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Review

Critical Care Paper Review 2012

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Care of patients with sepsis has improved over the last decade. However, in the recent two years, there was no significant progress in the development of a new drug for critically ill patients. In January 2011, it was announced that the worldwide phase 3 randomized trial of a novel anti-Toll-like receptor-4 compound, eritoran tetrasodium, had failed to demonstrate an improvement in the mortality of patients with severe sepsis. In October 2011, Xigris (drotrecogin alfa, a recombinant activated protein C) was withdrawn from the market following the failure of its worldwide trial that had attempted to demonstrate improved outcome. These announcements were disappointing. The recent failure of 2 promising drugs to further reduce mortality suggests that new approaches are needed. A study was published showing that sepsis can be associated to a state of immunosuppression and loss of immune function in human. However, the timing, incidence, and nature of the immunosuppression remain poorly characterized, especially in humans. This emphasizes the need for a better understanding of sepsis as well as new therapeutic strategies. Many clinical experiences of the extracorporeal membrane oxygenator (ECMO) treatment for adult acute respiratory distress syndrome (ARDS) patients, which is caused by the H1N1 influenza A virus, were reported. The use of ECMO in severe respiratory failure, particularly in the treatment of adult ARDS, is occurring more commonly.

Key Words: Critical Care; Review; Extracorporeal Membrane Oxygenation; Sepsis

Introduction

Acute respiratory distress syndrome (ARDS) and severe sepsis are major problems to be improved management in critical care medicine. Extracorporeal membrane oxygenation (ECMO) is an intensive treatment that is currently used to support patients with severe respiratory failure who are unresponsive to conventional therapeutic interventions. However, ECMO treatments for adult ARDS patients were controversial until a recent date even though the use of ECMO is occurring more commonly. The disappointing failures of clinical trials to further reduce mortality of severe sepsis suggest that new approaches are needed. In this article, I choose some papers showing promising results for severe respiratory failure and sepsis treatments published recent two years.

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Articles Selection

I choose some critical care papers with clinical significances published in major journals for recent two years.

ECMO

1. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A (H1N1). JAMA 2011;306:1659-68[1]

CONTEXT: Extracorporeal membrane oxygenation (ECMO) can support gas exchange in patients with severe acute res-

piratory distress syndrome (ARDS), but its role has remained controversial. ECMO was used to treat patients with ARDS during the 2009 influenza A (H1N1) pandemic.

OBJECTIVE: To compare the hospital mortality of patients with H1N1-related ARDS referred, accepted, and transferred for ECMO with matched patients who were not referred for ECMO.

DESIGN, SETTING, AND PATIENTS: A cohort study in which ECMO-referred patients were defined as all patients with H1N1-related ARDS who were referred, accepted, and transferred to 1 of the 4 adult ECMO centers in the United Kingdom during the H1N1 pandemic in winter 2009-2010. The ECMO-referred patients and the non-ECMO-referred patients were matched using data from a concurrent, longitudinal cohort study (Swine Flu Triage study) of critically ill patients with suspected or confirmed H1N1. Detailed demographic, physiological, and comorbidity data were used in 3 different matching techniques (individual matching, propensity score matching, and GenMatch matching).

MAIN OUTCME MEASURE: Survival to hospital discharge analyzed according to the intention-to-treat principle.

RESULTS: Of 80 ECMO-referred patients, 69 received ECMO (86.3%) and 22 died (27.5%) prior to discharge from the hospital. From a pool of 1756 patients, there were 59 matched pairs of ECMO-referred patients and non-ECMO-referred patients identified using individual matching, 75 matched pairs identified using propensity score matching, and 75 matched pairs identified using GenMatch matching. The hospital mortality rate was 23.7% for ECMO-referred patients vs 52.5% for non- ECMO-referred patients (relative risk [RR], 0.45 [95% CI, 0.26-0.79]; *P*=.006) when individual matching was used; 24.0% vs 46.7%, respectively (RR, 0.51 [95% CI, 0.31-0.81]; *P*=.008) when propensity score matching was used; and 24.0% vs 50.7%, respectively (RR, 0.47 [95% CI, 0.31-0.72]; *P*=.001) when GenMatch matching was used. The results were robust to sensitivity analyses, including amending the inclusion criteria and restricting the location where the non-ECMO referred patients were treated.

