pilot randomized controlled trials of conventional compared with conservative oxygen therapy.

Impact of Therapeutic Strategies on the Prognosis of Candidemia in the ICU*

Puig-Asensio, Mireia; Pemán, Javier; Zaragoza, Rafael; More

- Objectives: To determine the epidemiology of Candida bloodstream infections, variables influencing mortality, and antifungal resistance rates in ICUs in Spain.
- Design: Prospective, observational, multicenter population-based study.
- Setting: Medical and surgical ICUs in 29 hospitals distributed throughout five metropolitan areas of Spain.
- Patients: Adult patients (≥ 18 yr) with an episode of Candida bloodstream infection during admission to any surveillance area ICU from May 2010 to April 2011.
- Interventions: Candida isolates were sent to a reference laboratory for species identification by DNA sequencing and susceptibility testing using the methods and breakpoint criteria promulgated by the European Committee on Antimicrobial Susceptibility Testing. Prognostic factors associated with early (0–7 d) and late (8–30 d) mortality were analyzed using logistic regression modeling.
- Measurements and Main Results: We detected 773 cases of candidemia, 752 of which were included in the overall cohort. Among these, 168 (22.3%) occurred in adult ICU patients. The rank order of Candida isolates was as follows: **Candida albicans (52%), Candida parapsilosis (23.7%), Candida glabrata (12.7%), Candida tropicalis (5.8%), Candida krusei (4%), and others (1.8%)**. Overall susceptibility to fluconazole was 79.2%. Cumulative mortality at 7 and 30 days after the first episode of candidemia was 16.5% and 47%, respectively. Multivariate analysis showed that **early appropriate antifungal treatment** and **catheter removal** (odds ratio, 0.27; 95% CI, 0.08–0.91), **Acute Physiology and Chronic Health Evaluation II score** (odds ratio, 1.11; 95% CI, 1.04–1.19), and **abdominal source** (odds ratio, 8.15; 95% CI, 1.75–37.93) were independently associated with early mortality. Determinants of late mortality were **age** (odds ratio, 1.04; 95% CI, 1.01–1.07), **intubation** (odds ratio, 7.24; 95% CI, 2.24–23.40), **renal replacement therapy** (odds ratio, 6.12; 95% CI, 2.24–16.73), and **primary source** (odds ratio, 2.51; 95% CI, 1.06–5.95).
- Conclusions: Candidemia in ICU patients is caused by non-albicans species in 48% of cases, C. parapsilosis being the most common among these. Overall mortality remains high and mainly related with host factors. Prompt adequate antifungal treatment and catheter removal could be critical to decrease early mortality.

Microcirculatory Alterations in Traumatic Hemorrhagic Shock*

Tachon, Guillaume; Harrois, Anatole; Tanaka, Sebastien; More

- Objectives: Microcirculatory dysfunction has been well reported in clinical studies in septic shock. However, no clinical studies have investigated microcirculatory blood flow behavior in hemorrhagic shock. The main objective of this study was to assess the time course of sublingual microcirculation in traumatic hemorrhagic shock during the first 4 days after trauma.
- Design: Prospective observational study.
- Setting: ICU.
- Patients: **Eighteen** traumatic hemorrhagic shock patients.
- Interventions: **The sublingual microcirculation** was estimated at the study inclusion after surgical or angiographic embolization to control bleeding (D1), and then three times at 24-hour intervals (D2, D3, and D4).
- Measurements and Main Results: Sublingual microcirculation was impaired for 72 hours despite restoration of the macrovascular circulation after control of bleeding in traumatic hemorrhagic shock patients. Furthermore, we found significantly higher decreases in the **microvascular flow index** and **proportion of perfused vessels** in high Sequential Organ Failure Assessment score patients at D4 (Sequential Organ Failure Assessment score ≥ 6) compared to low Sequential Organ Failure Assessment score patients at D4 (Sequential Organ Failure Assessment score < 6) without any differences in global hemodynamics between these two groups. Finally, the initial proportion of perfused vessels at D1 appears to be a good predictor of high Sequential Organ Failure Assessment score at D4.
- Conclusions: Alterations of microcirculation in traumatic hemorrhagic shock patients result from the interplay among hemorrhage-induced tissue hypoperfusion, trauma injuries, inflammatory response, and subsequent resuscitation interventions. Despite restoration of the macrocirculation, the sublingual microcirculation was impaired for at least 72 hours. The initial proportion of perfused vessels appears to be a good predictor of high Sequential Organ Failure Assessment score at D4. Further studies are required to firmly establish the link between microvascular alterations and organ dysfunction in traumatic hemorrhagic shock patients.

Randomized ICU Trials Do Not Demonstrate an Association Between Interventions That Reduce Delirium Duration and Short-Term Mortality: A Systematic Review and Meta-Analysis*

Al-Qadheeb, Nada S.; Balk, Ethan M.; Fraser, Gilles L.; More

- Objectives: We reviewed randomized trials of adult ICU patients of interventions hypothesized to reduce delirium burden to determine whether interventions that are more effective at reducing delirium duration are associated with a reduction in short-term mortality.
- Data Sources: We searched CINHAHL, EMBASE, MEDLINE, and the Cochrane databases from 2001 to 2012.
- Study Selection: Citations were screened for randomized trials that enrolled critically ill adults, evaluated delirium at least daily, compared a drug or nondrug intervention hypothesized to reduce delirium burden with standard care (or control), and reported delirium duration and/or short-term mortality (≤ 45 d).
- Data Extraction: In duplicate, we abstracted trial characteristics and results and evaluated quality using the Cochrane risk of bias tool. We performed random effects model meta-analyses and meta-regressions.
- Data Synthesis: We included 17 trials enrolling 2,849 patients which evaluated a pharmacologic intervention ($n = 13$) (dexmedetomidine [$n = 6$], an antipsychotic [$n = 4$], rivastigmine [$n = 2$], and clonidine [$n = 1$]), a multimodal intervention ($n = 2$) (spontaneous awakening [$n = 2$]), or a nonpharmacologic intervention ($n = 2$) (early mobilization [$n = 1$] and increased perfusion [$n = 1$]). Overall, average delirium duration was lower in the intervention groups (difference = -0.64 d; 95% CI, -1.15 to -0.13 ; $p = 0.01$) being reduced by more than or equal to 3 days in three studies, **0.1 to less than 3 days in six studies**, **0 day in seven studies**, and less than 0 day in one study. Across interventions, for 13 studies where short-term mortality was reported, short-term mortality was not reduced (risk ratio = 0.90; 95% CI, 0.76–1.06; $p = 0.19$). Across 13 studies that reported mortality, meta-regression revealed that delirium duration was not associated with reduced short-term mortality ($p = 0.11$).
- Conclusions: A review of current evidence fails to support that ICU interventions **that reduce** delirium duration reduce short-term mortality. Larger controlled studies are needed to establish this relationship.

Arterial Blood Gas Tensions After Resuscitation From Out-of-Hospital Cardiac Arrest: Associations With Long-Term Neurologic Outcome*

Vaahersalo, Jukka; Bendel, Stepani; Reinikainen, Matti; More

- Objectives Optimal oxygen and carbon dioxide levels during postcardiac arrest care are currently undefined and observational studies have suggested harm from hyperoxia exposure. We aimed to assess whether mean and time-weighted oxygen and carbon dioxide levels during the first 24 hours of postcardiac arrest care correlate with 12-month neurologic outcome.
- Design Prospective observational cohort study.
- Setting Twenty-one ICUs in Finland.
- Patients Out-of-hospital cardiac arrest patients treated in ICUs in Finland between March 2010 and February 2011.
- Interventions None.
- Measurements and Main Results: Arterial blood Pao₂ and Paco₂ during the first 24 hours from admission were divided into predefined categories from the lowest to the highest. Proportions of time spent in different categories and the mean Pao₂ and Paco₂ values during the first 24 hours were included in separate multivariable regression models along with resuscitation factors. The cerebral performance category at 12 months was used as primary endpoint. A total of 409 patients with arterial blood gases analyzed at least once and with a complete set of resuscitation data were included. The average amount of Pao₂ and Paco₂ measurements was eight per patient. The mean 24 hours Paco₂ level was an independent predictor of good outcome (odds ratio, 1.054; 95% CI, 1.006–1.104; p = 0.027) but the mean Pao₂ value was not (odds ratio, 1.006; 95% CI, 0.998–1.014; p = 0.149). With multivariate regression analysis, time spent in the Paco₂ band **higher than 45 mm Hg** was associated with good outcome (odds ratio, 1.015; 95% CI, 1.002–1.029; p = 0.024, for each percentage point increase in time) but time spent in different oxygen categories were not.
- Conclusions: In this multicenter study, **hypercapnia** was associated with good 12-month outcome in patients resuscitated from out-of-hospital cardiac arrest. We were unable to verify any harm from hyperoxia exposure. Further trials should focus on whether moderate hypercapnia during postcardiac arrest care improves outcome.

In-Hospital Mortality and Long-Term Survival of Patients With Acute Intoxication Admitted to the ICU*

Brandenburg, Raya; Brinkman, Sylvia; de Keizer, Nicolette F.; More

- Objective: To assess in-hospital and long-term mortality of Dutch ICU patients admitted with an acute intoxication.
- Design: Cohort of ICU admissions from a national ICU registry linked to records from an insurance claims database.
- Setting: Eighty-one ICUs (85% of all Dutch ICUs).
- Patients: Seven thousand three hundred thirty-one admissions between January 1, 2008, and October 1, 2011.
- Interventions: None.
- Measurements and Main Results: Kaplan-Meier curves were used to compare the unadjusted mortality of the total intoxicated population and for specific intoxication subgroups based on the Acute Physiology and Chronic Health Evaluation IV reasons for admission: 1) alcohol(s), 2) analgesics, 3) antidepressants, 4) street drugs, 5) sedatives, 6) poisoning (carbon monoxide, arsenic, or cyanide), 7) other toxins, and 8) combinations. The case-mix adjusted mortality was assessed by the odds ratio adjusted for age, gender, severity of illness, intubation status, recurrent intoxication, and several comorbidities. The ICU mortality was 1.2%, and the in-hospital mortality was 2.1%. The mortality 1, 3, 6, 12, and 24 months after ICU admission was 2.8%, 4.1%, 5.2%, 6.5%, and 9.3%, respectively. Street drugs had the highest mortality 2 years after ICU admission (12.3%); a combination of different intoxications had the lowest (6.3%). The adjusted observed mortality showed that intoxications with street drugs and “other toxins” have a significant higher mortality 1 month after ICU admission (odds ratio_{adj} = 1.63 and odds ratio_{adj} = 1.73, respectively). Intoxications with alcohol or antidepressants have a significant lower mortality 1 month after ICU admission (odds ratio_{adj} = 0.50 and odds ratio_{adj} = 0.46, respectively). These differences were not found in the adjusted mortality 3 months upward of ICU admission.
- Conclusions: Overall, the mortality 2 years after ICU admission is relatively low compared with other ICU admissions. The first 3 months after ICU admission there is a difference in mortality between the subgroups, not thereafter. Still, the difference between the in-hospital mortality and the mortality after 2 years is substantial.

Corticosteroids and Transition to Delirium in Patients With Acute Lung Injury*

Schreiber, Matthew P.; Colantuoni, Elizabeth; Bienvenu, Oscar J.; More

- Objective: Delirium is common in mechanically ventilated patients in the ICU and associated with short- and long-term morbidity and mortality. The use of systemic corticosteroids is also common in the ICU. Outside the ICU setting, **corticosteroids are a recognized risk factor for delirium**, but their relationship with delirium in critically ill patients has not been fully evaluated. We hypothesized that systemic corticosteroid administration would be associated with a transition to delirium in mechanically ventilated patients with acute lung injury.
- Design: Prospective cohort study.
- Setting: Thirteen ICUs in four hospitals in Baltimore, MD.
- Patients: Five hundred twenty mechanically ventilated adult patients with acute lung injury.
- Interventions: None.
- Measurements and Main Results: Delirium evaluation was performed by trained research staff using the validated Confusion Assessment Method for the ICU screening tool. A total of 330 of the 520 patients (64%) had at least two consecutive ICU days of observation in which delirium was assessable (e.g., patient was noncomatose), with a total of 2,286 days of observation and a median (interquartile range) of 15 (9, 28) observation days per patient. These 330 patients had 99 transitions into delirium from a prior nondelirious, noncomatose state. The probability of transitioning into delirium on any given day was 14%. Using multivariable Markov models with robust variance estimates, the following factors (adjusted odds ratio; 95% CI) were independently associated with transition to delirium: **older age** (compared to < 40 years old, 40–60 yr [1.81; 1.26–2.62], and ≥ 60 yr [2.52; 1.65–3.87]) and administration of any **systemic corticosteroid in the prior 24 hours** (1.52; 1.05–2.21).
- Conclusions: After adjusting for other risk factors, systemic corticosteroid administration is significantly associated with transitioning to delirium from a nondelirious state. The risk of delirium should be considered when deciding about the use of systemic corticosteroids in critically ill patients with acute lung injury.

