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WHAT'S NEW IN SHOCK, MARCH 2019?

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The March 2019 issue of *Shock* provides a robust combination of clinical and basic science investigations addressing important gaps in knowledge in the fields of trauma, sepsis, and inflammation. The issue consists of 16 articles with specific focus on coagulopathy, blood transfusion, biomarkers, endothelial function, macrophage polarization, and cell-based therapy. We would like to congratulate all of the authors on their exciting work.

Fibrinolysis shutdown is an independent risk factor for increased mortality in trauma. The lead article is a *post hoc* secondary analysis of thrombelastography (TEG) fibrinolysis shutdown after trauma from the landmark Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) study group (1). The PROPPR trial was a multicenter, pragmatic, randomized study designed to compare the effectiveness of two different ratios of blood products in trauma patients predicted to require massive transfusion. The study enrolled 680 patients who were randomly given a 1:1:1 or 1:1:2 ratio of platelets, plasma, and red blood cells, respectively. In the current study, Cardenas et al. grouped the patients according to their degree of fibrinolytic activity by either TEG lysis at 30 min (LY30) or plasmin-antiplasmin (PAP) complex levels. Unlike recent studies that associate the TEG LY30 fibrinolysis shutdown phenotype with poor prognosis in severely injured patients attributed to a prothrombotic state leading to death by multiple organ failure, this article suggests that TEG LY30 fibrinolysis shutdown in actively bleeding trauma patients does not represent either a prothrombotic or antifibrinolytic state. Using TEG and PAP to classify patients by degree of fibrinolysis and fibrinolytic activation, they found that most low LY30 patients actually had moderate to high fibrinolytic activation assessed by PAP and evidence of platelet dysfunction with impaired clot formation. This was confirmed by significantly elevated D-Dimer levels in the low LY30 group. The authors conclude that the TEG LY30 shutdown phenotype found in severely bleeding trauma likely represents a coagulopathic state resulting from moderate fibrinolysis with concurrent fibrinogen consumption and platelet dysfunction. These findings suggest that procoagulant clinical interventions such as plasma and platelet transfusion should still be considered in patients with the TEG LY30 shutdown phenotype. Since PAP cannot be used clinically at this time, the best method to identify those patients most likely to benefit from antifibrinolytic agents remains to be determined.

The second clinical study examines the impact of early transfusion therapy in patients with hemorrhagic shock after trauma (2). London's Air Ambulance (LAA) was the first UK

civilian prehospital service to routinely offer prehospital red blood cell transfusion (phRTx). The effect of phRTx on mortality was investigated in 539 patients. Rehn et al. demonstrated that phRTx was associated with increased survival to hospital, but not overall survival. The “delay death” effect of phRTx challenges physicians to further develop in-hospital strategies to improve survival in severely bleeding patients.

In a study of biomarkers in sepsis, Zhao et al. measured soluble programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) levels in septic patients and correlated them to disease severity and 28-day mortality (3). Forty-five healthy volunteers and 112 patients with severe sepsis and septic shock were recruited. The authors demonstrated that initial serum sPD-1 levels positively correlated with the severity of sepsis, while day 1 and day 7 levels were both associated with 28 day mortality. While the areas under the curve for each level were similar to clinical risk adjustment tools such as APACHE II and SOFA, they did not appear to provide additive predictive benefit. However, the prognostic value of sPD-1 and sPD-L1 merits further investigation in a larger cohort of patients with sepsis.

In another study on sepsis biomarkers, Pierce et al. examined the diagnostic utility of angiopoietin-1 or -2 for severe sepsis and septic shock in children less than 5 years old (4). The authors found that angiopoietin (angpt)-2 and the angpt-2/1 ratio were significantly higher in young children with severe sepsis/septic shock than those with SIRS/sepsis or no SIRS. Interestingly, however, angpt-1 and -2 did not modulate endothelial permeability *in vitro* raising questions as to the role that they play in sepsis-related endothelial dysfunction.

Since the publication of the third international consensus definition of sepsis (5), there has been debate about the relative merits of the new definition compared to a SIRS-based definition. In this issue, Scheer et al. addresses the questions: does the sepsis-3 definition facilitate earlier recognition of sepsis and septic shock and does it better predict outcomes (6)? They compared the time to sepsis identification using the Sepsis-1 and Sepsis-3 criteria in 1,696 ICU patients prospectively diagnosed with sepsis. Applying the Sepsis-3 definition resulted in a higher proportion of patients being diagnosed with sepsis within the first three hours of ICU admission. Further, 50% of patients who developed sepsis while in the ICU met the definition of sepsis a full day earlier using Sepsis-3 as compared to Sepsis-1. Lastly, the Sepsis-3 definition of septic shock was associated with higher mortality rates than the Sepsis-1 definition. These data argue that the recent re-definition of sepsis may lead to earlier recognition and more accurate prediction of outcomes.