CONCLUSION: For patients with H1N1-related ARDS, referral and transfer to an ECMO center was associated with lower hospital mortality compared with matched non-ECMO-referred patients. (Noah et al. 2011[1])

Comments: ECMO is an intensive treatment that is currently used to support patients with respiratory or cardiac failure who are unresponsive to conventional therapeutic interventions. However, ECMO treatments for adult ARDS patients were controversial until a recent date even though the use of ECMO is occurring more commonly[2,3]. In 2009, a randomized controlled study (known as Central European Society for Anticancer Research [CESAR] study) indicated that more patients with severe ARDS survived significantly if they were treated in an ECMO center compared with patients who were managed conventionally[4]. CESAR study was the first randomized controlled trial (RCT) report to show positive result of ECMO for ARDS.

This study by Noah et al.[1] present evidence in support of ECMO as a treatment strategy early in the course of ARDS related to H1N1 infection. However, this study has some limitations. Some ARDS patients were required transfer to specialized ECMO centers. The design of this study makes it unclear whether the mortality benefit associated with ECMO was attributable to management of severe respiratory failure in a specialized center or to the use of ECMO. To consider ECMO as a potential treatment modality for severe ARDS from all causes, large RCTs are needed.

Steroid Treatment for Severe Viral Pneumonia

1. Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. Am J Respir Crit Care Med 2011;183:1207-14[5]

RATIONALE: Administration of adjuvant corticosteroids to patients with pandemic influenza A/H1N1 2009 (pH1N1) may reduce inflammation and improve outcomes.

OBJECTIVES: To assess the effect of adjuvant corticosteroid treatment on the outcome of critically ill patients with pH1N1 infection.

METHODS: All adult patients with confirmed pH1N1 admitted to the intensive care unit of 28 hospitals in South Korea

from September 2009 to February 2010 were enrolled. Patients with and without adjuvant corticosteroid treatment were retrospectively compared by two risk stratification models: (1) a retrospective cohort study that used propensity score analysis to adjust for confounding by treatment assignment and (2) a propensity-matched case-control study.

MEASUREMENTS AND MAIN RESULTS: A total of 245 patients were enrolled in the cohort study, 107 of whom (44%) received adjuvant steroid treatment. In the cohort study, the 90-day mortality rate of patients given steroids (58%, 62 of 107) was significantly higher than that of those not given steroids (27%, 37 of 138) ($P<0.001$). The steroid group was more likely to have superinfection such as secondary bacterial pneumonia or invasive fungal infection, and had more prolonged intensive care unit stays than the no-steroid group. Multivariate analysis indicated that steroid treatment was associated with increased 90-day mortality when independent predictors for 90-day mortality and propensity score were considered (adjusted odds ratio, 2.20; 95% confidence interval, 1.03-4.71). In the case-control study, the 90-day mortality rate in the steroid group was 54% (35 of 65) and 31% (20 of 65) in the no-steroid group (McNemar test, P=0.004).

CONCLUSIONS: Adjuvant corticosteroids were significantly associated with higher mortality in critically ill patients with influenza A H1N1 infection. (Kim et al. 2011[5])

Comments: Another study with very similar design of this study was reported in the same issue of the journal consicutively[6]. Both studies represent corticosteroids were harmful in critically ill patients with influenza A H1N1 infection. Many clinicians used corticosteroids to patients with acute lung injury (ALI)/ARDS to reduce lung inflammation and hope improving clinical outcomes. However, no randomized clinical trials have been performed to confirm the effects of steroids in ALI/ARDS by acute viral pneumonia. Given the acute nature of the H1N1 influenza pandemic, a prospective randomized trial was not possible. To overcome this problem, the authors used several analytic techniques to adjust for differences in the steroid-treated and non-treated groups to compare clinical outcomes. These two studies showed very similar results in spite of different ethnic groups. So, my view is that steroids should not be used in severe viral pneumonia, unless new study provides evidence that steroids are beneficial.

