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Concise Clinical Review

Critical Care

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Hospital Case Volume and Outcomes among Patients Hospitalized with Severe Sepsis

- **Rationale**
  - Processes of care are potential determinants of outcomes in patients with severe sepsis.
  - Whether hospitals with more experience caring for patients with severe sepsis also have improved outcomes is unclear.

- **Objectives**
  - To determine associations between hospital severe sepsis caseload and outcomes.

Methods

- We analyzed data from U.S. academic hospitals provided through University Health System Consortium.
- We used University Health System Consortium's sepsis mortality model (c-statistic, 0.826) for risk adjustment.
- Validated International Classification of Disease, 9th Edition, Clinical Modification algorithms were used to identify hospital severe sepsis case volume.
- Associations between risk-adjusted severe sepsis case volume and mortality, length of stay, and costs were analyzed using spline regression and analysis of covariance.

Measurements and Main Results

- We identified 56,997 patients with severe sepsis admitted to 124 U.S. academic hospitals during 2011
- Hospitals admitted 460 ± 216 patients with severe sepsis,
- with median length of stay 12.5 days (interquartile range, 11.1–14.2),
- median direct costs $26,304 (interquartile range, $21,900–$32,090),
- and average hospital mortality 25.6 ± 5.3%.
- Higher severe sepsis case volume was associated with lower unadjusted severe sepsis mortality ($R2 = 0.10$, $P = 0.01$) and risk-adjusted severe sepsis mortality ($R2 = 0.21$, $P < 0.001$).
- We did not identify associations between case volume and resource use.

Conclusions

- Academic hospitals with higher severe sepsis case volume have lower severe sepsis hospital mortality without higher costs.

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Critical Care

Rapidly Reversible, Sedation-related Delirium versus Persistent Delirium in the Intensive Care Unit

Rationale:

•ICU delirium is associated with ventilator, ICU, and hospital days; discharge functional status; and mortality.

•Whether rapidly reversible, sedation-related delirium (delirium that abates shortly after sedative interruption) occurs with the same frequency and portends the same prognosis as persistent delirium (delirium that persists despite a short period of sedative interruption) is unknown.

Objectives:

•To compare rapidly reversible, sedation-related delirium and persistent delirium.

Methods

- This was a prospective cohort study of 102 adult, intubated medical ICU subjects in a tertiary care teaching hospital.
- Confusion Assessment Method for the ICU evaluation was performed before and after daily interruption of continuous sedation (DIS).
- Investigators were blinded to each other's assessments and as to whether evaluations were before or after DIS.
- The primary outcome was proportion of days with no delirium versus rapidly reversible, sedation-related delirium versus persistent delirium.
- Secondary outcomes were ventilator, ICU, and hospital days; discharge disposition; and 1-year mortality.

Measurements and Main Results

- The median proportion of ICU days with delirium was 0.57 before versus 0.50 after DIS ($P < 0.001$).
- The Confusion Assessment Method for the ICU indicated patients are 10.5 times more likely to have delirium before DIS versus after ($P < 0.001$).
- Rapidly reversible, sedation-related delirium showed fewer
  - ventilator ($P < 0.001$), ICU ($P = 0.001$),
  - and hospital days ($P < 0.001$)
- Subjects with no delirium and rapidly reversible, sedation-related delirium were more likely to be discharged home ($P < 0.001$).
- Patients with persistent delirium had increased 1-year mortality versus those with no delirium and rapidly reversible, sedation-related delirium ($P < 0.001$).

Conclusions

- Rapidly reversible, sedation-related delirium does not signify the same poor prognosis as persistent delirium.

- Degree of sedation should be considered in delirium assessments.

- Coordinating delirium assessments with daily sedative interruption will improve such assessments' ability to prognosticate ICU delirium outcomes.

Statin Use and Risk of Delirium in the Critically Ill

- **Rationale**
  - Delirium is common in ICU patients and is a predictor of worse outcomes and neuroinflammation is a possible mechanism.
  - The antiinflammatory actions of statins may reduce delirium.