Perioperative Levels and Changes of High-Sensitivity Troponin T Are Associated With Cardiovascular Events in Vascular Surgery Patients*

Gillmann, Hans-Jörg; Meinders, Antje; Grohennig, Anika; More

- Objectives: Myocardial infarction after major surgery is frequent, drives outcome, and consumes health resources. Specific prediction and detection of perioperative myocardial infarction is an unmet clinical need. With the widespread use of high-sensitive cardiac troponin T assays, positive tests become frequent, but their diagnostic or prognostic impact is arguable. We, therefore, studied the association of routinely determined pre- and postoperative high-sensitive cardiac troponin T with the occurrence of major adverse cardiac events.
- Design: This study was a prospective noninterventional trial.
- Setting: This study was conducted at Hannover Medical School in Germany.
- Patients: A total of 455 patients undergoing open vascular surgery were followed for 30 days for the occurrence of major adverse cardiac events.
- Interventions: None.
- Measurements and Main Results: Preoperative and 24-hour postoperative high-sensitive cardiac troponin T measurements and the respective changes were correlated to medical history and the occurrence of major adverse cardiac events (cardiovascular death, myocardial infarction, and ischemia). Pre- and postoperative high-sensitive cardiac troponin T measurements demonstrated a majority of patients with detectable troponin levels preoperatively and an increase over the 24 hours after surgery. The level of high-sensitive cardiac troponin T was significantly associated with preexisting diseases that constitute the Lee's Revised Cardiac Risk Index. A preoperative high-sensitive cardiac troponin T greater than or equal to **17.8 ng/L** and a perioperative high-sensitive cardiac troponin T change greater than or equal to **6.3 ng/L** are independently associated with the occurrence of major adverse cardiac events. Adding high-sensitive cardiac troponin T absolute change to the Revised Cardiac Risk Index improves the risk predictive accuracy of the score as evidenced by increased area under receiver operating characteristic and significant reclassification effects.
- Conclusions: The risk predictive power of high-sensitive cardiac troponin T change in addition to the Revised Cardiac Risk Index could facilitate 1) detection of patients at highest risk for perioperative myocardial ischemia, 2) evaluation and development of cardioprotective therapeutic strategies, and 3) decisions for admission to and discharge from high-density care units.

Inducible Protein-10, a Potential Driver of Neurally Controlled Interleukin-10 and Morbidity in Human Blunt Trauma*

Zaaqoq, Akram M.; Namas, Rami; Almahmoud, Khalid; More

- Objective: Blunt trauma and traumatic spinal cord injury induce systemic inflammation that contributes to morbidity. Dysregulated neural control of systemic inflammation postinjury is likely exaggerated in patients with traumatic spinal cord injury. We used *in silico* methods to discern dynamic inflammatory networks that could distinguish systemic inflammation in traumatic spinal cord injury from blunt trauma.
- Design: Retrospective study.
- Settings: Tertiary care institution.
- Patients: Twenty-one severely injured thoracocervical traumatic spinal cord injury patients and matched 21 severely injured blunt trauma patients without spinal cord injury.
- Intervention: None.
- Measurements and Main Results: Serial blood samples were obtained from days 1 to 14 postinjury. Twenty-four plasma inflammatory mediators were quantified. Statistical significance between the two groups was determined by two-way analysis of variance. **Dynamic Bayesian network inference** was used to suggest dynamic connectivity and central inflammatory mediators. Circulating interleukin-10 was significantly elevated in thoracocervical traumatic spinal cord injury group versus non-spinal cord injury group, whereas interleukin-1 β , soluble interleukin-2 receptor- α , interleukin-4, interleukin-5, interleukin-7, interleukin-13, interleukin-17, macrophage inflammatory protein 1 α and 1 β , granulocyte-macrophage colony-stimulating factor, and interferon- γ were significantly reduced in traumatic spinal cord injury group versus non-spinal cord injury group. Dynamic Bayesian network suggested that post-spinal cord injury **interleukin-10 is driven by inducible protein-10**, whereas monocyte chemoattractant protein-1 was central in non-spinal cord injury dynamic networks. In a separate validation cohorts of 356 patients without spinal cord injury and 85 traumatic spinal cord injury patients, individuals with plasma inducible protein-10 levels more than or equal to **730 pg/mL** had significantly prolonged hospital and ICU stay and days on mechanical ventilator versus patients with plasma inducible protein-10 level less than 730 pg/mL.
- Conclusion: This is the first study to compare the dynamic systemic inflammatory responses of traumatic spinal cord injury patients versus patients without spinal cord injury, suggesting a key role for inducible protein-10 in driving systemic interleukin-10 and morbidity and **highlighting the potential utility of *in silico* tools** to identify key inflammatory drivers.

Quality of Communication in Interpreted Versus Noninterpreted PICU Family Meetings*

Van Cleave, Alisa C.; Roosen-Runge, Megan U.; Miller, Alison B.; More

- Objectives: To describe the quality of physician-family communication during interpreted and noninterpreted family meetings in the PICU.
- Design: Prospective, exploratory, descriptive observational study of noninterpreted English family meetings and interpreted Spanish family meetings in the pediatric intensive care setting.
- Setting: A single, university-based, tertiary children's hospital.
- Subjects: Participants in PICU family meetings, including medical staff, family members, ancillary staff, and interpreters.
- Interventions: Thirty family meetings (21 English and nine Spanish) were audio-recorded, transcribed, de-identified, and analyzed using the qualitative method of directed content analysis.
- Measurements and Main Results: Quality of communication was analyzed in three ways: 1) presence of elements of shared decision-making, 2) balance between physician and family speech, and 3) complexity of physician speech. Of the 11 elements of shared decision-making, only four occurred in more than half of English meetings, and only three occurred in more than half of Spanish meetings. Physicians spoke for a mean of 20.7 minutes, while families spoke for 9.3 minutes during English meetings. During Spanish meetings, physicians spoke for a mean of 14.9 minutes versus just 3.7 minutes of family speech. Physician speech complexity received a mean grade level score of 8.2 in English meetings compared to 7.2 in Spanish meetings.
- Conclusions: The quality of physician-family communication during PICU family meetings is poor overall. Interpreted meetings had poorer communication quality as evidenced by fewer elements of shared decision-making and greater imbalance between physician and family speech. However, physician speech may be less complex during interpreted meetings. Our data suggest that physicians can improve communication in both interpreted and noninterpreted family meetings by increasing the use of elements of shared decision-making, improving the balance between physician and family speech, and decreasing the complexity of physician speech.

Early Postresuscitation Hypotension Is Associated With Increased Mortality Following Pediatric Cardiac Arrest*

Topjian, Alexis A.; French, Benjamin; Sutton, Robert M.; More

- Objective: To describe the association of systolic hypotension during the first 6 hours after successful resuscitation from pediatric cardiopulmonary arrest with in-hospital mortality.
- Design: Retrospective cohort study.
- Setting: Fifteen children's hospitals associated with the Pediatric Emergency Care Applied Research Network.
- Patients: Patients between 1 day and 18 years old who had a cardiopulmonary arrest, received chest compressions more than 1 minute, had a return of spontaneous circulation more than 20 minutes, and had a systolic blood pressure documented within 6 hours of arrest.
- Interventions: None.
- Measurements and Main Results: Three hundred eighty-three patients had complete data for analysis. Patients with a documented minimum systolic blood pressure less than fifth percentile for age and sex within the first 6 hours following return of spontaneous circulation were considered to have early postresuscitation hypotension. Two hundred fourteen patients (56%) had early postresuscitation hypotension. One hundred eighty-four patients (48%) died prior to hospital discharge. After controlling for patient and cardiopulmonary arrest characteristics, hypotension in the first 6 hours following return of spontaneous circulation was associated with a significantly increased odds of in-hospital mortality (adjusted odds ratio = 1.71; 95% CI, 1.02–2.89; $p = 0.042$) and odds of unfavorable outcome (adjusted odds ratio = 1.83; 95% CI, 1.06–3.19; $p = 0.032$).
- Conclusions: **In the first 6 hours** following successful resuscitation from pediatric cardiac arrest, systolic hypotension was documented in 56% and was associated with a higher rate of in-hospital mortality and worse hospital discharge neurologic outcomes.

Cross-Sectional Changes in Lung Volume Measured by Electrical Impedance Tomography Are Representative for the Whole Lung in Ventilated Preterm Infants

van der Burg, Pauline S.; Miedema, Martijn; de Jongh, Frans H.; More

- Objective: **Electrical impedance tomography** measures lung volume in a cross-sectional slice of the lung. Whether these cross-sectional volume changes are representative of the whole lung has only been investigated in adults, showing conflicting results. This study aimed to compare cross-sectional and whole lung volume changes using electrical impedance tomography and respiratory inductive plethysmography.
- Design: A prospective, single-center, observational, nonrandomized study.
- Setting: The study was conducted in a neonatal ICU in the Netherlands.
- Patients: High-frequency ventilated preterm infants with respiratory distress syndrome.
- Interventions: Cross-sectional and whole lung volume changes were continuously and simultaneously measured by, respectively, electrical impedance tomography and respiratory inductive plethysmography during a stepwise recruitment procedure. End-expiratory lung volume changes were assessed by mapping the inflation and deflation limbs using both the pressure/impedance and pressure/inductance pairs and characterized by calculating the inflection points. In addition, oscillatory tidal volume changes were assessed at each pressure step.
- Measurements and Main Results: Twenty-three infants were included in the study. Of these, eight infants had to be excluded because the quality of the registration was insufficient for analysis (two electrical impedance tomography and six respiratory inductive plethysmography). In the remaining 15 infants (gestational age 28.0 ± 2.6 wk; birth weight $1,027 \pm 514$ g), end-expiratory lung volume changes measured by electrical impedance tomography were significantly correlated to **respiratory inductive plethysmography measurements** in 12 patients (mean $r = 0.93 \pm 0.05$). This was also true for the upper inflection point on the inflation ($r = 0.91$, $p < 0.01$) and deflation limb ($r = 0.83$, $p < 0.01$). In 13 patients, impedance and inductance data also correlated significantly on oscillatory tidal volume/pressure relationships (mean $r = 0.81 \pm 0.18$).
- Conclusions: This study shows that cross-sectional lung volume changes measured by electrical impedance tomography are representative for the whole lung and that this concept also applies to newborn infants.

Neuronal Nitric Oxide Synthase and Its Interaction With Soluble Guanylate Cyclase Is a Key Factor for the Vascular Dysfunction of Experimental Sepsis*

Nardi, Geisson M.; Scheschowitsch, Karin; Ammar, Dib; More

- Objective: Vascular dysfunction plays a central role in sepsis, and it is characterized by hypotension and hyporesponsiveness to vasoconstrictors. Nitric oxide is regarded as a central element of sepsis vascular dysfunction. The high amounts of nitric oxide produced during sepsis are mainly derived from the inducible isoform of nitric oxide synthase 2. We have previously shown that nitric oxide synthase 2 levels decrease in later stages of sepsis, whereas levels and activity of soluble guanylate cyclase increase. Therefore, we studied the putative role of other relevant nitric oxide sources, namely, the neuronal (nitric oxide synthase 1) isoform, in sepsis and its relationship with soluble guanylate cyclase. We also studied the consequences of nitric oxide synthase 1 blockade in the hyporesponsiveness to vasoconstrictors.
- Subjects: Female Wistar rats submitted to cecal ligation and puncture method.
- Interventions: 1) Six, 12, and 24 hours after cecal ligation and puncture, vascular reactivity to phenylephrine (3 and 30 nmol/kg) before and after 7-nitroindazole (45 $\mu\text{mol/kg}$, s.c.) or aminoguanidine (30 $\mu\text{mol/kg}$, s.c.) administration was evaluated. 2) Protein levels and interaction between nitric oxide synthase 1 and soluble guanylate cyclase were determined. 3) Six, 12, and 24 hours after cecal ligation and puncture, **thoracic aorta segments** were stimulated with phenylephrine in the presence or absence of 7-nitroindazole and cyclic guanosine monophosphate accumulation was determined. 4) After 24 hours of cecal ligation and puncture, norepinephrine was infused (10 $\mu\text{g/kg/min}$) in the presence or absence of 7-nitroindazole or S-methyl-l-thiocitrulline (1 $\mu\text{mol/kg}$, IV) and mean arterial pressure was registered.
- Measurements and Main Results: 1) Both nitric oxide synthase 1 and soluble guanylate cyclase are expressed in **higher levels in vascular tissues** during sepsis; 2) both proteins physically interact and nitric oxide synthase 1 blockade inhibits cyclic guanosine monophosphate production; 3) pharmacological **blockade of nitric oxide synthase 1** using 7-nitroindazole or S-methyl-l-thiocitrulline reverts the hyporesponsiveness to phenylephrine and increases the vasoconstrictor effect of norepinephrine and phenylephrine.
- Conclusions: Sepsis induces increased expression and physical association of **nitric oxide synthase 1/soluble guanylate cyclase** and a higher production of **cyclic guanosine monophosphate** that together may help explain sepsis-induced vascular dysfunction. In addition, selective inhibition of nitric oxide synthase 1 restores the responsiveness to vasoconstrictors. Therefore, inhibition of nitric oxide synthase 1 (and possibly soluble guanylate cyclase) may represent a valuable alternative to restore the effectiveness of vasopressor agents during late sepsis.