Lactate Monitor in Sepsis

1. Lactate clearance vs. central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA 2010;303:739-46[7]

CONTEXT: Goal-directed resuscitation for severe sepsis and septic shock has been reported to reduce mortality when applied in the emergency department.

OBJECTIVE: To test the hypothesis of noninferiority between lactate clearance and central venous oxygen saturation ($ScvO_2$) as goals of early sepsis resuscitation.

DESIGN, SETTING, AND PATIENTS: Multicenter randomized, noninferiority trial involving patients with severe sepsis and evidence of hypoperfusion or septic shock who were admitted to the emergency department from January 2007 to January 2009 at 1 of 3 participating US urban hospitals.

INTERVENTIONS: We randomly assigned patients to 1 of 2 resuscitation protocols. The $ScvO_2$ group was resuscitated to normalize central venous pressure, mean arterial pressure, and $ScvO_2$ of at least 70%; and the lactate clearance group was resuscitated to normalize central venous pressure, mean arterial pressure, and lactate clearance of at least 10%. The study protocol was continued until all goals were achieved or for up to 6 hours. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment.

MAIN OUTCOME MEASURE: The primary outcome was absolute in-hospital mortality rate; the noninferiority threshold was set at equal to −10%.

RESULTS: Of the 300 patients enrolled, 150 were assigned to each group and patients were well matched by demographic, comorbidities, and physiological features. There were no differences in treatments administered during the initial 72 hours of hospitalization. Thirty-four patients (23%) in the $ScvO_2$ group died while in the hospital (95% con-

fidence interval [CI], 17%-30%) compared with 25 (17%; 95% CI, 11%-24%) in the lactate clearance group. This observed difference between mortality rates did not reach the predefined −10% threshold (intent-to-treat analysis: 95% CI for the 6% difference, −3% to 15%). There were no differences in treatment-related adverse events between the groups.

CONCLUSION: Among patients with septic shock who were treated to normalize central venous and mean arterial pressure, additional management to normalize lactate clearance compared with management to normalize $ScvO_2$ did not result in significantly different in-hospital mortality. (Jones et al. 2010[7])

Comments: Early goal-directed quantitative resuscitation refers to the use of a specific protocol that targets predefined physiological or laboratory goals to be achieved within the first several hours. Results of a recent meta-analysis indicated a survival benefit associated with the use of this strategy applied to heterogeneous populations of patients with sepsis[8].

The optimal method for determining tissue oxygen delivery remains uncertain. Published practice surveys have shown that the expertise technique and specialized equipment required to measure $ScvO_2$ make a major barrier to the completion of this protocol[9]. In contrast, lactate clearance, derived from calculating the change in lactate concentration from 2 blood specimens drawn at different times, potentially represents a more accessible method to assess tissue oxygen delivery. The authors of this study observed that management to normalize lactate clearance in initial sepsis treatment has suspicious benefit. However, only a small fraction (10%) of enrolled patients received therapies (dobutamine or transfusions) that influenced by the resuscitation targets being compared. So interpretation of the results is somewhat complicated. Nevertheless, the data support the noninferiority of the lactate guidance strategy.

2. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med 2010; 182:752-61[10]

RATIONALE: It is unknown whether lactate monitoring aimed to decrease levels during initial treatment in critically ill patients improves outcome.

OBJECTIVES: To assess the effect of lactate monitoring and resuscitation directed at decreasing lactate levels in intensive care unit (ICU) patients admitted with a lactate level of greater than or equal to 3.0 mEq/L.

METHODS: Patients were randomly allocated to two groups. In the lactate group, treatment was guided by lactate levels with the objective to decrease lactate by 20% or more per 2 hours for the initial 8 hours of ICU stay. In the control group, the treatment team had no knowledge of lactate levels (except for the admission value) during this period. The primary outcome measure was hospital mortality.

MEASUREMENTS AND MAIN RESULTS: The lactate group received more fluids and vasodilators. However, there were no significant differences in lactate levels between the groups. In the intention-to-treat population (348 patients), hospital mortality in the control group was 43.5% (77/177) compared with 33.9% (58/171) in the lactate group (P=0.067). When adjusted for predefined risk factors, hospital mortality was lower in the lactate group (hazard ratio, 0.61; 95% confidence interval, 0.43-0.87; P=0.006). In the lactate group, Sequential Organ Failure Assessment scores were lower between 9 and 72 hours, inotropes could be stopped earlier, and patients could be weaned from mechanical ventilation and discharged from the ICU earlier.