- **Objectives:**
  - To determine whether critically ill patients receiving statin therapy had a reduced risk of delirium than those not on statins.

Methods

- A prospective cohort analysis of data from consecutive ICU patients
  - admitted to a UK mixed medical and surgical ICU
  - between August 2011 and February 2012;

- the Confusion Assessment Method for ICU was used to determine the days each patient was assessed as being free of delirium during ICU admission.

Measurements and Main Results

- Delirium-free days, daily administration of statins, and serum C-reactive protein (CRP) were recorded.

- 470 consecutive critical care patients were followed, of whom 151 patients received statins.

- Using random-effects multivariable logistic regression, statin administration the previous evening was associated
  - with the patient being assessed as free of delirium (odds ratio, 2.28; confidence interval, 1.01–5.13; $P < 0.05$)
  - and with lower CRP ($\beta = -0.52$; $P < 0.01$) the following day.

Conclusions

- Ongoing statin therapy is associated with a lower daily risk of delirium in critically ill patients.

- An ongoing clinical trial, informed by this study, is investigating if statins are a potential therapy for delirium in the critically ill.

The Beta Agonist Lung Injury Trial Prevention. A Randomized Controlled Trial

Rationale:

- Experimental studies suggest that pretreatment with β-agonists might prevent acute lung injury (ALI).

Objectives:

- To determine if in adult patients undergoing elective esophagectomy, perioperative treatment with inhaled β-agonists effects the development of early ALI.

Methods

- We conducted a randomized placebo-controlled trial in 12 UK centers (2008–2011).
- Adult patients undergoing elective esophagectomy were allocated to prerandomized, sequentially numbered treatment packs containing inhaled salmeterol (100 μg twice daily) or a matching placebo.
- Patients, clinicians, and researchers were masked to treatment allocation. The primary outcome was development of ALI within 72 hours of surgery.
- Secondary outcomes were ALI within 28 days, organ failure, adverse events, survival, and health-related quality of life.
- An exploratory substudy measured biomarkers of alveolar-capillary inflammation and injury.

Measurements and Main Results

- A total of 179 patients were randomized to salmeterol and 183 to placebo.
- Baseline characteristics were similar.
- Treatment with salmeterol did not prevent early lung injury
  - 32 [19.2%] of 168 vs. 27 [16.0%] of 170;
  - odds ratio [OR], 1.25; 95% confidence interval [CI], 0.71–2.22
- There was no difference in organ failure, survival, or health-related quality of life.
- Adverse events were less frequent in the salmeterol group (55 vs. 70; OR, 0.63; 95% CI, 0.39–0.99), predominantly because of a lower number of pneumonia (7 vs. 17; OR, 0.39; 95% CI, 0.16–0.96).
- Salmeterol reduced some biomarkers of alveolar inflammation and epithelial injury.

Conclusion

- Perioperative treatment with inhaled salmeterol was well tolerated but did not prevent ALI.

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Critical Care

Transforming Growth Factor β–induced Protein Promotes Severe Vascular Inflammatory Responses

- **Rationale:**
  - Sepsis is a systemic inflammatory condition resulting from bacterial infections; it has a high mortality rate and limited therapeutic options.
  - Despite extensive research into the mechanisms driving bacterial sepsis, the target molecules controlling vascular leakage are still largely unknown.
  - Transforming growth factor β–induced protein (TGFBIp) is an extracellular matrix protein expressed in several cell types, which is known to interact with integrins.

- **Objectives:**
  - The aim of this study was to determine the roles of TGFBIp in vascular proinflammatory responses, and the mechanisms of action driving these responses.

Methods

- Circulating levels of TGFBIp were measured in patients admitted to the hospital with sepsis, severe sepsis, and septic shock and in cecal ligation and puncture (CLP)-induced septic mice.

- Effects of TGFBIp knockout on CLP-induced septic mortality and effects of TGFBIp on multiple vascular proinflammatory responses were determined.