Effects of Renal Denervation on Regional Hemodynamics and Kidney Function in Experimental Hyperdynamic Sepsis

Calzavacca, Paolo; Bailey, Michael; Velkoska, Elena; More

- Objective: To determine the influence of the renal sympathetic nerves on the pathogenesis of septic acute kidney injury.
- Design: Interventional control study to determine the effects of renal denervation in ovine hyperdynamic sepsis.
- Setting: Research Institute.
- Subjects: Twenty-four adult Merino ewes.
- Interventions: The effects of infusion of angiotensin II and norepinephrine and induction of hyperdynamic sepsis by administration of live *Escherichia coli* were examined in control sheep and in sheep at 2 weeks after bilateral renal denervation (n = 10/group).
- Measurements and Main Results: Systemic hemodynamics and renal function were measured in conscious sheep instrumented with flow probes on the pulmonary and renal arteries. Angiotensin II, but not norepinephrine, had a greater pressor effect in denervated animals. **Sepsis increased cardiac output by 60%, renal blood flow by 35%, and arterial lactate by approximately four-fold.** The denervated compared with the control group had a greater degree of hypotension during sepsis (68 vs 81 mm Hg; p = 0.003) and a reduction in the early polyuric response (from 496 to 160 mL at 2–8 hr of sepsis; p < 0.001). Creatinine clearance decreased similarly in both groups.
- Conclusions: In experimental hyperdynamic sepsis, renal denervation was associated with greater hypotension and a loss of the initial diuresis, but no significant change in creatinine clearance. In sepsis, the renal nerves help support arterial pressure and determine the initial diuretic response, but septic acute kidney injury developed **similarly** in the innervated and denervated groups.

Effects of Levosimendan on Hemodynamics, Local Cerebral Blood Flow, Neuronal Injury, and Neuroinflammation After Asphyctic Cardiac Arrest in Rats

Kelm, Robert F.; Wagenführer, Jürgen; Bauer, Henrike; More

- **Objectives:** Despite advances in cardiac arrest treatment, high mortality and morbidity rates after successful cardiopulmonary resuscitation are still a major clinical relevant problem. The post cardiac arrest syndrome subsumes myocardial dysfunction, impaired microcirculation, systemic inflammatory response, and neurological impairment. The calcium-sensitizer levosimendan was able to improve myocardial function and initial resuscitation success after experimental cardiac arrest/cardiopulmonary resuscitation. We hypothesized that levosimendan exerts beneficial effects on cerebral blood flow, neuronal injury, neurological outcome, and inflammation 24 hours after experimental cardiac arrest/cardiopulmonary resuscitation.
- **Subjects:** Sixty-one male Sprague-Dawley rats.
- **Interventions:** Animals underwent asphyxial cardiac arrest/cardiopulmonary resuscitation, randomized to groups with levosimendan treatment (bolus 12 µg/kg and infusion for 3 hr [0.3 µg/min/kg]) or vehicle (saline 0.9% bolus and infusion for 3 hr [equivalent fluid volume]). Cardiac index, local cerebral blood flow, and hemodynamic variables were measured for 180 minutes after cardiac arrest/cardiopulmonary resuscitation. Behavioral and neurological evaluations were conducted 24 hours after cardiac arrest/cardiopulmonary resuscitation. Furthermore, neuronal injury, expressed as Fluoro-Jade B–positive cells in the hippocampal formation, cortical and hippocampal inflammatory cytokine gene expression, and blood plasma interleukin-6 values were assessed.
- **Measurements and Main Results:** Treatment with levosimendan reduced neuronal injury and improved neurological outcome after 24 hours of reperfusion and resulted in elevated cardiac index and local cerebral blood flow compared with vehicle after cardiac arrest/cardiopulmonary resuscitation. Mean arterial blood pressure was reduced during the early reperfusion period in the levosimendan group. Cortical and hippocampal inflammatory cytokine gene expression and blood plasma interleukin-6 levels were not influenced.
- **Conclusions:** Levosimendan(左西孟旦) **increased cerebral blood flow** after experimental cardiac arrest/cardiopulmonary resuscitation. This effect coincided with reduced neuronal injury and improved neurologic outcome. Findings seem to be independent of inflammatory effects because no effects by levosimendan on cerebral or systemic inflammation could be detected. In summary, levosimendan is a promising agent to improve neurological outcome after cardiac arrest/cardiopulmonary resuscitation.

Local Burn Injury Impairs Epithelial Permeability and Antimicrobial Peptide Barrier Function in Distal Unburned Skin*

Plichta, Jennifer K.; Droho, Steve; Curtis, Brenda J.; More

- Objectives: Our objective was to characterize the mechanisms by which local burn injury compromises epithelial barrier function in burn margin, containing the elements necessary for healing of the burn site, and in distal unburned skin, which serves as potential donor tissue.
- Subjects: C57/Bl6 Male mice, 8–12 weeks old.
- Interventions: To confirm that dehydration was not contributing to our observed barrier defects, in some experiments mice received 1 mL of saline fluid immediately after burn, while a subgroup received an additional 0.5 mL at 4 hours and 1 mL at 24 hours following burn. We then assessed skin pH and transepidermal water loss every 12 hours on the burn wounds for 72 hours postburn.
- Measurements and Main Results: Burn margin exhibited increased epidermal barrier permeability indicated by higher pH, greater transepidermal water loss, and reduced lipid synthesis enzyme expression and structural protein production up to 96 hours postburn. By contrast, antimicrobial peptide production and protease activity were elevated in burn margin. Skin extracts from burn margin did not exhibit changes in the ability to inhibit bacterial growth. However, distal unburned skin from burned mice also demonstrated an impaired response to barrier disruption, indicated by elevated transepidermal water loss and reduced lipid synthesis enzyme and structural protein expression up to 96 hours postburn. Furthermore, skin extracts from distal unburned skin exhibited greater protease activity and a reduced capacity to inhibit bacterial growth of several skin pathogens. Finally, we established that antimicrobial peptide levels were also altered in the lung and bladder, which are common sites of secondary infection in burn-injured patients.
- Conclusions: These findings reveal several undefined deficiencies in epithelial barrier function at the **burn margin, potential donor skin sites, and organs susceptible to secondary infection**. These functional and biochemical data provide novel insights into the mechanisms for graft failure and secondary infection after burn injury.

Advantages of Strain Echocardiography in Assessment of Myocardial Function in Severe Sepsis: An Experimental Study*

Hestenes, Siv M.; Halvorsen, Per S.; Skulstad, Helge; More

- Objectives: Cardiovascular failure is an important feature of severe sepsis and mortality in sepsis. The aim of our study was to explore myocardial dysfunction in severe sepsis.
- Design: Prospective experimental study.
- Setting: Operating room at Intervention Centre, Oslo University Hospital.
- Subjects: Eight Norwegian Landrace pigs.
- Interventions: The pigs were anesthetized, a medial sternotomy performed and miniature sensors for wall-thickness measurements attached to the epicardium and invasive pressure monitoring established, and an infusion of *Escherichia coli* started. Hemodynamic response was monitored and myocardial strain assessed by echocardiography.
- Measurements and Main Results: Left ventricular myocardial function was significantly reduced assessed by longitudinal myocardial strain ($-17.2\% \pm 2.8\%$ to $-12.3\% \pm 3.2\%$, $p = 0.04$), despite a reduced afterload as expressed by the left ventricular end-systolic meridional wall stress (35 ± 13 to 18 ± 8 kdyn/cm², $p = 0.04$). Left ventricular ejection fraction remained unaltered ($48\% \pm 7\%$ to $49\% \pm 5\%$, $p = 0.4$) as did cardiac output (6.3 ± 1.3 to 5.9 ± 3 L/min, $p = 0.7$). The decline in left ventricular function was further supported by significant reductions in the index of regional work by pressure-wall thickness loop area (121 ± 45 to 73 ± 37 mm × mm Hg, $p = 0.005$). Left ventricular myocardial wall thickness increased in both end diastole (11.5 ± 2.7 to 13.7 ± 2.4 mm, $p = 0.03$) and end systole (16.1 ± 2.9 to 18.5 ± 1.8 mm, $p = 0.03$), implying edema of the left ventricular myocardial wall. Right ventricular myocardial function by strain was reduced ($-24.2\% \pm 4.1\%$ to $-16.9\% \pm 5.7\%$, $p = 0.02$). High right ventricular pressures caused septal shift as demonstrated by the end-diastolic transseptal pressure gradient (4.1 ± 3.3 to -2.2 ± 5.8 mm Hg, $p = 0.01$).
- Conclusions: The present study demonstrates myocardial dysfunction in severe sepsis. Strain echocardiography reveals myocardial dysfunction **before** significant changes in ejection fraction and cardiac output and could prove to be a useful tool in clinical evaluation of septic patients.

Depletion of Natural Killer Cells Increases Mice Susceptibility in a *Pseudomonas aeruginosa* Pneumonia Model*

Broquet, Alexis; Roquilly, Antoine; Jacqueline, Cédric; More

- Objectives: *Pseudomonas aeruginosa* infection is a clinically relevant infection involved in pneumonia in ICUs. Understanding the type of immune response initiated by the host during pneumonia would help defining new strategies to interfere with the bacteria pathogenicity. In this setting, the role of natural killer cells remains controversial. We assessed the role of systemic natural killer cells in a *Pseudomonas aeruginosa* mouse pneumonia model.
- Design: Experimental study.
- Setting: Research laboratory from a university hospital.
- Subjects: RjOrl:SWISS and BALB/cJ mice (weight, 20–24 g).
- Interventions: Lung injuries were assessed by bacterial load, myeloperoxidase activity, endothelial permeability (pulmonary edema), immune cell infiltrate (histological analysis), proinflammatory cytokine release, and Ly6-G immunohistochemistry. Bacterial loads were assessed in the lungs and spleen. Natural killer cell number and status were assessed in spleen (flow cytometry and quantitative polymerase chain reaction). Depletion of natural killer cells was achieved through an IV anti-asialo-GM1 antibody injection.
- Measurements and Main Results: *Pseudomonas aeruginosa* tracheal instillation led to an acute pneumonia with a rapid decrease of bacterial load in lungs and with an increase of endothelial permeability, proinflammatory cytokines (tumor necrosis factor- α and interleukin- 1β), and myeloperoxidase activity followed by Ly6-G positive cell infiltrate in lungs. *Pseudomonas aeruginosa* was detected in the spleen. Membrane markers of activation and maturation (CD69 and KLRG1 molecules) were increased in splenic natural killer cells during *Pseudomonas aeruginosa* infection. Splenic natural killer cells activated upon *Pseudomonas aeruginosa* infection produced interferon- γ but not interleukin-10. Ultimately, mice depleted of natural killer cells displayed an increased neutrophil numbers in the lungs and an increased mortality rate without bacterial load modifications in the lungs, indicating that mice depleted of natural killer cells were much more susceptible to infection compared with control animals.
- Conclusions: We report for the first time that natural killer cells play a major role in the mice susceptibility toward a *Pseudomonas aeruginosa*-induced acute pneumonia model.

Low Respiratory Rate Plus Minimally Invasive Extracorporeal Co2 Removal Decreases Systemic and Pulmonary Inflammatory Mediators in Experimental Acute Respiratory Distress Syndrome*

Grasso, Salvatore; Stripoli, Tania; Mazzone, Palma; More

- Objective: The Acute Respiratory Distress Syndrome Network protocol recommends limiting tidal volume and plateau pressure; it also recommends increasing respiratory rate to **prevent hypercapnia**. We tested a strategy that combines the low tidal volume with lower respiratory rates and minimally invasive Co2 removal.
- Subjects: Ten lung-damaged pigs (instilled hydrochloride).
- Interventions: Two conditions randomly applied in a crossover fashion: the Acute Respiratory Distress Syndrome Network protocol and the Acute Respiratory Distress Syndrome Network protocol plus lower respiratory rate plus minimally invasive Co2 removal. A similar arterial Co2 partial pressure was targeted in the two conditions.
- Measurements and Main Results: Physiological parameters, computed tomography scans, plasma and bronchoalveolar lavage concentrations of interleukin-1 β , interleukin-6, interleukin-8, interleukin-10, interleukin-18, and tumor necrosis factor- α . During the lower respiratory rate condition, respiratory rate was reduced from 30.5 ± 3.8 to 14.2 ± 3.5 ($p < 0.01$) breaths/min and minute ventilation from 10.4 ± 1.6 to 4.9 ± 1.7 L/min ($p < 0.01$). The **extracorporeal device** removed $38.9\% \pm 6.1\%$ (79.9 ± 18.4 mL/min) of Co2 production. During the lower respiratory rate condition, interleukin-6, interleukin-8, and tumor necrosis factor- α concentrations were significantly lower in plasma; interleukin-6 and tumor necrosis factor- α concentrations were lower in bronchoalveolar lavage, whereas the concentrations of the other cytokines remained unchanged.
- Conclusion: The strategy of lower respiratory rate plus minimally invasive extracorporeal Co2 removal was feasible and safe and, as compared with the Acute Respiratory Distress Syndrome Network protocol, reduced the concentrations of some, but not all, of the tested cytokines without affecting respiratory mechanics, gas exchange, and hemodynamics.