CONCLUSIONS: In patients with hyperlactatemia on ICU admission, lactate-guided therapy significantly reduced hospital mortality when adjusting for predefined risk factors. As this was consistent with important secondary endpoints, this study suggests that initial lactate monitoring has clinical benefit. (Jansen et al. 2010[10])

Comments: Despite many studies have emphasized the importance of lactate targeted treatment in prognosis

of sepsis, little evidence exists on what interventions would benefit patients with increased lactate levels or a failure to reduce lactate[11]. In this study, patients with increased lactate level on ICU admission, lactate lowering treatment significantly reduced ICU length of stay, ICU and hospital. This study suggests that initial treatment aimed at reducing lactate levels has clinical benefit.

Medical Treatment for ARDS

1. Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. Lancet 2012;379:229-35[12]

BACKGROUND: In a previous randomised controlled phase 2 trial (BALTI study), intravenous infusion of salbutamol for up to 7 days in patients with acute respiratory distress syndrome (ARDS) reduced extravascular lung water and plateau airway pressure. The authors assessed the effects of this intervention on mortality in patients with ARDS.

METHODS: The authors did a multicentre, placebo-controlled, parallel-group, randomised trial at 46 UK intensive-care units between December, 2006, and March, 2010. Intubated and mechanically ventilated patients (aged ≥16 years) within 72 h of ARDS onset were randomly assigned to receive either salbutamol (15 μg/ kg/hr) or placebo for up to 7 days. Randomisation was done by a central telephone or web-based randomisation service with minmisation by centre, pressure of arterial oxygen to fractional inspired oxygen concentration (PaO_2/FIO_2) ratio, and age. All participants, caregivers, and investigators were masked to group allocation. The primary outcome was death within 28 days of randomisation. Analysis was by intention-to-treat. This trial is registered, ISRCTN38366450 and EudraCT number 2006-002647-86.

FINDINGS: We randomly assigned 162 patients to the salbutamol group and 164 to the placebo group. One patient in each group withdrew consent. Recruitment was stopped after the second interim analysis because of safety concerns. Salbutamol increased 28-day mortality (55 [34%] of 161 patients died in the salbutamol group vs 38 (23%) of 163 in the placebo group; risk ratio [RR] 1.47, 95% CI; 1.03-2.08).

INTERPRETATION: Treatment with intravenous salbutamol early in the course of ARDS was poorly tolerated. Treatment is unlikely to be beneficial, and could worsen outcomes. Routine use of β-2 agonist treatment in ventilated patients with this disorder cannot be recommended. (Gao Smith et al. 2012[12])

Comments: Beta-2 agonists activate Beta-2 receptors on alveolar type-1 and type-2 cells, which increases intracellular cAMP, leading to increased sodium transport and acceleration of alveolar fluid reabsorption. Findings from the β-agonist lung injury trial (BALTI) showed that an infusion of salbutamol caused significant reductions in extravascular lung[13]. However, the results of the truncated BALTI-2 trial are very disappointed and sufficient to change practice. Beta-2 agonist treatment in patients with ARDS should be limited to the treatment of clinically important reversible airway obstruction and should not be part of routine care.

2. Randomized, placebo-controlled clinical trial of an aerosolized beta 2-agonist for treatment of acute lung injury. Am J Respir Crit Care Med 2011;184: 561-8[14]

RATIONALE: β_2-Adrenergic receptor agonists accelerate resolution of pulmonary edema in experimental and clinical studies.

OBJECTIVES: This clinical trial was designed to test the hypothesis that an aerosolized b2-agonist, albuterol, would improve clinical outcomes in patients with acute lung injury (ALI).

METHODS: We conducted a multicenter, randomized, placebo-controlled clinical trial in which 282 patients with ALI receiving mechanical ventilation were randomized to receive aerosolized albuterol (5 mg) or saline placebo every 4 hours for up to 10 days. The primary outcome variable for the trial was ventilator-free days.