Measurements and Main Results

- Circulating levels of TGFBIp were significantly elevated compared with healthy controls, and were strongly correlated with disease severity.
- High blood TGFBIp levels were also observed in CLP-induced septic mice.
- The absence of the TGFBIp gene in mice attenuated CLP-induced sepsis.
- TGFBIp enhanced vascular proinflammatory responses including
  - vascular permeability,
  - adhesion and migration of leukocytes,
  - and disruption of adherence junctions through interacting with integrin αvβ5.

Conclusions

- Collectively, our findings demonstrate that the TGFBIp-αvβ5 axis can elicit severe inflammatory responses, suggesting it to be a potential target for development of diagnostics and therapeutics for sepsis.

Aging Mesenchymal Stem Cells Fail to Protect Because of Impaired Migration and Antiinflammatory Response

- **Rationale:**
  - Aging is characterized by functional impairment and reduced capacity to respond appropriately to environmental stimuli and injury.
  - With age, there is an increase in the incidence and severity of chronic and acute lung diseases.
  - However, the relationship between age and the lung's reduced ability to repair is far from established and necessitates further research in the field.

Measurements and Main Results

- We demonstrated that old mice have more inflammation in response to acute lung injury.
- To investigate the causes, we compared the global gene expression of aged and young bone marrow–derived MSCs (B-MSCs).
- Our results revealed that the expression levels of inflammatory response genes depended on the age of the B-MSCs.
- We demonstrated that the age-dependent decrease in expression of several cytokine and chemokine receptors is important for the migration and activation of B-MSCs.
- Finally, we showed by adoptive transfer of aged B-MSCs to young endotoxemic mice that aged cells lacked the antiinflammatory protective effect of their young counterparts.

Conclusions

- Taken together,
- the decreased expression of cytokine and chemokine receptors in aged B-MSCs compromises their protective role by perturbing the potential of B-MSCs to become activated and mobilize to the site of injury.

Pseudomonas aeruginosa Type-3 Secretion System Dampens Host Defense by Exploiting the NLRC4-coupled Inflammasome

- **Rationale:**

- Pseudomonas aeruginosa, a major problem pathogen responsible for severe infections in critically ill patients, triggers, through a functional type-3 secretion system (T3SS), the activation of an intracellular cytosolic sensor of innate immunity, NLRC4.

- Although the NLRC4-inflammasome–dependent response contributes to increased clearance of intracellular pathogens, it seems that NLRC4 inflammasome activation decreases the clearance of P. aeruginosa, a mainly extracellular pathogen.

Pseudomonas aeruginosa Type-3 Secretion System Dampens Host Defense by Exploiting the NLRC4-coupled Inflammasome

Objectives

•We sought to determine the underlying mechanisms of this effect of the activation of NLRC4 by P. aeruginosa.

Methods

- We established acute lung injury in wild-type and Nlrc4−/− mice using sublethal intranasal inocula of P. aeruginosa strain CHA expressing or not a functional T3SS.

- We studied 96-hour survival, lung injury, bacterial clearance from the lungs, cytokine secretion in bronchoalveolar lavage, lung antimicrobial peptide expression by quantitative polymerase chain reaction, and flow cytometry analysis of lung cells.

Measurements and Main Results

- Nlrc4−/− mice showed enhanced bacterial clearance and decreased lung injury contributing to increased survival against extracellular P. aeruginosa strain expressing a functional T3SS.
- The mechanism involved
  - decreased NLRC4-inflammasome–driven IL-18 secretion attenuating lung injury caused by excessive neutrophil recruitment.
  - Additionally, in the lungs of Nlrc4−/− mice secretion of IL-17 by innate immune cells was increased and responsible for increased expression of lung epithelial antimicrobial peptides.
  - Furthermore, IL-18 secretion was found to repress IL-17 and IL-17–driven lung antimicrobial peptide expression.