Increased Activation of the Rho-A/Rho-Kinase Pathway in the Renal Vascular System Is Responsible for the Enhanced Reactivity to Exogenous Vasopressin in Endotoxemic Rats*

Guarido, Karla L.; Gonçalves, Ronald P. M.; Júnior, Arquimedes Gasparotto;
More

- Objective: We evaluated the role of the renal vascular system and the Rho-A/Rho-kinase pathway in the maintenance of the pressor effects of vasopressin in endotoxemic rats.
- Design: In vitro and in vivo animal study.
- Setting: University research laboratory.
- Subjects: Male Wistar rats (200–300 g).
- Intervention: Rats received either saline or lipopolysaccharide (10 mg/kg, intraperitoneal) 6 or 24 hours before the experiments. The effects of vasopressin on isolated aortic rings, cardiac function, mean arterial pressure, and both the renal vascular perfusion pressure of perfused kidneys in vitro and renal blood flow in situ were evaluated. The role of Rho-kinase in the renal and systemic effects of vasopressin was investigated through administration of the selective inhibitor Y-27632 and Western blot analysis.
- Measurements and Main Results: The effect of vasopressin on mean arterial pressure was unaltered and that on renal vascular perfusion pressure enhanced in endotoxemic rats at both 6 and 24 hours after lipopolysaccharide, despite reduced contractile responses in aortic rings and the lack of effect on cardiac function. Vasopressin (3, 10, and 30 pmol/kg, IV) produced increased reduction in renal blood flow in endotoxemic rats. In perfused kidneys from lipopolysaccharide groups, administration of Y-27632 reverted the hyperreactivity to vasopressin. Treatment with Y-27632 partially inhibited the effects of vasopressin on mean arterial pressure and significantly reduced the effects of vasopressin on renal blood flow in control but not in endotoxemic rats. Although the protein levels of Rho-A and Rho-kinase I and II had not been impaired, the levels of phosphorylated myosin phosphatase–targeting subunit 1, the regulatory subunit of myosin phosphatase that is inhibited by Rho-kinase, were increased in both the renal cortex and the renal medulla of endotoxemic rats.
- Conclusion: Our data suggest that activation of Rho-kinase potentiates the vascular effects of vasopressin in the kidneys, contributing to the maintenance of the hypertensive effects of this agent during septic shock.

Acute Insulin Resistance Mediated by Advanced Glycation Endproducts in Severely Burned Rats

Zhang, Xing; Xu, Jie; Cai, Xiaoqing; More

- Objective:Hyperglycemia often occurs in severe burns; however, the underlying mechanisms and importance of managing postburn hyperglycemia are not well recognized. This study was designed to investigate the dynamic changes of postburn hyperglycemia and the underlying mechanisms and to evaluate whether early glycemic control is beneficial in severe burns.
- Design:Prospective, randomized experimental study.
- Setting:Animal research laboratory.
- Subjects:Sprague-Dawley rats.
- Interventions:Anesthetized rats were subjected to a full-thickness burn injury comprising 40% of the total body surface area and were randomized to receive vehicle, insulin, and a soluble form of receptor for advanced glycation endproducts treatments. An in vitro study was performed on cultured H9C2 cells subjected to vehicle or carboxymethyllysine treatment.
- Measurements and Main Results:We found that blood glucose change presented a distinct pattern with two occurrences of hyperglycemia at 0.5- and 3-hour postburn, respectively. Acute insulin resistance evidenced by impaired insulin signaling and glucose uptake occurred at 3-hour postburn, which was associated with the second hyperglycemia and positively correlated with mortality. Mechanistically, we found that serum carboxymethyllysine, a dominant species of advanced glycation endproducts, increased within 1-hour postburn, preceding the occurrence of insulin resistance. More importantly, treatment of animals with soluble form of receptor for advanced glycation endproducts, blockade of advanced glycation endproducts signaling, alleviated severe burn–induced insulin resistance. In addition, early hyperglycemic control with insulin not only reduced serum carboxymethyllysine but also blunted postburn insulin resistance and reduced mortality.
- Conclusions:These findings suggest that severe burn–induced insulin resistance is partly at least mediated by serum advanced glycation endproducts and positively correlated with mortality. Early glycemic control with insulin or inhibition of advanced glycation endproducts with soluble form of receptor for advanced glycation endproducts ameliorates postburn insulin resistance.

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Effectiveness and Safety of the Awakening and Breathing Coordination, Delirium Monitoring/Management, and Early Exercise/Mobility Bundle*

Balas, Michele C.; Vasilevskis, Eduard E.; Olsen, Keith M.; More

- Objective: The debilitating and persistent effects of ICU-acquired delirium and weakness warrant testing of prevention strategies. The purpose of this study was to evaluate the effectiveness and safety of implementing the **Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility bundle** into everyday practice.
- Design: Eighteen-month, prospective, cohort, before-after study conducted between November 2010 and May 2012.
- Setting: Five adult ICUs, one step-down unit, and one oncology/hematology special care unit located in a 624-bed tertiary medical center.
- Patients: Two hundred ninety-six patients (146 prebundle and 150 postbundle implementation), who are 19 years old or older, managed by the institutions' medical or surgical critical care service.
- Interventions: Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility bundle.
- Measurements and Main Results: For mechanically ventilated patients (n = 187), we examined the association between bundle implementation and ventilator-free days. For all patients, we used regression models to quantify the relationship between Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility bundle implementation and the prevalence/duration of delirium and coma, early mobilization, mortality, time to discharge, and change in residence. Safety outcomes and bundle adherence were monitored. Patients in the postimplementation period spent three more days breathing without mechanical assistance than did those in the preimplementation period (median [interquartile range], 24 [7–26] vs 21 [0–25]; p = 0.04). After adjusting for age, sex, severity of illness, comorbidity, and mechanical ventilation status, patients managed with the Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility bundle experienced a near halving of the odds of delirium (odds ratio, 0.55; 95% CI, 0.33–0.93; p = 0.03) and increased odds of mobilizing out of bed at least once during an ICU stay (odds ratio, 2.11; 95% CI, 1.29–3.45; p = 0.003). No significant differences were noted in self-extubation or reintubation rates.
- Conclusions: Critically ill patients managed with the Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility bundle spent **three more days** breathing without assistance, experienced **less delirium**, and were **more likely to be mobilized** during their ICU stay than patients treated with usual care.

Infection Hospitalization Increases Risk of Dementia in the Elderly*

Tate, Judith A.; Snitz, Beth E.; Alvarez, Karina A.; More

- Objectives: Severe infections, often requiring ICU admission, have been associated with persistent cognitive dysfunction. Less severe infections are more common and whether they are associated with an increased risk of dementia is unclear. We determined the association of pneumonia hospitalization with risk of dementia in well-functioning older adults.
- Design: Secondary analysis of a randomized multicenter trial to determine the effect of *Gingko biloba* on incident dementia.
- Setting: Five academic medical centers in the United States.
- Subjects: Healthy community volunteers (n = 3,069) with a median follow-up of 6.1 years.
- Interventions: None.
- Measurement and Main Results: We identified pneumonia hospitalizations using International Classification of Diseases, 9th Edition—Coding Manual codes and validated them in a subset. Less than 3% of pneumonia cases necessitated ICU admission, mechanical ventilation, or vasopressor support. Dementia was adjudicated based on **neuropsychological evaluation, neurological examination, and MRI**. Two hundred twenty-one participants (7.2%) incurred at least one hospitalization with pneumonia (mean time to pneumonia = 3.5 yr). Of these, dementia was developed in 38 (17%) after pneumonia, with half of these cases occurring 2 years after the pneumonia hospitalization. Hospitalization with pneumonia was associated with increased risk of time to dementia diagnosis (unadjusted hazard ratio = 2.3; CI, 1.6–3.2; p < 0.0001). The association remained significant when adjusted for age, sex, race, study site, education, and baseline mini-mental status examination (hazard ratio = 1.9; CI, 1.4–2.8; p < 0.0001). Results were unchanged when additionally adjusted for smoking, hypertension, diabetes, heart disease, and preinfection functional status. Results were similar using propensity analysis where participants with pneumonia were matched to those without pneumonia based on age, probability of developing pneumonia, and similar trajectories of cognitive and physical function prior to pneumonia (adjusted prevalence rates, 91.7 vs 65 cases per 1,000 person-years; adjusted prevalence rate ratio = 1.6; CI, 1.06–2.7; p = 0.03). Sensitivity analyses showed that the higher risk also occurred among those hospitalized with other infections.
- Conclusion: **Hospitalization with pneumonia is associated with increased risk of dementia.**

Comparison of Severity-of-Illness Scores in Critically Ill Obstetric Patients: A 6-Year Retrospective Cohort*

Rojas-Suarez, José; Paternina-Caicedo, Angel J.; Miranda, Jezid; More

- Objective: The purpose of this research was to evaluate the discrimination and calibration of mortality prediction of Simplified Acute Physiology Score 2, Simplified Acute Physiology Score 3, Mortality Probability Model II, and Mortality Probability Model III in peripartum women.
- Design: A retrospective cohort study.
- Setting: Rafael Calvo Maternity Hospital, a large teaching hospital in Cartagena (Colombia).
- Patients: All obstetric patients admitted to the ICU from 2006 to 2011.
- Interventions: None.
- Measurements and Main Results: Seven hundred twenty-six obstetric critical care patients were included. All scores showed good discrimination (area under the receiver operator characteristic curve > 0.86). Simplified Acute Physiology Score 2, Simplified Acute Physiology Score 3, and Mortality Probability Model III **inaccurately** estimated mortality. The only mortality prediction score that showed good calibration through mortality ratio and Hosmer-Lemeshow test was **Mortality Probability Model II**. Mortality ratio for Mortality Probability Model II was 0.88 (95% CI, 0.60–1.25). Hosmer-Lemeshow test was not significant ($p = 0.571$).
- Conclusions: Simplified Acute Physiology Score 2 and Simplified Acute Physiology Score 3 overestimate mortality in obstetric critical care patients. Mortality Probability Model III was inadequately calibrated. Mortality Probability Model II showed good fit to predict mortality in a developing country setting. Future studies in developed and developing countries are needed to further confirm our findings.

Hospital Factors Associated With Discharge Bias in ICU Performance Measurement*

Reineck, Lora A.; Pike, Francis; Le, Tri Q.; More

- **Objective:** Performance assessments based on in-hospital mortality for ICU patients can be affected by discharge practices such that differences in mortality may reflect variation in discharge patterns rather than quality of care. Time-specific mortality rates, such as 30-day mortality, are preferred but are harder to measure. The degree to which the difference between 30-day and in-hospital ICU mortality rates—or “discharge bias”—varies by hospital type is unknown. The aim of this study was to quantify variation in discharge bias across hospitals and determine the hospital characteristics associated with greater discharge bias.
- **Design:** Retrospective cohort study.
- **Setting:** Nonfederal Pennsylvania hospital discharges in 2008.
- **Patients:** Eligible patients were 18 years old or older and admitted to an ICU.
- **Interventions:** None.
- **Measurements and Main Results:** We used logistic regression with hospital-level random effects to calculate hospital-specific risk-adjusted 30-day and in-hospital mortality rates. We then calculated discharge bias, defined as the difference between 30-day and in-hospital mortality rates, and used multivariable linear regression to compare discharge bias across hospital types. A total of 43,830 patients and 134 hospitals were included in the analysis. Mean (sd) risk-adjusted hospital-specific in-hospital and 30-day ICU mortality rates were 9.6% (1.3) and 12.7% (1.5), respectively. Hospital-specific discharge biases ranged from –1.3% to 6.6%. Discharge bias was smaller in large hospitals compared with small hospitals, making **large hospitals** appear comparatively **worse** from a benchmarking standpoint when using in-hospital mortality instead of 30-day mortality.
- **Conclusions:** Discharge practices bias in-hospital ICU mortality measures in a way that disadvantages large hospitals. Accounting for discharge bias will prevent these hospitals from being unfairly disadvantaged in public reporting and pay-for-performance.