Muscle weakness is a common sequelae among sepsis survivors. Borges et al. (7) examined the association between the rectus femoris cross-sectional area (RF_{CSA}) and muscular strength among patients with severe sepsis and septic shock. RF_{CSA} was assessed by ultrasound on ICU day two and monitored during hospitalization and patients performed serial tests of muscle strength when able to follow instructions. In 37 patients hospitalized for sepsis, there was a significant decline in RF_{CSA} between the 2nd day of ICU and hospital discharge; however, there was a concomitant increase in muscle strength. Thus, while ultrasound appears to be useful tool in monitoring muscle mass among sepsis survivors, its ability to predict muscle function is likely limited.

Elevations in serum lactate suggest organ hypoperfusion and are associated with poor outcomes in cardiogenic shock; however, their prognostic role in suspected acute ST elevation myocardial infarction (STEMI) is unknown. In this issue, Frydland et al. analyzed lactate concentrations in 2094 patients who presented with suspected STEMI (8). The authors demonstrated that lactate concentration added prognostic information beyond signs of peripheral hypoperfusion, systolic blood pressure, and left ventricular ejection fraction, and was independently associated with 30-day mortality. Based on these findings, the authors recommend lactate measurement in STEMI subjects, especially when signs of compromised hemodynamics are present.

In the last clinical study of the issue, Davidson et al. explored blood endotoxin activity in infants undergoing cardiopulmonary bypass while concomitantly focusing on alkaline phosphatase (AP) levels and their impact on endotoxemia (9). This work was based on the previous *in vitro* observation that AP reduces endotoxin toxicity. This prospective cohort study collected blood serially from 62 infants less than 120 days of age undergoing cardiopulmonary bypass. AP activity and endotoxin activity assay (EAA) were measured pre-operatively, during rewarming, and 24 hours after cardiac intensive care unit admission. The authors demonstrated that AP activity significantly decreased during cardiopulmonary bypass while EAA rose and remained stably elevated at 24 hours. The *ex vivo* addition of AP significantly reduced endotoxin activity suggesting the possibility of a clinically relative relationship. These findings should serve as the basis for future investigation into the role of AP as a potential preventative therapeutic during cardiopulmonary bypass.

Progressing into the basic science section, there are eight exciting articles, which cover an array of topics including: neonatal sepsis, experimental bacteremia, acute lung injury, and cardiac fibrosis. The employed models also vary between pigs, sheep, mice, and cells. The first article used a preterm newborn pig model to determine the protective effect of bovine colostrum on parentally nourished newborns with sepsis and neuro inflammation from a bloodstream infection (10). *Staphylococcus epidermidis* (SE) was injected to induce sepsis, followed by administration of total parenteral nutrition or oral bovine colostrum with supplementary parenteral nutrition. The authors demonstrated that colostrum supplementation reduced the SE abundance in blood and cerebrospinal fluid. Furthermore, colostrum feeding normalized arterial blood pressure and lactate and increased motor activity to control levels, as well as reduced blood-cerebrospinal fluid barrier permeability and cerebrospinal fluid leukocyte levels. The authors concluded that early oral supplementation with bovine colostrum prevents septic shock and ameliorates brain barrier disruption and neuro-inflammation during bloodstream infection in preterm pigs. Whether this effect was due to IgG or other components of colostrum or due to the simple presence of enteral nutrition should be an important area of future investigation.

There is increasing interest in the treatment of sepsis with adjunctive clonidine. Calzavacca et al. evaluated the effects of clonidine at clinically relevant doses in an experimental bacteremia model by infusion of live *Escherichia coli* in sheep (11). The authors demonstrated that the effects of clonidine at clinically relevant doses are dose dependent and more complicated than expected. High clinical doses of clonidine attenuated sepsis-induced increases in heart rate and cardiac output, with no reduction in mean arterial pressure. Low-

dose clonidine, by contrast, led to peripheral vasodilation with an associated increase in cardiac output. Both doses induced an increase in urine output and arginine vasopressin release and increased IL-10 release. These data demonstrate that clonidine has complex effects on sepsis physiology. More research is clearly needed to characterize whether it has a role in human disease.

Moving back to mouse models, the effect of amitriptyline (AMIT), an antidepressant drug on cecal ligation and puncture (CLP)-induced sepsis was investigated by Xia et al. (12). AMIT inhibits ceramide generation, which has been reported to mediate inflammation. Using thromboelastometry and ferric chloride-induced carotid artery thrombosis to measure coagulation, the authors demonstrated a dynamic early hypercoagulability, followed by delayed hypocoagulability in septic mice. AMIT treatment suppressed macrophage TNF α expression and M1 polarization while mitigating both early and late coagulopathy. Thus, AMIT may represent a promising therapeutic approach for sepsis-associated coagulopathy and inflammation.