MEASUREMENTS AND MAIN RESULTS: Ventilator-free days were not significantly different between the albuterol and

placebo groups (means of 14.4 and 16.6 d, respectively; 95% confidence interval for the difference, −4.7 to 0.3 d; P=0.087). Rates of death before hospital discharge were not significantly different between the albuterol and placebo groups (23.0 and 17.7%, respectively; 95% confidence interval for the difference, −4.0 to 14.7%; P=0.30). In the subset of patients with shock before randomization, the number of ventilator -free days was lower with albuterol, although mortality was not different. Overall, heart rates were significantly higher in the albuterol group by approximately 4 beats/minute in the first 2 days after randomization, but rates of new atrial fibrillation (10% in both groups) and other cardiac dysrhythmias were not significantly different.

CONCLUSIONS: These results suggest that aerosolized albuterol does not improve clinical outcomes in patients with ALI. Routine use of beta 2-agonist therapy in mechanically ventilated patients with ALI cannot be recommended. (National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, et al. 2011[14])

Comments: The potential value of aerosolized beta 2-agonist therapy for treatment of acute lung injury has not been tested previously in a phase III, randomized clinical trial. The results of this randomized double-blind clinical trial demonstrate that aerosolized b2-agonist therapy with albuterol did not improve clinical outcomes in patients with acute lung injury. However, the majority of animal studies of ALI demonstrating a benefit used beta2-agonists as a pre-injury treatment. Though treatment role of beta-agonists for ALI has not been proved, the potential role in the prophylactic setting is expected. Several studies are ongoing to investigate this possibility.

3. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. JAMA 2011;306:1574-81[15]

CONTEXT: The omega-3 (n-3) fatty acids docosahexaenoic acid and eicosapentaenoic acid, along with gamma-linolenic acid and antioxidants, may modulate systemic inflammatory response and improve oxygenation and outcomes in patients with acute lung injury.

OBJECTIVE: To determine if dietary supplementation of these substances to patients with acute lung injury would increase ventilator-free days to study day 28.

DESIGN, SETTING, AND PARTICIPANTS: The OMEGA study, a randomized, double-blind, placebo-controlled, multicenter trial conducted from January 2, 2008, through February 21, 2009. Participants were 272 adults within 48 hours of developing acute lung injury requiring mechanical ventilation whose physicians intended to start enteral nutrition at 44 hospitals in the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. All participants had complete follow-up. Twice-daily enteral supplementation of n-3 fatty acids, gamma-linolenic acid, and antioxidants compared with an iso-caloric control. Enteral nutrition, directed by a protocol, was delivered separately from the study supplement.

MAIN OUTCOME MEASURE: Ventilator-free days to study day 28.

RESULTS: The study was stopped early for futility after 143 and 129 patients were enrolled in the n-3 and control groups. Despite an 8-fold increase in plasma eicosapentaenoic acid levels, patients receiving the n-3 supplement had fewer ventilator-free days (14.0 vvs 17.2; P = .02) (difference, −3.2 [95% CI, −5.8 to −0.7]) and intensive care unit-free days (14.0 vs 16.7; P = .04). Patients in the n-3 group also had fewer nonpulmonary organ failure-free days (12.3 vs 15.5; P = .02). Sixty-day hospital mortality was 26.6% in the n-3 group vs 16.3% in the control group (P = .054), and adjusted 60-day mortality was 25.1% and 17.6% in the n-3 and control groups, respectively (P = .11). Use of the n-3 supplement resulted in more days with diarrhea (29% vs 21%; P = .001).

CONCLUSIONS: Twice-daily enteral supplementation of n-3 fatty acids, gamma-linolenic acid, and antioxidants did not improve the primary end point of ventilator-free days or other clinical outcomes in patients with acute lung injury and may be harmful. (Rice et al. 2011[15])

Comments: Because artificial nutrition showed potential effects on clinical outcomes in critically ill patients

during the last decade, nutrition is now considered therapy not supportive care[16,17]. Therefore, it was unexpected and disappointing that enrollment was suspended early in the OMEGA trial because of perceived futility. There are several possible explanations for these negative results. For example, although all patients in the OMEGA trial received a similar number of calories (but by design a different composition of lipids), the control group received up to 20 g of additional protein per day from the control solution. Delivery of a different amount of protein perhaps favorably influenced outcomes in that group. An alternative explanation is that because continuous administration of these supplements appeared beneficial in prior trials, perhaps the bolus delivery method used in this trial blunted the inflammation modulation effect.