Low Preoperative Cholesterol Level Is a Risk Factor of Sepsis and Poor Clinical Outcome in Patients Undergoing Cardiac Surgery With Cardiopulmonary Bypass*

Lagrost, Laurent; Girard, Claude; Grosjean, Sandrine; More

- **Objectives:** Systemic inflammatory response syndrome and sepsis frequently occur after cardiac surgery with cardiopulmonary bypass. The aim of the present study was to investigate whether preoperative cholesterol levels can predict sepsis onset and postoperative complications in patients undergoing cardiac surgery with cardiopulmonary bypass.
- **Patients:** Two hundred and seventeen consecutive patients older than 18 years admitted for planned cardiac surgery with cardiopulmonary bypass.
- **Interventions:** Measurements of plasma blood lipids and inflammation markers before anesthesia induction (baseline), at cardiopulmonary bypass start, at cardiopulmonary bypass end, and 3 and 24 hours after cardiac surgery. Outcomes were compared in systemic inflammatory response syndrome patients with sepsis (n = 15), systemic inflammatory response syndrome patients without sepsis (n = 95), and non-systemic inflammatory response syndrome patients (n = 107).
- **Measurements and Main Results:** A **gradual decrease** in plasma cholesterol concentration occurred during surgery with cardiopulmonary bypass but was **no longer present** after correction for hemodilution. Corrected cholesterol levels were significantly **lower** at baseline in sepsis patients than in other subgroups, and it remained lower in the sepsis group during and after cardiopulmonary bypass. With regard to sepsis, the discriminatory power of baseline cholesterol was fairly good as indicated by receiver operating characteristic curve analysis (area under the curve, 0.78; 95% CI, 0.72–0.84). The frequency of sepsis progressively decreased with increasing baseline cholesterol level quintiles (18.6% and 0% in the bottom and top quintiles, respectively, p = 0.005). In multivariate analysis, **baseline cholesterol levels** and cardiopulmonary bypass **duration** were significant and independent determinants of the 3-hour postcardiopulmonary bypass increase in concentrations of **procalcitonin and interleukin-8**, but not of interleukin-6.
- **Conclusions:** Low cholesterol levels before elective cardiac surgery with cardiopulmonary bypass may be a simple biomarker for the early identification of patients with a high risk of sepsis.

Risk Factors and Outcome Analysis of Acinetobacter baumannii Complex Bacteremia in Critical Patients*

Lee, Hao-Yuan; Chen, Chyi-Liang; Wu, Si-Ru; More

- Objectives: Acinetobacter baumannii complex bacteremia has been identified increasingly in critical patients admitted in ICUs. Notably, A. baumannii complex bacteremia has a high mortality rate, yet the risk factors associated with mortality remain unclear and controversial.
- SETTING: All adult ICUs at a tertiary care medical center.
- Patients: All patients with A. baumannii complex bacteremia admitted in 2009–2010.
- Interventions: None.
- Measurements and Main Results: Risk factors for mortality were analyzed. Bacterial isolates were identified by 16S-23S ribosomal RNA intergenic spacer region sequencing for genospecies and genotyped by pulsed-field gel electrophoresis. Carbapenemase genes were detected by polymerase chain reaction and sequencing. A total of 298 patients met the inclusion criteria, including 73 (24.5%) infected by imipenem-resistant A. baumannii complex. The overall 30-day mortality was **33.6% (100 of 298)**. Imipenem-resistant A. baumannii complex bacteremia specifically showed **a high mortality (69.9%)** and was associated with prior use of **broad-spectrum antibiotics for more than 5 days** for treating ventilator-associated pneumonia before the occurrence of bacteremia. Mortality was associated with inappropriate initial antimicrobial therapy, which was correlated with imipenem-resistant A. baumannii complex but not with any specific genospecies. ISAbal-blaOXA-23-ISAbal (Tn2006) was found in most (66.7%, 40 of 68) imipenem-resistant A. baumannii (genospecies 2) and also spread beyond species border to all imipenem-resistant genospecies 3 (2), 13TU (2), and 10 (1).
- Conclusions: For critical patients with A. baumannii complex infection, ventilator-associated pneumonia in particular, the selective pressure from prior use of broad-spectrum antibiotics for 5 days or more increased risk of subsequent imipenem-resistant A. baumannii complex bacteremia. To reduce mortality, rapid identification of imipenem-resistant A. baumannii complex and early initiation of appropriate antimicrobial therapy in these high-risk patients are crucial.

Impact of Critical Care Nursing on 30-Day Mortality of Mechanically Ventilated Older Adults*

Kelly, Deena M.; Kutney-Lee, Ann; McHugh, Matthew D.; More

- **Objectives:**The mortality rate for mechanically ventilated older adults in ICUs is high. A robust research literature shows a significant association between nurse staffing, nurses' education, and the quality of nurse work environments and mortality following common surgical procedures. A distinguishing feature of ICUs is greater investment in nursing care. The objective of this study is to determine the extent to which variation in ICU nursing characteristics—staffing, work environment, education, and experience—is associated with mortality, thus potentially illuminating strategies for improving patient outcomes.
- **Design:**Multistate, cross-sectional study of hospitals linking nurse survey data from 2006 to 2008 with hospital administrative data and Medicare claims data from the same period. Logistic regression models with robust estimation procedures to account for clustering were used to assess the effect of critical care nursing on 30-day mortality before and after adjusting for patient, hospital, and physician characteristics.
- **Setting:**Three hundred and three adult acute care hospitals in California, Florida, New Jersey, and Pennsylvania.
- **Patients:**The patient sample included 55,159 older adults on mechanical ventilation admitted to a study hospital.
- **Measurements and Main Results:**Patients in critical care units with better nurse work environments experienced 11% lower odds of 30-day mortality than those in worse nurse work environments. Additionally, each 10% point increase in the proportion of ICU nurses with a bachelor's degree in nursing was associated with a 2% reduction in the odds of 30-day mortality, which implies that the odds on patient deaths in hospitals with 75% nurses with a bachelor's degree in nursing would be 10% lower than in hospitals with 25% nurses with a bachelor's degree in nursing. Critical care nurse staffing did not vary substantially across hospitals. Staffing and nurse experience were not associated with mortality after accounting for these other nurse characteristics.
- **Conclusions:**Patients in hospitals with **better critical care nurse work environments** and higher proportions of critical care nurses with a **bachelor's degree** in nursing experienced significantly lower odds of death.

Levels of Circulating miR-133a Are Elevated in Sepsis and Predict Mortality in Critically Ill Patients

Tacke, Frank; Roderburg, Christoph; Benz, Fabian; More

- **Objective:** Serum levels of microRNA have been proposed as biomarkers in various inflammatory diseases. However, up to now, their clinical relevance in critical illness and sepsis is unclear.
- **Subjects and Patients:** Experimental sepsis model in C57Bl/6 mice; 223 critically ill patients in comparison with 76 healthy volunteers.
- **Interventions:** We used the model of cecal pole ligation and puncture for induction of polymicrobial sepsis in mice and measured alterations in serum levels of six different microRNAs with a known function in inflammatory diseases upon induction of septic disease. These results from mice were translated into a large and well-characterized cohort of critically ill patients admitted to the medical ICU.
- **Measurements and Main Results:** Serum miR-133a was then measured in 223 critically ill patients (138 with sepsis and 85 without sepsis) and 76 controls and associated with disease severity, organ failure, and prognosis. Significant alterations of miR-133a, miR-150, miR-155, and miR-193b* were found in mice after cecal pole ligation and puncture-induced sepsis. Among all regulated microRNAs, miR-133a displayed the most prominent and concordant up-regulation in sepsis, and this microRNA was therefore chosen for further investigation in the human. Here, significantly elevated miR-133a levels were found in critically ill patients at ICU admission, when compared with healthy controls, especially in patients with sepsis. Correlation analyses revealed significant correlations of miR-133a with disease severity, classical markers of inflammation and bacterial infection, and organ failure. Strikingly, high miR-133a levels were predictive for an unfavorable prognosis and represented a strong independent predictor for both ICU and long-term mortality in critically ill patients.
- **Conclusions:** miR-133a serum levels were significantly elevated in critical illness and sepsis. **High miR-133a levels** were associated with the severity of disease and predicted an unfavorable outcome of critically ill patients.

Sex- and Diagnosis-Dependent Differences in Mortality and Admission Cytokine Levels Among Patients Admitted for Intensive Care*

Guidry, Christopher A.; Swenson, Brian R.; Davies, Stephen W.; More

- Objectives: To investigate the role of sex on cytokine expression and mortality in critically ill patients.
- Design: A cohort of patients admitted to were enrolled and followed over a 5-year period.
- Setting: Two university-affiliated hospital surgical and trauma ICUs.
- Patients: Patients 18 years old and older admitted for at least 48 hours to the surgical or trauma ICU.
- Interventions: Observation only.
- Measurements and Main Results: Major outcomes included admission cytokine levels, prevalence of ICU-acquired infection, and mortality during hospitalization conditioned on trauma status and sex. The final cohort included 2,291 patients (1,407 trauma and 884 nontrauma). The prevalence of ICU-acquired infection was similar for men (46.5%) and women (44.5%). All-cause in-hospital mortality was 12.7% for trauma male patient and 9.1% for trauma female patient ($p = 0.065$) and 22.9% for nontrauma male patients and 20.6% for nontrauma female patients ($p = 0.40$). Among trauma patients, logistic regression analysis identified **female sex as protective** for all-cause mortality (odds ratio, 0.57). Among trauma patients, men had significantly higher admission serum levels of **interleukin-2, interleukin-12, interferon- γ , and tumor necrosis factor- α** , and among nontrauma patients, men had higher admission levels of **interleukin-8 and tumor necrosis factor- α** .
- Conclusions: The relationship between sex and outcomes in critically ill patients is complex and depends on underlying illness. Women appear to be better adapted to survive traumatic events, while sex may be less important in other forms of critical illness. The mechanisms accounting for this gender dimorphism may, in part, involve differential cytokine responses to injury, with men expressing a more robust proinflammatory profile.

Short-term decline in all-cause acquired infections with the routine use of a decontamination regimen combining topical polymyxin, tobramycin, and amphotericin B with mupirocin and chlorhexidine in the ICU: a single-center experience

Camus, Christophe; Salomon, Sylvain; Bouchigny, Claire; More

- Objectives: In a multicenter, placebo-controlled, randomized, double-blind trial, we showed that acquired infections in intubated patients were reduced by the combination of topical polymyxin plus tobramycin and nasal mupirocin plus chlorhexidine body wash. Because intubated patients are particularly at risk for acquired infections, we reassessed the impact of this protocol as a routine procedure to control acquired infections in the ICU.
- 多粘菌素，妥布霉素和两性霉素B与莫匹罗星和氯己定
- Design: Nonrandomized study comparing acquired infections in ICU patients during two 1-year periods: the last year before (group A, n = 925) and the first year after the implementation of the protocol (group B, n = 1,022). Acquired infections were prospectively recorded.
- Interventions: Administration of polymyxin/tobramycin/amphotericin B in the oropharynx and the gastric tube plus a mupirocin/chlorhexidine regimen in intubated patients and standard care in the other patients.
- Measurements and Main Results: The comparison of acquired infection rates between groups was adjusted for differences at baseline. Infection rates were lower in group B compared with group A (5.3% vs 11.0%; $p < 0.001$), as were the incidence rates of total acquired infections (9.4 vs 23.6 per 1,000 patient-days; $p < 0.001$), intubation-related pneumonia (5.1 vs 17.1 per 1,000 ventilator-days; $p < 0.001$), and catheter-related bloodstream infections (1.0 vs 3.5 per 1,000 catheter-days; $p = 0.03$). There were fewer acquired infections caused by ceftazidime-resistant Enterobacteriaceae (0.8‰ vs 3.6‰; $p < 0.001$), ciprofloxacin-resistant Enterobacteriaceae (0.8‰ vs 2.5‰; $p = 0.02$), ciprofloxacin-resistant *Pseudomonas aeruginosa* (0.5‰ vs 1.6‰; $p = 0.05$), and colistin-resistant Gram-negative bacilli (0.7‰ vs 1.9‰; $p = 0.04$). Fewer patients got acquired infections due to multidrug-resistant aerobic Gram-negative bacilli ($p = 0.008$).
- Conclusions: In intubated patients, the use of topical polymyxin/tobramycin/amphotericin B plus mupirocin/chlorhexidine was associated with the reduction of all-cause ICU-acquired infections. Long-term emergence of multidrug-resistant organisms deserves further investigation.

