Commentary

WHAT’S NEW IN SHOCK, AUGUST 2021?

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The 2021 August edition of SHOCK features four excellent review articles, seven clinical reports, and seven basic science reports that cover a range of diversified topics to include sepsis, myocardial shock and arrest, cardiopulmonary bypass, hemorrhagic shock, and burn. The articles are insightful and will help readers understand the current problems encountered in these pathologic states, and possible clinical solutions that come out of both the clinical and basic science realm.

SHOCK begins with a review by Yue et al. (1). This group performed a review and meta-analysis on mortality associated with the use of bolus injection in children with septic shock. The authors address the debate on whether bolus injection influences mortality in pediatric septic patients. A total of 9,321 pediatric patients with severe sepsis or septic shock were included (1999–2020) from India, Kenya, Tanzania, Uganda, Vietnam, Mexico, Philippines, United Kingdom, and China. Their findings show that “no bolus” is associated with a lower mortality at 48 h.

The second review article by Gupta et al. (2) presents an extensive review of Pattern Recognition Receptors, focusing on Toll-like Receptors (TLR), their ligands and the downstream signaling processes in leukocytes. The review discusses the structural similarities of the all the 10 known (human) TLR, the adaptor proteins that are associated with these receptors, including description of MyD88, MAL, TRIF, TRAM, and SARM. The review discusses TLR-4 in depth, its major ligand lipopolysaccharides (LPS), the LPS-binding proteins, and downstream signaling after ligation. The review concludes with a discussion of S100 protein ligation of TLR4, and the downstream signaling that entails. Readers will find this of great interest as a current review of Toll-like receptors and their signaling.

The third review in this month’s SHOCK is a timely discussion on the relationship between sex, gender, and clinical outcomes to sepsis. Indeed, Zhang et al. (3) have written a convincing article on why preclinical and clinical studies must include female subjects to balance the “translational” success of drug development. The authors point out that both preclinical and clinical studies are “biased” in the inclusion of male subjects. Studies that have compared male and female responses to sepsis show clear differences in the responses to trauma and sepsis, and these differences must be noted when developing pharmaceutical remedies. The authors point out that between 1997 and 2000, eight out of 10 prescription drugs were withdrawn by the FDA because of greater health risks to women. The article discusses studies that have compared male/female responses, from mesenchymal stem cell expression of cytokines to the effects of estrogen or testosterone on the response to sepsis, and will no doubt convince the reader that the inclusion of female subjects is essential for all future preclinical and clinical studies.

The final review by Liu et al. (4) discusses a paradoxical condition in COVID-19 patients that involves both hyper-inflammation and immunosuppression that eventually leads to multiple organ failure and death. The pathophysiology includes activation of both pro- and anti-inflammatory cytokines that leads to lung inflammation, T-cell depletion, myelopoiesis, with dysfunctions in the endothelial and coagulation systems. The article also discusses the pathological progression of the disease in the patients, and current therapies use against the SARS-CoV-2 infection. Like the previous article, this review is timely in that it addresses the pathophysiology of a pandemic that has swept over the world causing thousands of deaths.

The clinical science section of SHOCK begins with three articles also concerning the COVID-19 pandemic. Li et al. (5) begin with a prospective study that identified features of COVID-19 pneumonia using Ultrasonography as a method to assess severity of the disease. The authors describe thickened pleural lines, interstitial syndrome, and alveolar consolidation. The authors also show that the Lung Ultrasonic Score (LUS) on ICU admission was significantly correlated with 28-day mortality, with LUS an independent risk factor for worse outcome. The study clearly shows that lung ultrasonography can be used to assess the severity of COVID-19 pneumonia.

Bermea et al. (6) continue the COVID-19 theme with an article studying intracranial hemorrhage associated with COVID patients on extracorporeal membrane oxygenation (ECMO). ECMO is often used to support respiration in patients with pneumonia. Because COVID patients present with unique inflammatory and coagulatory issues, the author did a retrospective study, and found that ECMO can be safely used as a bridge to successful recovery. However, they found that an unexpectedly high rate of intracranial hemorrhage occurred in the COVID patients as compared with patients with other viral respiratory infections.