Immuno Suppression in Sepsis

1. Immunosuppression in patients who die of sepsis and multiple organ failure. JAMA 2011;306:2594-605[18]

CONTEXT: Severe sepsis is typically characterized by initial cytokine-mediated hyper-inflammation. Whether this hyper-inflammatory phase is followed by immunosuppression is controversial. Animal studies suggest that multiple immune defects occur in sepsis, but data from humans remain conflicting.

OBJECTIVES: To determine the association of sepsis with changes in host innate and adaptive immunity and to examine potential mechanisms for putative immunosuppression.

DESIGN, SETTING, AND PARTICIPANTS: Rapid postmortem spleen and lung tissue harvest was performed at the bedsides of 40 patients who died in intensive care units (ICUs) of academic medical centers with active severe sepsis to characterize their immune status at the time of death (2009-2011). Control spleens (n=29) were obtained from patients who were declared brain-dead or had emergent splenectomy due to trauma; control lungs (n=20) were obtained from transplant donors or from lung cancer resections.

MAIN OUTCOME MEASURES: Cytokine secretion assays and immunophenotyping of cell surface receptor-ligand expression profiles were performed to identify potential mechanisms of immune dysfunction. Immunohistochemical staining was performed to evaluate the loss of immune effector cells.

RESULTS: The mean ages of patients with sepsis and controls were 71.7 (SD, 15.9) and 52.7 (SD, 15.0) years, respectively. The median number of ICU days for patients with sepsis was 8 (range, 1-195 days), while control patients were in ICUs for 4 or fewer days. The median duration of sepsis was 4 days (range, 1-40 days). Compared with controls, anti-CD3/anti-CD28-stimulated splenocytes from sepsis patients had significant reductions in cytokine secretion at 5 hours: tumor necrosis factor, 5361 (95% CI, 3327-7485) pg/mL vs 418 (95% CI, 98-738) pg/mL; interferon-gamma, 1374 (95% CI, 550-2197) pg/mL vs 37.5 (95% CI, −5 to 80) pg/mL; interleukin 6, 3691 (95% CI, 2313-5070) vs 365 (95% CI, 87-642) pg/mL; and interleukin 10, 633 (95% CI, −269 to 1534) vs 58 (95% CI, −39 to 156) pg/mL; ($P<.001$ for all). There were similar reductions in 5-hour lipopolysaccharide- stimulated cytokine secretion. Cytokine secretion in sepsis patients was generally less than 10% that in controls, independent of age, duration of sepsis, corticosteroid use, and nutritional status. Although differences existed between spleen and lung, flow cytometric analysis showed increased expression of selected inhibitory receptors and ligands and expansion of suppressor cell populations in both organs. Unique differences in cellular inhibitory molecule expression existed in immune cells isolated from lungs of sepsis patients vs cancer patients and vs transplant donors. Immunohistochemical staining showed extensive depletion of splenic CD4, CD8, and HLA-DR cells and expression of ligands for inhibitory receptors on lung epithelial cells.

CONCLUSIONS: Patients who die in the ICU following sepsis compared with patients who die of nonsepsis etiologies have biochemical, flow cytometric, and immunohistochemical findings consistent with immunosuppression. Targeted immune enhancing therapy may be a valid approach in selected patients with sepsis. (Boomer et al. 2011[18])