Tissue factor (TF) and thrombomodulin (TM) are expressed by endothelial cells and exert opposing influences on coagulation with TF inducing thrombosis and TM opposing it. In the next article, Matsubara et al. examined the role of budding uninhibited by benzimidazole-1 (Bub1) in CLP-induced acute renal failure (13). Bub1 modulates Akt and JNK signaling and, therefore, may govern coagulation by affecting TF and TM expression. The authors generated Low Bub1-expressing (Bub1^{L/L}) mice that were subjected to CLP-induced sepsis. Reduction of Bub1 expression resulted in an increase in mice survival, amelioration of renal injury and a decrease in TF expression. *In vitro* studies demonstrated that Bub1 siRNA attenuates both tissue factor expression and thrombomodulin suppression by blocking Akt and JNK phosphorylation, respectively. This work provides the first evidence that Bub1 is involved in sepsis-induced acute renal failure. The authors concluded that Bub1 could be targeted for sepsis treatment.

Angiotensin II (Ang II) has been recently FDA approved to treat distributive shock; however, chronic exposure to it has been associated with cardiac fibrosis. In the next article, Yang et al. determined the involvement of CD44 in the development of cardiac fibrosis via Ang II-AT1 receptor signaling (14). WT and CD44 knockout mice were subjected to Ang II infusion with administration of the AT1 receptor blocker telmisartan. The authors demonstrated that Ang II increases expression of the AT1 receptor, TNF α , NF κ B, and CD44 as well as downregulates I κ B. Further analyses indicate that Ang II increases macrophage migration, augments myofibroblast proliferation, and induces vascular/interstitial fibrosis. Telmisartan significantly reduced expression of the AT1 receptor and TNF α , decreased NF κ B, increased I κ B, and downregulated CD44 in the intra-cardiac vessels and intermyocardium. Moreover, macrophage migration and myofibroblast proliferation were inhibited and fibrosis was attenuated. Knockout of CD44 did not affect Ang II-induced signaling, but significantly reduced macrophage/myofibroblast-mediated fibrosis. These results suggest that the AT1 receptor is involved in the development of cardiac fibrosis by stimulating TNF α /NF κ B/I κ B and triggering CD44 signaling pathways. Selective inhibition of CD44 may be considered as a potential therapeutic target for attenuating Ang II-induced deleterious cardiovascular effects.

Mesenchymal stem cells (MSCs) have been shown to decrease mortality, as well as systemic and local inflammatory responses in experimental sepsis. A limitation to using MSCs as a therapeutic agent for septic patients is the need for cells to be expanded in culture *ex vivo* for several days, while patients would most benefit from treatment in the first few hours. *Ex vivo* culturing also increases the risk of contamination and immunological reaction. A plausible alternative to MSCs could be bone marrow-derived mononuclear cells (BMDMCs), which can be harvested in larger quantities. Lorigados et al. studied the effect of BMDMCs on the systemic inflammatory response to infection (15). The authors demonstrated that an early single intravenous injection of BMDMCs in animals subjected to the murine models of endotoxemia and cecal ligation and puncture (CLP) resulted in improved survival rate, decreased necrosis and apoptosis of mononuclear cells, reduced plasma TNF α , and increased plasma IL-10 levels. Further, *in vitro* experiments suggested that direct contact between BMDMCs and macrophages could be important to the production of IL-6, IL-10, and nitric oxide while TNF α production is negatively regulated by PGE₂. BMDMCs may provide a promising therapeutic option for sepsis.

Macrophage polarization may contribute to the progression of acute lung injury. Wang et al. reported an interesting study on a selective $\alpha 7$ nicotinic acetylcholine receptor agonist, GTS-21 in LPS-induced acute lung injury (16). The authors focused on the effect of GTS-21 on alveolar macrophage polarization and demonstrated that the adoptive transfer of M1-polarized alveolar macrophages enhances LPS-induced lung inflammation in contrast to the adoptive transfer of M2-polarized macrophages. Intraperitoneal GTS-21 protected the lung from LPS-induced injury, decreased the number of alveolar macrophages, and reduced pro-inflammatory cytokine and high mobility group box 1 levels in alveolar macrophages. GTS-21 also significantly decreased the number of M1-polarized alveolar macrophages and increased the number of M2-polarized alveolar macrophages. These data suggest that GTS-21 protects against LPS-induced lung injury by altering alveolar macrophage polarization and function.

The final article by Zhao et al. is a mechanistic study revealing the role of histone methylation in inflammatory responses (17). Using Raw 264.7 cells and bone marrow-derived macrophages, the authors demonstrated that LPS stimulation resulted in enhanced methylation at H3K4 and H3K9. H3K4me2 was enriched at the promoter sites of both IL-6 and TNF α and LPS-stimulated release of IL-6 and TNF α were significantly reduced by MTA, a specific inhibitor of H3K4 methylation. These studies emphasized the importance of histone methylation in LPS-induced inflammation, which may represent a new target for the pharmacological therapy of sepsis.

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