Glucocorticoid has recently come into the spotlight for treatment for the most severe cases of COVID-19 and SARS. The next article in SHOCK by Li et al. (7) performed a meta
analysis on a large patient population (>45K) looking at glucocorticoid use in COVID and SARS patients. They found that glucocorticoids reduced mortality in both diseases. These authors also performed a subgroup analysis and found that the beneficial effects of glucocorticoids occurred in the severe, but not mild ARDS. Other differences were mainly found in aspects regarding sex- and age-specific effects, doses, and timing of glucocorticoids treatment. The reader will find this analysis extremely thorough and contains a wealth of information.

Cold inducible RNA-binding protein (CIRP) is an intracellular cold shock protein that is released into the extracellular space during hypoxia and can act as a proinflammatory cytokine. Wang et al. (8) looked at extracellular CIRP after restoration of spontaneous circulation in patients with cardiac arrest and found that CIRP was elevated on days 3, 5, and 7 especially in non-survivors. The elevation in CIRP was correlated with plasma levels of pro-inflammatory cytokines, neurological biomarkers (NSE and S100β), lactate, and the SOFA and APACHE II scores. These authors also found that CIRP had a strong predictive value for 28-day mortality. CIRP appears to be another pro-inflammatory substance that is secreted/released after hypoxia and may be a good predictor of outcome after cardiac arrest.

Syndecan-1 (SDC1) and tissue factor pathway inhibitor (TFPI) are associated with the endothelial glycocalyx and are shed after tissue damage, inflammation, shock, and ischemia. Keyloun et al. (9) have performed a clinical study looking at both SDC1 and TFPI in 4 h blood samples from patients with burn injury. This group reported significant elevations in SDC1 and TFPI in burn patients, and both SDC1 and TFPI were strong and independent predictors for mortality. The authors suggest that either of these factors could be early predictors of mortality in burn patients as well as a predictor for the degree of endotheliopathy.

In the next article, Greenwood et al. (10) show that lactic acidosis (after Cardiopulmonary Bypass) is associated with changes in microcirculatory heterogeneity and vessel density. This group performed an exploratory prospective study using video imaging of the sublingual microcirculation. After cardiac surgery, there was an association between the increases in lactic acidosis and in perfused vessel density and heterogeneity of the microcirculation. The authors conclude that a prolonged hyperlactatemia is the result of persistent microcirculatory impairment.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a glycoprotein released from mature neutrophils after inflammation. NGAL is associated with poor outcome in patients with acute kidney injury and has therefore been used a biomarker for kidney injury. In SHOCK’s last clinical report, Fryland et al. (11) looked at plasma NGAL levels in patients with ST-elevated myocardial infarction, and found that NGAL levels were independently associated with 30-day mortality, and were predictive of late cardiogenic shock. This report suggests that NGAL may be a good biomarker to predict outcome for cardiac arrest patients.

The Basic Science portion of SHOCK starts with article showing the beneficial effects of bone marrow-derived mononuclear cells (BMMNC) on inflammatory responses in septic rats. Matsubara et al. (12) demonstrated that BMMNCs injected into septic rats (cecal ligation and puncture) severely attenuated the elevation in proinflammatory cytokines (IL1β, IL6, TNFα), Histone H3, and syndecan-1. The authors also showed that BMMNCs also decrease the severity of acute lung injury, and prolonged survival. Bone marrow-derived cells contain differentially matured monocytes, T cells, B cells, and progenitor cells, and this report suggests that BMMNCs may be a good candidate for treatment of sepsis.

The presence of NADPH oxidase-2 (Nox2) in endothelial cells and leukocytes mitigates the life-threatening organ dysfunction that occurs during severe sepsis. Trevelin et al. (13) have shown that Nox2 deficient mice have exaggerated proinflammatory responses (IL6, TNFα), elevated aspartate aminotransferase in plasma, and elevated lung neutrophil infiltration after sepsis. These authors also show that the Nox2 controls NF-κ activation and TRL-4 expression in endothelial cells. And they conclude that Nox2 attenuates the severity of sepsis (LPS) by limiting expression of NF-κ activation and TRL-4 on endothelial cells.