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Conclusions

- We report a new role of the T3SS apparatus itself, independently of exotoxin translocation.

- Through NLRC4 inflammasome activation, the T3SS promotes IL-18 secretion, which dampens a beneficial IL-17–mediated antimicrobial host response.

Validation of Cell-Cycle Arrest Biomarkers for Acute Kidney Injury Using Clinical Adjudication

Rationale:

•We recently reported two novel biomarkers for acute kidney injury (AKI),

•tissue inhibitor of metalloproteinases (TIMP)-2 and insulin-like growth factor binding protein 7 (IGFBP7), both related to G1 cell cycle arrest.

Objectives:

•We now validate a clinical test for urinary [TIMP-2]·[IGFBP7] at a high-sensitivity cutoff greater than 0.3 for AKI risk stratification in a diverse population of critically ill patients.

Methods

- A prospective multicenter study of 420 critically ill patients.
- The primary analysis was the ability of urinary [TIMP-2]·[IGFBP7] to predict moderate to severe AKI within 12 hours.
- AKI was adjudicated by a committee of three independent expert nephrologists who were masked to the results of the test.

Measurements and Main Results

- The primary endpoint was reached in 17% of patients.
- For a single urinary [TIMP-2]·[IGFBP7] test,
- sensitivity at the prespecified high-sensitivity cutoff of 0.3 $(ng/ml)^2/1,000$ was 92% (95% confidence interval [CI], 85–98%)
- with a negative likelihood ratio of 0.18 (95% CI, 0.06–0.33).
- Critically ill patients with urinary [TIMP-2]·[IGFBP7] greater than 0.3 had seven times the risk for AKI (95% CI, 4–22) compared with critically ill patients with a test result below 0.3.
- In a multivariate model including clinical information, urinary [TIMP-2]·[IGFBP7] remained statistically significant and a strong predictor of AKI (area under the curve, 0.70, 95% CI, 0.63–0.76 for clinical variables alone, vs. area under the curve, 0.86, 95% CI, 0.80–0.90 for clinical variables plus [TIMP-2]·[IGFBP7]).

Conclusions

- Urinary [TIMP-2]·[IGFBP7] greater than 0.3 $(ng/ml)^2/1{,}000$ identifies patients at risk for imminent AKI.

Corticosteroids Are Associated with Repression of Adaptive Immunity Gene Programs in Pediatric Septic Shock

Rationale

•Corticosteroids are prescribed commonly for patients with septic shock, but their use remains controversial and concerns remain regarding side effects.

Objectives

•To determine the effect of adjunctive corticosteroids on the genomic response of pediatric septic shock.

Methods

- Retrospectively analyzed an existing transcriptomic database of pediatric septic shock.
- Subjects receiving any formulation of systemic corticosteroids at the time of blood draw for microarray analysis were classified in the septic shock corticosteroid group.
- We compared
  - normal control subjects (n = 52)
  - a septic shock no corticosteroid group (n = 110)
  - a septic shock corticosteroid group (n = 70) using analysis of variance.

Measurements and Main Results

- The two study groups did not differ with respect to illness severity, organ failure burden, mortality, or mortality risk.
- There were 319 gene probes differentially regulated between the no corticosteroid group and the corticosteroid group.
- These genes corresponded predominately to adaptive immunity–related signaling pathways, and were down-regulated relative to control subjects.
- Notably, the degree of down-regulation was significantly greater in the corticosteroid group, compared with the no corticosteroid group.
- A similar pattern was observed for genes corresponding to the glucocorticoid receptor signaling pathway.

Conclusions

- Administration of corticosteroids in pediatric septic shock is associated with additional repression of genes corresponding to adaptive immunity.

- These data should be taken into account when considering the benefit to risk ratio of adjunctive corticosteroids for septic shock.

Electronic Implementation of a Novel Surveillance Paradigm for Ventilator-associated Events. Feasibility and Validation

Rationale:

• Accurate surveillance of ventilator-associated pneumonia (VAP) is hampered by subjective diagnostic criteria.