A Randomized, Double-Blind, Placebo-Controlled Dose Range Study of Dexmedetomidine as Adjunctive Therapy for Alcohol Withdrawal*

Mueller, Scott W.; Preslaski, Candice R.; Kiser, Tyree H.; More

- Objectives: To evaluate dexmedetomidine as adjunctive therapy to lorazepam for severe alcohol withdrawal.
- Patients: Twenty-four adult patients with a Clinical Institute Withdrawal Assessment score greater than or equal to 15 despite greater than or equal to 16 mg of lorazepam over a 4-hour period.
- Interventions: Patients received a symptom-triggered Clinical Institute Withdrawal Assessment protocol with lorazepam and were randomized to dexmedetomidine 1.2 µg/kg/hr (high dose), 0.4 µg/kg/hr (low dose), or placebo as adjunctive therapy for up to 5 days or resolution of withdrawal symptoms.
- Measurement and Main Results: High-dose and low-dose groups were combined as a single dexmedetomidine group for primary analysis with secondary analysis exploring a dose-response relationship. The difference in 24-hour lorazepam requirements after versus before study drug was greater in the dexmedetomidine group compared with the placebo group (−56 mg vs −8 mg, $p = 0.037$). Median differences were similar for high dose and low dose. The 7-day cumulative lorazepam requirements were not statistically different between dexmedetomidine and placebo (159 mg vs 181 mg). Clinical Institute Withdrawal Assessment or Riker sedation-agitation scale scores representing severe agitation (13% vs 25%) or moderate agitation (27% vs 22%) within 24 hours of initiating study drug were similar for dexmedetomidine and placebo groups, respectively. Bradycardia occurred more frequently in the dexmedetomidine group versus placebo group (25% vs 0%, $p =$ not significant), with the majority of bradycardia occurring in the high-dose group (37.5%). Study drug rate adjustments occurred more often in the dexmedetomidine group compared with the placebo group (50% vs 0%, $p = 0.02$). Neither endotracheal intubation nor seizure occurred in any group while on study drug.
- Conclusions: Adjunctive dexmedetomidine for severe alcohol withdrawal maintains symptom control and reduces lorazepam exposure in the short term, but not long term, when using a symptom-triggered protocol. Monitoring for bradycardia is needed with dexmedetomidine but the occurrence may be lessened with low dose. Further study is needed to evaluate the clinical impact of dexmedetomidine.

Metabolic Profiling of Serum Samples by ^1H Nuclear Magnetic Resonance Spectroscopy as a Potential Diagnostic Approach for Septic Shock*

Mickiewicz, Beata; Duggan, Gavin E.; Winston, Brent W.; More

- Objectives: To determine whether a nuclear magnetic resonance–based metabolomics approach can be useful for the early diagnosis and prognosis of septic shock in ICUs.
- Design: Laboratory-based study.
- Setting: University research laboratory.
- Subjects: Serum samples from septic shock patients and ICU controls (ICU patients with systemic inflammatory response syndrome but not suspected of having an infection) were collected within 24 hours of admittance to the ICU.
- Interventions: None.
- Measurements and Main Results: ^1H nuclear magnetic resonance spectra of septic shock and ICU control samples were analyzed and quantified using a targeted profiling approach. By applying multivariate statistical analysis (e.g., orthogonal partial least squares discriminant analysis), we were able to distinguish the patient groups and detect specific metabolic patterns. Some of the metabolites were found to have a significant impact on the separation between septic shock and control samples. These metabolites could be interpreted in terms of a biological human response to septic shock and they might serve as a biomarker pattern for septic shock in ICUs. Additionally, nuclear magnetic resonance–based metabolomics was evaluated in order to detect metabolic variation between septic shock survivors and nonsurvivors and to predict patient outcome. The area under the receiver operating characteristic curve indicated an excellent predictive ability for the constructed orthogonal partial least squares discriminant analysis models (septic shock vs ICU controls: area under the receiver operating characteristic curve = 0.98; nonsurvivors vs survivors: area under the receiver operating characteristic curve = 1).
- Conclusions: Our results indicate that nuclear magnetic resonance–based metabolic profiling could be used for **diagnosis and mortality prediction** of septic shock in the ICU.

Risk Factors for Postoperative Pneumonia After Cardiac Surgery and Development of a Preoperative Risk Score*

Allou, Nicolas; Bronchard, Regis; Guglielminotti, Jean; More

- Objectives: The aims of this study were, first, to identify risk factors for microbiology-proven postoperative pneumonia after cardiac surgery and, second, to develop and validate a preoperative scoring system for the risk of postoperative pneumonia.
- Design and Setting: A single-center cohort study.
- Patients: All consecutive patients undergoing cardiac surgery between January 2006 and July 2011.
- Interventions: None.
- Measurements and Main Results: Multivariate analysis of risk factors for postoperative pneumonia was performed on data from patients operated between January 2006 and December 2008 (training set). External temporal validation was performed on data from patients operated between January 2009 and July 2011 (validation set). Preoperative variables identified in multivariate analysis of the training set were then used to develop a preoperative scoring system that was validated on the validation set. Postoperative pneumonia occurred in 174 of the 5,582 patients (3.1%; 95% CI, 2.7–3.6). Multivariate analysis identified four risk factors for postoperative pneumonia: **age** (odds ratio, 1.02; 95% CI, 1.01–1.03), **chronic obstructive pulmonary disease** (odds ratio, 2.97; 95% CI, 1.8–4.71), **preoperative left ventricular ejection fraction** (odds ratio, 0.98; 95% CI, 0.96–0.99), and the interaction between **RBC transfusion** during surgery and **duration** of cardiopulmonary bypass (odds ratio, 2.98; 95% CI, 1.96–4.54). A 6-point score including the three preoperative variables then defined two risk groups corresponding to postoperative pneumonia rates of 1.8% (score < 3) and 6.5% (score ≥ 3).
- Conclusion: Assessing preoperative risk factors for postoperative pneumonia with the proposed scoring system could help to implement a preventive policy in high-risk patients with a risk of postoperative pneumonia greater than 4% (i.e., patients with a score ≥ 3).

Outcomes and Complications of Intracranial Pressure Monitoring in Acute Liver Failure: A Retrospective Cohort Study*

Karvellas, Constantine J.; Fix, Oren K.; Battenhouse, Holly; More

- Objective: To determine if intracranial pressure monitor placement in patients with acute liver failure is associated with significant clinical outcomes.
- Patients: Adult critically ill patients with acute liver failure presenting with grade III/IV hepatic encephalopathy (n = 629) prospectively enrolled between March 2004 and August 2011.
- Intervention: Intracranial pressure monitored (n = 140) versus nonmonitored controls (n = 489).
- Measurements and Main Results: Intracranial pressure monitored patients were younger than controls (35 vs 43 yr, $p < 0.001$) and more likely to be on renal replacement therapy (52% vs 38%, $p = 0.003$). Of 87 intracranial pressure monitored patients with detailed information, 44 (51%) had evidence of **intracranial hypertension** (intracranial pressure > 25 mm Hg) and overall 21-day mortality was **higher** in patients with intracranial hypertension (43% vs 23%, $p = 0.05$). During the first 7 days, intracranial pressure monitored patients received **more** intracranial hypertension-directed therapies (mannitol, 56% vs 21%; hypertonic saline, 14% vs 7%; hypothermia, 24% vs 10%; $p < 0.03$ for each). Forty-one percent of intracranial pressure monitored patients received liver transplant (vs 18% controls; $p < 0.001$). Overall 21-day mortality was similar (intracranial pressure monitored 33% vs controls 38%, $p = 0.24$). Where data were available, hemorrhagic complications were rare in intracranial pressure monitored patients (4 of 56 [7%]; three died). When stratifying by **acetaminophen status** and adjusting for confounders, intracranial pressure monitor placement did not impact 21-day mortality in acetaminophen patients ($p = 0.89$). However, intracranial pressure monitor was associated with **increased 21-day mortality** in nonacetaminophen patients (odds ratio, ~ 3.04 ; $p = 0.014$).
- Conclusions: In intracranial pressure monitored patients with acute liver failure, intracranial hypertension is commonly observed. The use of intracranial pressure monitor in acetaminophen acute liver failure did not confer a significant 21-day mortality benefit, whereas in nonacetaminophen acute liver failure, it may be associated with worse outcomes. Hemorrhagic complications from intracranial pressure monitor placement were uncommon and cannot account for mortality trends. Although our results cannot conclusively confirm or refute the utility of intracranial pressure monitoring in patients with acute liver failure, patient selection and ancillary **assessments of cerebral blood flow** likely have a significant role. Prospective studies would be required to conclusively account for confounding by illness severity and transplant.

The Effects of Different IV Fat Emulsions on Clinical Outcomes in Critically Ill Patients*

Edmunds, Christina E.; Brody, Rebecca A.; Parrott, J. Scott; More

- Objective: To examine the effects of different IV fat emulsions on clinical outcomes in critically ill patients.
- Patients: Adult patients who were admitted to the ICU for more than 72 hours, were mechanically ventilated within 48 hours, received exclusive parenteral nutrition for more than or equal to 5 days, and did not change IV fat emulsion type during the data collection period.
- Interventions: Demographic and clinical data were collected for up to 12 days, until death, or discharge from the ICU, whichever came first. Clinical outcomes were recorded at 60 days following ICU admission.
- Measurements: Lipid-free, soybean, medium-chain triglyceride, olive, and fish oils in parenteral nutrition were compared using an adjusted Cox proportional hazard model to examine time to termination of mechanical ventilation alive, time to ICU discharge alive, and time to hospital discharge alive.
- Main Results: A total of 451 patients were included in this study: 70 (15.5%) in the lipid-free group, 223 (49.5%) in the soybean oil group, 65 (14.4%) in the medium-chain triglyceride group, 74 (16.4%) in the olive oil group, and 19 (4.9%) in the fish oil group. When compared with lipid-free parenteral nutrition, patients who received fish oil had a faster time to ICU discharge alive (hazard ratio, 1.84; 95% CI, 1.01–3.34; $p = 0.05$). When compared with soybean oil, patients who received olive oil or fish oil had a shorter time to termination of mechanical ventilation alive (hazard ratio, 1.43; 95% CI, 1.06–1.93; $p = 0.02$ and hazard ratio, 1.67; 95% CI, 1.00–2.81; $p = 0.05$, respectively) and a shorter time to ICU discharge alive (hazard ratio, 1.76; 95% CI, 1.30–2.39; $p < 0.001$ and hazard ratio, 2.40; 95% CI, 1.43–4.03; $p = 0.001$, respectively).
- Conclusions: Use of alternative IV fat emulsions in parenteral nutrition, particularly olive and fish oil, was associated with improved clinical outcomes.

Early Mobilization of Mechanically Ventilated Patients: A 1-Day Point-Prevalence Study in Germany*

Nydahl, Peter; Ruhl, A. Parker; Bartoszek, Gabriele; More

- Objectives: There is growing evidence to support early mobilization of adult mechanically ventilated patients in ICUs. However, there is little knowledge regarding early mobilization in routine ICU practice. Hence, the interdisciplinary German ICU Network for Early Mobilization undertook a 1-day point-prevalence survey across Germany.
- Design: One-day point-prevalence study.
- Setting: One hundred sixteen ICUs in Germany in 2011.
- Patients: All adult mechanically ventilated patients.
- Interventions: None.
- Measurements and Main Results: For a 24-hour period, data were abstracted on hospital and ICU characteristics, the level of patient mobilization and associated barriers, and complications occurring during mobilization. One hundred sixteen participating ICUs provided data for 783 patients. Overall, 185 patients (24%) were mobilized out of bed (i.e., sitting on the edge of the bed or higher level of mobilization). Among patients with an endotracheal tube, tracheostomy, and noninvasive ventilation, 8%, 39%, and 53% were mobilized out of bed, respectively ($p < 0.001$ for difference between three groups). The most common perceived barriers to mobilizing patients out of bed were cardiovascular instability (17%) and deep sedation (15%). Mobilization out of bed versus remaining in bed was not associated with a higher frequency of complications, with no falls or extubations occurring in those mobilized out of bed.
- Conclusions: In this 1-day point-prevalence study conducted across Germany, only 24% of all mechanically ventilated patients and only 8% of patients with an endotracheal tube were mobilized out of bed as part of routine care. Addressing modifiable barriers for mobilization, such as deep sedation, will be important to increase mobilization in German ICUs.