The next article describes lung inflammation after blast injury and the association of red blood cells with infiltration of leukocytes and platelets. Arnold et al. (14) show that red cells (whole or lysed) infused into the lungs of mice elicited an elevation in inflammatory cells. Whole red cells elicited a greater response in macrophages, lysed red cells elicited a greater response in neutrophils and neutrophil–platelet complexes. Lysed red cells also elicited a rise in the neutrophil chemoattractant CXCL1. These results show that lung inflammation can be elicited by leaking RBC, and are not only relevant to blast injury, but likely also relevant to lung injury where infiltration of red cells may occur (severe ARDS, Covid-19).

Peritonitis involves inflammatory responses to bacterial, viral, or fungal invasion, and is a serious life-threatening event. Ngamsri et al. (15) studied this condition in the context of a chemokine (Fractalkine, CX3CL1) that has been implicated in the regulation of inflammatory responses to peritonitis. CX3CL1 null mice have greater inflammatory responses (neutrophils, neutrophil–platelet complexes, myeloperoxidase activity, TNFα, IL6, CXCL1, CXCL2/3) after induction of peritonitis. The authors suggest that these responses may be related to the elevation in phosphorylated extracellular signal-regulated kinase 1/2 and expression of A Disintegrin and Metalloprotease 17. The study of these crucial regulatory mechanisms in peritonitis will allow better clinical understanding for treatment of this disease.

Hemorrhagic shock with subsequent resuscitation is associated with reperfusion injury that has been described for many organs, including the brain. Severe trauma and hemorrhage can lead to alterations in blood–brain barrier, anxiety, and sleep disturbance after recovery, even without direct brain injury at the time of trauma. The next article by L’Ecuyer et al. (16) addresses this secondary brain injury and its association with elevated blood uric acid levels. Using a rat mode of hemorrhagic shock, elimination of the elevated uric acid with uricase (urate oxidase), eliminated the elevation in brain uric acid, inflammatory cytokines, neutrophil infiltration, ICAM-1 expression, apoptosis, and blunted the changes in anxiety-like behavior. The authors suggest that circulating uric acid is detrimental and removal may be a
good additive therapeutic solution to reduce brain dysfunction related to hemorrhagic shock.

Acute cardiac dysfunction can lead to circulatory compromise, with disruption of the intestinal mucosal barrier function and bacterial translocation. Potent vasodilators and vasoconstrictors have been used clinically to combat the cardiovascular and metabolic effects of low flow in this condition, to mixed affects. Seilitz et al. (17) have developed a swine model of cardiac dysfunction to test two inodilators (Levosimendan and milrinone) and two vasoconstrictors (vasopressin and norepinephrine) commonly used in this condition. The authors found that inodilators had negligible vasodilatory effects on the gastrointestinal circulation. Both Vasopressin and norepinephrine caused vasconstriction in the gastrointestinal circulation, and vasopressin affected the mesenteric more than the systemic circulation.

Patients with massive burn show a variability in survival. This variability is postulated to be due to the patients’ responsiveness to endogenous glucocorticoids that are released during stress. In this last article, Grigsby et al. (18) found a hyperactive variant of the human glucocorticoid receptor (GR) in a population of burn patients. This variant has a single-nucleotide polymorphism changing glutamine to valine at site 459 (G459V), in the DNA-binding domain of the glucocorticoid receptor. This variant had an elevated response to hydrocortisone, methylprednisolone, and dexamethasone compared with the normal human GR. Furthermore, the variant was stimulated, not inhibited, by the GR antagonist, RU486. These data suggest that variants of human GR have the potential to alter a person’s response to stress, and may be a factor as to why glucocorticoid treatment has been variable.

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REFERENCES