Comments: Abundant evidence exists in sepsis for the appearance of high plasma levels of proinflammatory cytokines and chemokines characterized by clinical signs of fever, tachycardia, and tachypnea and followed rapidly by development of shock, multiorgan failure, and death. Additional evidence indicates that sepsis can be associated with a state of immunosuppression, broadly defined as lymphopenia and loss of immune function, though the timing, incidence, and nature of the immunosuppression remain poorly characterized, especially in humans. Numerous investigative agents have been directed at down modulating this initial hyperimmune phase. After numerous unsuccessful trials of anti-inflammatory agents in patients with sepsis, a major shift has occurred in the way investigators view the problem of sepsis[19]. Those who survive early sepsis often develop nosocomial infections with organisms not typically pathogenic in immunocompetent hosts and have reactivation of latent viruses. Sepsis may not be attributable solely to a "cytokine storm" but may indicate an immune system that is severely compromised and unable to eradicate pathogens. Although animal studies demonstrate progression to an immunosuppressive phase, epidemiologic studies in clinical sepsis are lacking[20]. In this study, the authors have presented an informative report documenting immunosuppression in humans with septic shock. A next step might be to determine why during sepsis immune cells switch to anti-immune cells. Another question is whether such derangements in sepsis can be reversed by treatment with immune restoring agents.

Inotropics for Shock Treatment

1. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362: 779-89[21]

BACKGROUND: Both dopamine and norepinephrine are recommended as first-line vasopressor agents in the treatment of shock. There is a continuing controversy about whether one agent is superior to the other.

METHODS: In this multicenter, randomized trial, the authors assigned patients with shock to receive either dopamine or norepinephrine as first-line vasopressor therapy to restore and maintain blood pressure. When blood pressure could not be maintained with a dose of 20 μg per kilogram of body weight per minute for dopamine or a dose of 0.19 μg per kilogram per minute for norepinephrine, open-label norepinephrine, epinephrine, or vasopressin could be added. The primary outcome was the rate of death at 28 days after randomization; secondary end points included the number of days without need for organ support and the occurrence of adverse events.

RESULTS: The trial included 1679 patients, of whom 858 were assigned to dopamine and 821 to norepinephrine. The baseline characteristics of the groups were similar. There was no significant between-group difference in the rate of death at 28 days (52.5% in the dopamine group and 48.5% in the norepinephrine group; odds ratio with dopamine, 1.17; 95% confidence interval, 0.97 to 1.42; P=0.10). However, there were more arrhythmic events among the patients treated with dopamine than among those treated with norepinephrine (207 events [24.1%] vs. 102 events [12.4%], P<0.001). A subgroup analysis showed that dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock but not among the 1,044 patients with septic shock or the 263 with hypovolemic shock (P=0.03 for cardiogenic shock, P=0.19 for septic shock, and P=0.84 for hypovolemic shock, in Kaplan- Meier analyses).

CONCLUSIONS: Although there was no significant difference in the rate of death between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine, the use of dopamine was associated with a greater number of adverse events. (De Backer et al. 2010[21])

Comments: Irrespective of the underlying cause, the treatment of shock includes initial resuscitation with vasopressor and volume. A critical question is which vasopressor should be used initially. Dopamine and norepinephrine may have different effects on the kidney, the splanchnic region, and the pituitary axis, but the

clinical implications of these differences are still uncertain. Guidelines recommend that either agent may be used as a first-choice vasopressor in patients with shock. However, observational studies have shown that the administration of dopamine may be associated with higher rates of death than those associated with the administration of norepinephrine. In this study, the authors conclude that their study raises serious concerns about the safety of dopamine. However, a few important limitations of this study are noted. First, the authors defined the adequate administration of fluids as at least 1 L of crystalloids or 500 mL of colloids. This seems to be not sufficient for septic or hypovolemic shock. Second, the authors suggest that they used "equipotent" doses of vasopressors, equating 20 μg per kilogram of body weight per minute of dopamine with 0.19 μg per kilogram per minute of norepinephrine. However, the evidence of this equipotent does not exist. A remaining question is the role of vasopressin as a therapeutic agent for shock. In this study, the authors used vasopressin as rescue therapy, and only two patients in each group received vasopressin. Vasopressin is another direct-acting agent. Previous studies have compared that norepinephrine and vasopressin among patients with septic shock[22]. Vasopressin may be as effective as norepinephrine.

Summary

In recent two years, new positive data about ECMO for ARDS treatment were introduced. Moreover, a study showing that sepsis can be associated with another pathogenetic mechanism, a state of immuno-suppression and loss of immune function in human was published. These are expected that presentation of the direction for further study and development of treatment guidelines for critical care medicine.

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