Postoperative Polymyxin B Hemoperfusion and Mortality in Patients With Abdominal Septic Shock: A Propensity-Matched Analysis*

Iwagami, Masao; Yasunaga, Hideo; Doi, Kent; More

- **Objectives:**To examine the effect of postoperative polymyxin B hemoperfusion on mortality in patients with abdominal septic shock triggered by lower gastrointestinal tract perforation, identifying subpopulations of patients who may benefit from this treatment.
- **Patients:**We included patients who are 18 years old or older hospitalized during a period of 34 months between July 2007 and October 2011, who had open abdominal surgery on the day of admission (day 0) for perforation of lower gastrointestinal tract, and who required noradrenaline and/or dopamine. We excluded patients who died on day 0 or 1 and patients starting polymyxin B hemoperfusion on day 2 or later.
- **Measurements and Main Results:**The main outcome was 28-day mortality. Of 2,925 eligible patients, 642 received one or two polymyxin B hemoperfusion sessions, starting the first one on day 0 or 1. Propensity score matching created a matched cohort of 1,180 patients (590 pairs with and without polymyxin B hemoperfusion). The 28-day mortality was 17.1% (101 of 590) in the polymyxin B hemoperfusion group and 16.3% (96 of 590) in the control group ($p = 0.696$). Subgroup analyses by number of polymyxin B hemoperfusion sessions (one or two), timing of polymyxin B hemoperfusion initiation (day 0 or 1), the use of noradrenaline, and number of dysfunctional organs (one to six) **did not show any significant difference** in 28-day mortality between the groups. Multiple logistic did not show a significant association between the use of polymyxin B hemoperfusion and 28-day mortality (adjusted odds ratio, 1.10; 95% CI, 0.80–1.51; $p = 0.569$). **Age**, end-stage renal disease requiring maintenance **hemodialysis**, the use of **noradrenaline**, and **number of dysfunctional organs** were positively associated with 28-day mortality.
- **Conclusions:**In this retrospective study, postoperative polymyxin B hemoperfusion did not show any survival benefit for the overall study population or any of the studied subgroups of patients with abdominal septic shock. A large multicentered prospective randomized trial is warranted to identify the true role of polymyxin B hemoperfusion in sepsis caused by Gram-negative bacteria.

A Cost-Effectiveness Analysis of Postoperative Goal-Directed Therapy for High-Risk Surgical Patients*

Ebm, Claudia; Cecconi, Maurizio; Sutton, Les; More

- Objectives: Patients undergoing major surgery are at high risk of increased postoperative morbidity and mortality. Goal-directed therapy has been shown to improve outcomes when commenced in the early postoperative period, yet the economic impact remains unclear. The aim of our study was to assess the cost effectiveness of goal-directed therapy as part of postoperative management.
- Design: Cost-effectiveness analysis to determine short and long term clinical and financial benefits. A decision tree was constructed to determine short-term “in-hospital” costs, based on outcome data derived from a previous study. For a long-term cost-effectiveness analysis, we created a simulation model to estimate life expectancy (quality-adjusted) and lifetime costs for a hypothetical cohort of major noncardiac surgical patients. Cost and outcome comparisons were made between postoperative goal-directed therapy and best standard therapy and described as cost/hospital survivor and cost/patient for the short-term analysis and as incremental cost/quality-adjusted life year for the long-term model. One-way, multiway, and probabilistic analyses were performed to address uncertainties in the model input values, and results were presented graphically in a cost-effectiveness acceptability curve.
- Setting: **Simulation** of a tertiary care department in the United Kingdom.
- Patients: A **hypothetical** cohort of high risk surgical patients.
- Interventions: Patients undergoing high-risk surgery were stratified to receive **goal-directed therapy or standard best practice to improve tissue oxygenation** in the postoperative setting.
- Measurements and Main Results: In our short-term model, goal-directed therapy decreased costs by £2,631.77/patient and by £2,134.86/hospital survivor. The most sensitive variables were relative risk of complication and length of stay. When assuming the worst-case scenario (prolonged ICU and in-hospital stay, highest complication costs, and maximum cost for monitoring), goal-directed therapy still achieved cost savings (£471.70). Our findings also predict that goal-directed therapy **not only** prolongs quality-adjusted life expectancy (0.83 yr or 9.8 mo) **but also** leads to incremental cost savings over a lifetime projection of £1,285.77, resulting in a negative incremental cost-effectiveness ratio of – £1,542.16/quality-adjusted life year.
- Conclusion: The implementation of goal-directed therapy is both clinical and cost-effective. Additional implementation expenditures can be offset by savings due to reduced costs accrued from a reduction in complication rates and hospital length of stay. We conclude that goal-directed therapy provides significant benefits with respect to clinical and financial outcomes.

Early Bispectral Index and Sedation Requirements During Therapeutic Hypothermia Predict Neurologic Recovery Following Cardiac Arrest*

Burjek, Nicholas E.; Wagner, Chad E.; Hollenbeck, Ryan D.; More

- Objectives: To test the hypothesis that low bispectral index scores and low sedative requirements during therapeutic hypothermia predict poor neurologic outcome.
- Patients: One hundred sixty consecutive cardiac arrest patients treated with therapeutic hypothermia.
- Interventions: None.
- Measurements and Results: Eighty-four of the 141 subjects (60%) who survived hypothermia induction were discharged from the ICU with poor neurologic outcome, defined as a cerebral performance category score of 3, 4, or 5. These subjects had lower bispectral index ($p < 0.001$) and sedative requirements ($p < 0.001$) during hypothermia compared with the 57 subjects discharged with good outcome. Early prediction of neurologic recovery was best 7 hours after ICU admission, and median bispectral index scores at that time were 31 points lower in subjects discharged with poor outcome (11 [interquartile range, 4–29] vs 42 [37–49], $p < 0.001$). Median sedation requirements decreased by 17% (interquartile range, –50 to 0%) 7 hours after ICU admission in subjects with poor outcome but increased by 50% (interquartile range, 0–142%) in subjects with good outcome ($p < 0.001$). Each 10-point decrease in bispectral index was independently associated with a 59% increase in the odds of poor outcome (95% CI, 32–76%; $p < 0.001$). The model including bispectral index and sedative requirement correctly reclassified 15% of subjects from good to poor outcome and 1% of subjects from poor to good outcome. The model incorrectly reclassified 1% of subjects from poor to good outcome but did not incorrectly reclassify any from good to poor outcome.
- Conclusions: Bispectral index scores and sedative requirements early in the course of therapeutic hypothermia improve the **identification** of patients who will not recover from brain anoxia. The ability to accurately predict nonrecovery after cardiac arrest could facilitate discussions with families, reduce patient suffering, and limit use of ICU resources in futile cases.

Hemolysis in Pediatric Patients Receiving Centrifugal-Pump Extracorporeal Membrane Oxygenation: Prevalence, Risk Factors, and Outcomes*

Lou, Song; MacLaren, Graeme; Best, Derek; More

- Objectives: To explore the prevalence and risk factors for hemolysis in children receiving extracorporeal membrane oxygenation and examine the relationship between hemolysis and adverse outcomes.
- Patients: Two hundred seven children receiving extracorporeal membrane oxygenation.
- Interventions: None.
- Measurements and Main Results: Plasma-free hemoglobin was tested daily and hemolysis was diagnosed based on peak plasma-free hemoglobin as mild (< 0.5 g/L), moderate (0.5 – 1.0 g/L), or severe (> 1.0 g/L). Gender, age, weight, diagnosis, oxygenator type, cannulation site, mean venous inlet pressure, mean pump speed, mean flow, and visible clots in the extracorporeal membrane oxygenation circuit were entered into the ordered logistic regression model to identify risk factors of hemolysis. Complications and clinical outcomes were compared across four hemolysis groups. Of the 207 patients, **69 patients** (33.3%; 95% CI, 27.0–40.2%) did not have hemolysis, **98 patients** (47.3%; 95% CI, 40.4–54.4%) had mild hemolysis, **26 patients** (12.5%; 95% CI, 8.4–17.9%) had moderate hemolysis, and **14 patients** (6.8%; 95% CI, 3.7–11.1%) had severe hemolysis with a median peak plasma-free hemoglobin of 1.51 g/L (1.18–2.05 g/L). The independent risk factors for hemolysis during extracorporeal membrane oxygenation were use of **Quadrox D** (odds ratio, 7.25; 95% CI, 3.10–16.95; $p < 0.001$) or **Lilliput** (odds ratio, 37.32; 95% CI, 8.95–155.56; $p < 0.001$) oxygenators, **mean venous inlet pressure** (odds ratio, 0.95; 95% CI, 0.91–0.98; $p = 0.002$), and **mean pump speed** (odds ratio, 2.89; 95% CI, 1.36–6.14; $p = 0.006$). Patients with hemolysis were more likely to experience a longer extracorporeal membrane oxygenation run and require more blood products. After controlling for age, weight, pediatric index of mortality 2, and diagnosis, patients with severe hemolysis were more likely to die in the ICU (odds ratio, 5.93; 95% CI, 1.64–21.43; $p = 0.007$) and in hospital (odds ratio, 6.34; 95% CI, 1.71–23.54; $p = 0.006$).
- Conclusions: Hemolysis during extracorporeal membrane oxygenation with centrifugal pumps was **common** and associated with a number of adverse outcomes. Risk factors for hemolysis included oxygenator types, mean venous inlet pressure, and mean pump speed. Further studies are warranted comparing pump types while controlling both physical and nonphysical confounders.

Hypoglycemia Is Associated With Increased Postburn Morbidity and Mortality in Pediatric Patients*

Jeschke, Marc G.; Pinto, Ruxandra; Herndon, David N.; More

- **Objective:**The objective of this study was to determine the prevalence of hypoglycemia after burn injury and whether hypoglycemia is associated with increased postburn morbidity and mortality.
- **Patients:**This analysis included 760 pediatric burn patients, who were stratified according the number of hypoglycemic episodes (< 60 mg/dL glucose) they experienced while in the ICU. Clinical outcomes and metabolic and inflammatory biomarkers were analyzed during the first 60 days post admission. Patients with one or more hypoglycemic events were matched with patients not experiencing any event using propensity score matching, and outcomes and biomarker expression were compared between groups.
- **Measurements and Main Results:**Eighty-four patients had one episode of hypoglycemia, 108 patients had two or more episodes of hypoglycemia, and 568 patients never experienced hypoglycemia. Patients with one or more hypoglycemic episodes had longer hospitalization, as well as more frequent infections, sepsis, multiple organ failure, and death ($p < 0.05$). The 166 propensity score–matched patients with one or more hypoglycemic events had greater inflammatory and metabolic responses, prevalence of sepsis, multiple organ failure, and mortality than burn patients without hypoglycemic ($p < 0.05$).
- **Conclusions:**Hypoglycemic episodes correlate with injury severity and inhalation injury. When adjusted for injury severity, hypoglycemia is associated with significantly **higher** postburn morbidity and mortality.

A Multinational Study of Thromboprophylaxis Practice in Critically Ill Children*

Faustino, Edward Vincent S.; Hanson, Sheila; Spinella, Philip C.; More

- Objectives: Although critically ill children are at increased risk for developing deep venous thrombosis, there are few pediatric studies establishing the prevalence of thrombosis or the efficacy of thromboprophylaxis. We tested the hypothesis that thromboprophylaxis is infrequently used in critically ill children even for those in whom it is indicated.
- Patients: All patients less than 18 years old in the PICU during the study dates and times were included in the study, unless the patients were 1) boarding in the unit waiting for a bed outside the PICU or 2) receiving therapeutic anticoagulation.
- Interventions: None.
- Measurements and Main Results: Of 2,484 children in the study, 2,159 (86.9%) had greater than or equal to 1 risk factor for thrombosis. Only 308 children (12.4%) were receiving pharmacologic thromboprophylaxis (e.g., aspirin, low-molecular-weight heparin, or unfractionated heparin). Of 430 children indicated to receive pharmacologic thromboprophylaxis based on consensus recommendations, only 149 (34.7%) were receiving it. Mechanical thromboprophylaxis was used in 156 of 655 children (23.8%) 8 years old or older, the youngest age for that device. Using nonlinear mixed effects model, presence of cyanotic congenital heart disease (odds ratio, 7.35; $p < 0.001$) and spinal cord injury (odds ratio, 8.85; $p = 0.008$) strongly predicted the use of pharmacologic and mechanical thromboprophylaxis, respectively.
- Conclusions: Thromboprophylaxis is infrequently used in critically ill children. This is true even for children at high risk of thrombosis where consensus guidelines recommend pharmacologic thromboprophylaxis.

Rehabilitation Interventions for Postintensive Care Syndrome: A Systematic Review*

Mehlhorn, Juliane; Freytag, Antje; Schmidt, Konrad; More

The Efficacy and Safety of Prone Positional Ventilation in Acute Respiratory Distress Syndrome: Updated Study-Level Meta-Analysis of 11 Randomized Controlled Trials*

Lee, Joo Myung; Bae, Won; Lee, Yeon Joo; More

The Highs and Lows of Blood Pressure: Toward Meaningful Clinical Targets in Patients With Shock

Magder, Sheldon A.

Training Internists to Meet Critical Care Needs in the United States: A Consensus Statement from the Critical Care Societies Collaborative (CCSC)*

Prepared by the CCSC Task Force on Critical Care Educational Pathways in Internal Medicine

Is selective antegrade cerebral perfusion superior to retrograde cerebral perfusion for brain protection during deep hypothermic circulatory arrest?