• A novel surveillance paradigm for ventilator-associated events (VAEs) was introduced.

Objectives:

• To determine the validity of surveillance using the new VAE algorithm.

Methods

- Prospective cohort study in two Dutch academic medical centers (2011–2012).
- VAE surveillance was electronically implemented and included assessment of (infection-related) ventilator-associated conditions (VAC, IVAC) and VAP.
- Concordance with ongoing prospective VAP surveillance was assessed, along with clinical diagnoses underlying VAEs and associated mortality of all conditions.
- Consequences of minor differences in electronic VAE implementation were evaluated.

Measurements and Main Results

- The study included 2,080 patients with 2,296 admissions.
- Incidences of VAC, IVAC, VAE-VAP, and VAP according to prospective surveillance were 10.0, 4.2, 3.2, and 8.0 per 1000 ventilation days, respectively.
- The VAE algorithm detected at most 32% of the patients with VAP identified by prospective surveillance.
- VAC signals were most often caused by volume overload and infections, but not necessarily VAP.
- Subdistribution hazards for mortality were 3.9 (95% confidence interval, 2.9–5.3) for VAC, 2.5 (1.5–4.1) for IVAC, 2.0 (1.1–3.6) for VAE-VAP, and 7.2 (5.1–10.3) for VAP identified by prospective surveillance.
- In sensitivity analyses, mortality estimates varied considerably after minor differences in electronic algorithm implementation.

Conclusions

- Concordance between the novel VAE algorithm and VAP was poor.
- Incidence and associated mortality of VAE were susceptible to small differences in electronic implementation.
- More studies are needed to characterize the clinical entities underlying VAE and to ensure comparability of rates from different institutions.

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Chronic Obstructive Pulmonary Disease/Critical Care

Critical Care

Outcomes Associated with Corticosteroid Dosage in Critically Ill Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Rationale

•Studies evaluating corticosteroid (CS) dosing for patients hospitalized with an AECOPD have largely excluded patients admitted directly to the intensive care unit (ICU), and none have evaluated the effect of CS dosing regimens on mortality.

Objectives:

•To examine the effectiveness and safety of lower- versus high-dose CS in patients admitted to the ICU with an AECOPD.

Methods

- This pharmacoepidemiologic cohort study evaluated
  - ICU patients with AECOPD
  - admitted to one of 473 hospitals
  - and treated with CS within the first 2 days
  - between January 1, 2003 and December 31, 2008.
- Lower-dose (methylprednisolone, ≤240 mg/d) or high-dose (methylprednisolone, >240 mg/d) groups based on CS dosage on hospital Day 1 or 2.
- The primary outcome was hospital mortality.

Measurements and Main Results

- A total of 17,239 patients were included;
  - 6,156 (36%) were in the lower-dose
  - and 11,083 (64%) in the high-dose CS group.
- After propensity score matching and adjustment for unbalanced covariates,
  - lower-dose CS was not associated with a significant reduction in mortality (odds ratio, 0.85; 95% confidence interval [CI], 0.71–1.01; P = 0.06),
  - but it was associated with reduced hospital (−0.44 d; 95% CI, −0.67 to −0.21; P < 0.01) and ICU (−0.31 d; 95% CI, −0.46 to −0.16; P < 0.01) length-of-stay,
  - hospital costs (−$2,559; 95% CI, −$4,508 to −$609; P = 0.01),
  - length of invasive ventilation (−0.29 d; 95% CI, −0.52 to −0.06; P = 0.01),
  - need for insulin therapy (22.7% vs. 25.1%; P < 0.01),
  - and fungal infections (3.3% vs. 4.4%; P < 0.01).

Conclusions

- Two-thirds of patients admitted to the ICU with an AECOPD are treated with high doses of CS that are associated with worse outcomes and more frequent adverse effects.

- Lower dosage strategies should be encouraged for patients admitted to the ICU and the optimum dose should be determined through clinical trials.

Thank You !

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