Metabolic evidence from microdialysis.

Liang, Meng-Ya; Tang, Zhi-Xian; Chen, Guang-Xian; More

- Objectives: This study aimed to investigate whether selective antegrade cerebral perfusion or retrograde cerebral perfusion is a better technique for brain protection in deep hypothermic circulatory arrest by obtaining metabolic evidence from microdialysis.
- Subjects: Eighteen piglets of either sex (9.8 ± 3.1 kg).
- Interventions: Animals were randomly assigned to 40 minutes of circulatory arrest at 18° C without cerebral perfusion (deep hypothermic circulatory arrest group, $n = 6$) or with selective antegrade cerebral perfusion (selective antegrade cerebral perfusion group, $n = 6$) or retrograde cerebral perfusion (retrograde cerebral perfusion group, $n = 6$). Reperfusion was continued for 3 hours.
- Measurements and Main Results: Microdialysis (glucose, lactate, pyruvate, and glycerol) variables in the cortex dialysate were measured every 30 minutes. Intracerebral pressure and serum S-100 levels were also monitored. After 3 hours of reperfusion, cortical tissue was harvested for terminal deoxynucleotidyl transferase dUTP nick-end labeling staining. After 40 minutes of circulatory arrest, the deep hypothermic circulatory arrest group presented marked elevations of intracerebral pressure, and serum S-100 levels were higher in the deep hypothermic circulatory arrest group than in the other two groups ($p < 0.001$, respectively). The selective antegrade cerebral perfusion group exhibited higher glucose, lower lactate, and lower glycerol levels and a lower lactate-to-pyruvate ratio in comparison to the deep hypothermic circulatory arrest group ($p < 0.05$, respectively); the retrograde cerebral perfusion group had lower lactate and glycerol levels and a lower lactate-to-pyruvate ratio ($p < 0.05$, respectively) but similar glucose levels compared to deep hypothermic circulatory arrest alone. Furthermore, selective antegrade cerebral perfusion provided better preservation of energy and cell integrity than retrograde cerebral perfusion with higher glucose and lower glycerol levels ($p < 0.05$, respectively). After 3 hours of reperfusion, fewer apoptotic neurons were found in selective antegrade cerebral perfusion animals than in the other two groups ($p < 0.05$, respectively).
- Conclusions: Both selective antegrade cerebral perfusion and retrograde cerebral perfusion were superior to deep hypothermic circulatory arrest alone during circulatory arrest. Retrograde cerebral perfusion was a moderate technique that had similar **advantages** with regard to less cerebral edema, better clearance of metabolic waste, and lower levels of biomarkers of injury than selective antegrade cerebral perfusion, **but** its capacity for energy preservation, maintenance of cellular integrity, and protection against apoptosis was lower than that of selective antegrade cerebral perfusion.

Small-volume 7.5% NaCl adenosine, lidocaine, and Mg²⁺ has multiple benefits during hypotensive and blood resuscitation in the pig following severe blood loss: rat to pig translation.

Granfeldt, Asger; Letson, Hayley L.; Hyldebrandt, Janus A.; More

- Objectives: Currently, there is no effective small-volume fluid for traumatic hemorrhagic shock. Our objective was to translate small-volume 7.5% NaCl adenosine, lidocaine, and Mg²⁺ hypotensive fluid resuscitation from the rat to the pig.
- Design: Pigs (35–40 kg) were anesthetized and bled to mean arterial pressure of 35–40 mm Hg for 90 minutes, followed by 60 minutes of hypotensive resuscitation and infusion of shed blood. Data were collected continuously.
- Interventions: Pigs were randomly assigned to a single IV bolus of 4 mL/kg 7.5% NaCl + adenosine, lidocaine and Mg²⁺ (n = 8) or 4 mL/kg 7.5% NaCl (n = 8) at hypotensive resuscitation and 0.9% NaCl ± adenosine and lidocaine at infusion of shed blood.
- Measurements and Main Results: At 60 minutes of hypotensive resuscitation, treatment with 7.5% NaCl + adenosine, lidocaine, and Mg²⁺ generated significantly higher mean arterial pressure (48 mm Hg [95% CI, 44–52] vs 33 mm Hg [95% CI, 30–36], p < 0.0001), cardiac index (76 mL/min/kg [95% CI, 63–91] vs 47 mL/min/kg [95% CI, 39–57], p = 0.002), and oxygen delivery (7.6 mL O₂/min/kg [95% CI, 6.4–9.0] vs 5.2 mL O₂/min/kg [95% CI, 4.4–6.2], p = 0.003) when compared with controls. Pigs that received adenosine, lidocaine, and Mg²⁺/adenosine and lidocaine also had significantly lower blood lactate (7.1 mM [95% CI, 5.7–8.9] vs 11.3 mM [95% CI, 9.0–14.1], p = 0.004), core body temperature (39.3 °C [95% CI, 39.0–39.5] vs 39.7 °C [95% CI, 39.4–39.9]), and higher base excess (–5.9 mEq/L [95% CI, –8.0 to –3.8] vs –11.2 mEq/L [95% CI, –13.4 to –9.1]). One control died from cardiovascular collapse. Higher cardiac index in the adenosine, lidocaine, and Mg²⁺/adenosine and lidocaine group was due to a two-fold increase in stroke volume. Left ventricular systolic ejection times were significantly higher and inversely related to heart rate in the adenosine, lidocaine, and Mg²⁺/adenosine and lidocaine group. Thirty minutes after blood return, whole-body oxygen consumption decreased in pigs that received adenosine, lidocaine, and Mg²⁺/adenosine and lidocaine (5.7 mL O₂/min/kg [95% CI, 4.7–6.8] to 4.9 mL O₂/min/kg [95% CI, 4.2–5.8]), whereas it increased in controls (4.2 mL O₂/min/kg [95% CI, 3.5–5.0] to 5.8 mL O₂/min/kg [95% CI, 4.9–5.8], p = 0.02). After 180 minutes, pigs in the adenosine, lidocaine, and Mg²⁺/adenosine and lidocaine group had three-fold higher urinary output (2.1 mL/kg/hr [95% CI, 1.2–3.8] vs 0.7 mL/kg/hr [95% CI, 0.4–1.2], p = 0.001) and lower plasma creatinine levels.
- Conclusion: Small-volume resuscitation with 7.5% NaCl + adenosine, lidocaine, and Mg²⁺/adenosine and lidocaine provided **superior** cardiovascular, acid-base, metabolic, and renal recoveries following severe hemorrhagic shock in the pig compared with 7.5% NaCl alone.

Deletion of Soluble Epoxide Hydrolase Attenuates Cardiac Hypertrophy via Down-Regulation of Cardiac Fibroblasts–Derived Fibroblast Growth Factor-2

Zhang, Huanji; Wang, Tong; Zhang, Kun; More

- Objective: Inhibition of soluble epoxide hydrolase (Ephx2) has been shown to play a protective role in cardiac hypertrophy, but the mechanism is not fully understood. We tested the hypothesis that deletion of soluble epoxide hydrolase attenuates cardiac hypertrophy via down-regulation of cardiac fibroblasts–derived fibroblast growth factor-2.
- Subjects: Male wild-type C57BL/6 mice and Ephx2 (–/–) mice.
- Interventions: Male wild-type or Ephx2 (–/–) mice were subjected to transverse aorta constriction surgery.
- Measurements and Main Results: Four weeks after transverse aorta constriction, Ephx2 (–/–) mice did not develop significant cardiac hypertrophy as that of wild-type mice, indicated by no changes in the ratio of heart weight/body weight and ventricular wall thickness after transverse aorta constriction. Cardiac fibroblast growth factor-2 increased in wild-type-transverse aorta constriction group but this did not change in Ephx2 (–/–)-transverse aorta constriction group, and the serum level of fibroblast growth factor-2 did not change in both groups. In vitro, cardiac fibroblasts were stimulated by angiotensin II to analyze the expression of fibroblast growth factor-2. The effect of increased fibroblast growth factor-2 from cardiac fibroblasts induced by angiotensin II was attenuated by soluble epoxide hydrolase deletion. ERK1/2, p38, and AKT kinase were involved in fibroblast growth factor-2 expression regulated by angiotensin II, and soluble epoxide hydrolase deletion lowered the phosphorylation of ERK1/2 not p38 or AKT to mediate fibroblast growth factor-2 expression. In addition, soluble epoxide hydrolase deletion did not attenuate cardiomyocytes hypertrophy induced by exogenous fibroblast growth factor-2.
- Conclusions: Our present data demonstrated that deletion of soluble epoxide hydrolase prevented cardiac hypertrophy not only directly to cardiomyocytes but also to cardiac fibroblasts by reducing expression of fibroblast growth factor-2.

Transient Receptor Potential Melastatin 8 Channel Inhibition Potentiates the Hypothermic Response to Transient Receptor Potential Vanilloid 1 Activation in the Conscious Mouse

Feketa, Viktor V.; Zhang, Yi; Cao, Zhijuan; More

- Objectives: Mild decrease in core temperature (therapeutic hypothermia) provides lasting neuroprotection following cardiac arrest or cerebral ischemia. However, current methods for producing therapeutic hypothermia trigger a cold-defense response that must be countered by sedatives, muscle paralytics, and mechanical ventilation. We aimed to determine methods for producing hypothermia in the conscious mouse by targeting two transient receptor potential channels involved in thermoregulation, two transient receptor potential (TRP) channels involved in thermoregulation, TRP vanilloid 1 (TRPV1) and TRP melastatin 8 (TRPM8).
- Design: Controlled prospective animal study.
- Setting: Research laboratory at academic medical center.
- Subjects: Conscious unrestrained young and aged male mice.
- Interventions: Mice were treated with the TRPV1 agonist dihydrocapsaicin, a TRPM8 inhibitor (“compound 5”), or their combination and the effects on core temperature (T_{core}) were measured by implanted thermocouples and wireless transponders.
- Measurements and Main Results: TRPV1 agonist dihydrocapsaicin produced a dose-dependent (2–4 mg/kg s.c.) drop in T_{core}. A loading dose followed by continuous infusion of dihydrocapsaicin produced a rapid and prolonged (> 6 hr) drop of T_{core} within the therapeutic range (32–34° C). The hypothermic effect of dihydrocapsaicin was augmented in aged mice and was not desensitized with repeated administration. TRPM8 inhibitor “compound 5” (20 mg/kg s.c.) augmented the drop in core temperature during cold exposure (8° C). When “compound 5” (30 mg/kg) was combined with dihydrocapsaicin (1.25–2.5 mg/kg), the drop in T_{core} was amplified and prolonged.
- Conclusions: Activating warm receptors (TRPV1) produced rapid and lasting hypothermia in young and old mice. Furthermore, hypothermia induced by TRPV1 agonists was potentiated and prolonged by simultaneous inhibition of TRPM8.

C4d Deposits on the Surface of RBCs in Trauma Patients and Interferes With Their Function*

Muroya, Takashi; Kannan, Lakshmi; Ghiran, Ionita C.; More

- **Objective:** Complement system is activated in patients with trauma. Although complement activation is presumed to contribute to organ damage and constitutional symptoms, little is known about the involved mechanisms. Because complement components may deposit on RBCs, we asked whether complement deposits on the surface of RBC in trauma and whether such deposition alters RBC function.
- **Subjects:** Blood samples collected from 42 trauma patients and 21 healthy donors.
- **Intervention:** None.
- **Measurements and Main Results:** RBC and sera were collected from trauma patients and control donors. RBCs from trauma patients (n = 40) were found to display significantly higher amounts of C4d on their surface by flow cytometry compared with RBCs from control (n = 17) ($p < 0.01$). Increased amounts of iC3b were found in trauma sera (n = 27) (vs 12 controls, $p < 0.01$) by enzyme-linked immunosorbent assay. Incubation of RBC from universal donors (type O, Rh negative) with trauma sera (n = 10) promoted C4d deposition on their surface (vs six controls, $p < 0.05$). Complement-decorated RBC (n = 6) displayed limited their deformability (vs six controls, $p < 0.05$) in two-dimensional microchannel arrays. Incubation of RBC with trauma sera (n = 10) promoted the phosphorylation of band 3, a cytoskeletal protein important for the function of the RBC membrane (vs eight controls, $p < 0.05$), and also accelerated calcium influx (n = 9) and enhanced nitric oxide production (n = 12) (vs four and eight controls respectively, $p < 0.05$) in flow cytometry.
- **Conclusions:** Our study found the presence of extensive complement activation in trauma patients and presents new evidence in support of the hypothesis that **complement activation products deposit on the surface of RBC**. Such deposition could limit RBC deformability and promote the production of nitric oxide. Our findings suggest that RBC in trauma patients malfunctions, which may explain organ damage and constitutional symptoms that is not accounted for otherwise by previously known pathophysiologic mechanisms.

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