Published in final edited form as:

*Shock*. 2019 December ; 52(6): 566–567. doi:10.1097/SHK.0000000000001438.

# WHAT'S NEW IN *SHOCK*, DECEMBER 2019?

**Russell B. Hawkins**, **Philip A. Efron**, **Shawn D. Larson**

Department of Surgery, University of Florida, Gainesville, Florida

This issue of *Shock* contains 13 excellent manuscripts furthering our understanding of the pathophysiology of inflammation, shock, organ dysfunction, and sepsis. A major theme this month is the potential for personalized medicine and novel therapeutics to help patients suffering from shock. Yepuri et al. (1) present an excellent review of Sparstolonin B, an ingredient in traditional Chinese medicine, summarizing its anti-inflammatory effects and selective suppression of Toll-like receptors. The authors comprehensively summarize the molecular structure of Sparstolonin B and highlight exciting recent animal work regarding its potential to reduce mortality and obesity-associated inflammation in an endotoxin mouse model.

Multiple studies in this issue present novel methods of determining prognosis for shock patients. Li et al. (2) performed a retrospective study of 35 septic shock patients, demonstrating that variations in ventricular-arterial coupling helped to predict which patients responded well to volume resuscitation. The authors performed highly detailed physiologic measurements in patients, furthering our understanding of hemodynamic changes during septic shock and the effects of volume resuscitation in patients with different levels of ventricular-arterial coupling.

Continuing the theme of prognosis determination in sepsis, Kahn et al. (3) studied the value of heparin-binding protein to determine the extent of organ dysfunction in emergency department patients with suspected sepsis. The authors performed a rigorous, multicenter, prospective study demonstrating that heparin-binding protein levels performed well (AUC 0.73) at predicting organ dysfunction, and that the prediction model improved (AUC 0.82) when considering only patients adjudicated as definitely having an infection. The authors suggest that heparin-binding protein has potential as a biomarker to predict outcomes in sepsis, and may offer the potential for personalized medicine.

Chen et al. (4) sought to predict outcomes, evaluating central venous-to-arterial $CO_2$ content as a predictor of poor outcomes following cardiac surgery. In this study, the authors performed a retrospective, propensity-matched analysis of cardiac surgery cases, finding that patients with poor outcomes had a much higher venous-to-arterial $CO_2$ difference. Here the AUC was 0.837 to predict poor outcomes following cardiac surgery, outperforming central venous $O_2$ saturation and lactate, opening the possibility for additional important physiologic measurements to predict outcomes in this population.

Nutrition is an important factor in survival and outcome from a wide array of physiologic insults. Cha et al. (5) studied the association of vitamin D levels with neurologic outcome and mortality after sudden cardiac arrest. On multivariate analysis, the authors found that

severe vitamin D deficiency on patient presentation was a strong independent predictor of mortality and poor neurologic outcomes, highlighting the importance of adequate nutrition and further showing the importance of population-based public health initiatives.

It is increasingly apparent that patients respond differently to similar physiologic derangements and interventions. Previous studies have shown remarkable differences in patient response to glucocorticoid administration in sepsis, with limited large-scale demonstration of benefit. Green et al. (6) hypothesized that differential patient responses to glucocorticoids may be due to variations in the human glucocorticoid receptor. The authors screened for human glucocorticoid receptor variants in burn patients and in peripheral blood mononuclear cells stimulated with lipopolysaccharide (LPS). The authors found three novel splice variants with cryptic exons upregulated after LPS exposure and discovered that these splice variants were also expressed by burn patients at various times during their clinical course. This exciting work raises the possibility of personalizing glucocorticoid therapy to patients by determining their human glucocorticoid receptor expression profile during sepsis or trauma.

Continuing our theme of prediction of outcomes, Baek et al. (7) present an excellent manuscript seeking to better understand the clinical factors that influence the duration of continuous renal replacement therapy (CRRT) among patients with acute kidney injury. In a retrospective analysis of all patients requiring CRRT for acute kidney injury, the authors found that urine output, use of mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) support were all significant independent predictors of requiring over 6 days of CRRT on multivariate analysis. Creatinine and lipocalin levels were not independent predictors of long-duration CRRT. Knowledge of these clinical factors may help us better predict CRRT duration, guiding resource allocation and better personalizing treatment.

Wang et al. (8) next present very interesting work regarding the importance of the omentum in response to intra-abdominal infection. Here, the authors induced polymicrobial sepsis by performing cecal ligation and puncture (CLP) on experimental mice, subjecting mice to omentectomy with CLP or to CLP alone. The authors observed significantly higher mortality in the omentectomy group, as well as significant alterations in cytokine production and immune cell composition at various time points following surgery. These results suggest a critical early role of the omentum in response to intra-abdominal sepsis.

Acute aspiration can be a devastating event for hospitalized patients. Suresh et al. (9) present thought-provoking work regarding the importance of hypoxia-inducible factor 1-alpha (HIF-1α) in the inflammatory response to aspiration. The authors evaluated the function of HIF-1α in type 2 alveolar cells following acid aspiration, which resulted in marked increases in HIF-1α levels and an acute inflammatory response in the lung. This excellent work shows that acute aspiration-associated hypoxia involves multifactorial inflammation with neutrophil accumulation, macrophage apoptosis, and increased permeability. Furthermore, this manuscript suggests that HIF-1α may be a promising target for therapeutic modulation following acute aspiration events, potentially opening a new avenue of research for this important clinical problem.

Mitochondrial dysfunction may cause lasting cellular damage, and the effects of sepsis on mitochondria have thus far been unclear. Makrecka-Kuka et al. (10) evaluated tissue-specific changes in mitochondrial function after endotoxin injection in mice. The authors found that both the heart and kidney underwent significant organ dysfunction after LPS administration, with concurrent decreases in mitochondrial fatty acid oxidation in both organs. However, the heart rapidly recovered mitochondrial function while the kidneys failed to recover. Brain mitochondrial function was largely unaffected. This novel work suggests that, following endotoxin stress, the kidneys undergo significant mitochondrial dysfunction that does not recover and may lead to long-term organ dysfunction as seen in sepsis with acute kidney injury.

Continuing the theme evaluating novel therapeutics for shock-related organ dysfunction, Li et al. (11) evaluated the protective effect of methane-rich saline (MRS) on sepsis-induced liver injury. In this study, the authors performed CLP on mice followed by intraperitoneal MRS injection 30 minutes and 12 hours after surgery. MRS treatment was associated with decreased markers of liver cell damage, decreased liver histopathology, and reduced local liver inflammation. Additionally, MRS treatment reduced Toll-like receptor 4/NFκB activation and prevented liver damage in the CLP model via an anti-inflammatory, anti-oxidative, and anti-apoptotic fashion involving the PPAR-γ and NFκB pathways. This work raises the possibility of methane-rich saline treatment in reducing inflammation and organ injury acutely during sepsis, offering another avenue of novel therapeutic research.

In another addition to our understanding of potential therapeutics in sepsis, Cui et al. (12) evaluated the use of N-acetylcysteine to reduce gentamicin-associated nephrotoxicity in a novel animal study. Gentamicin is a powerful antibiotic, but its use is limited due to its well-known nephrotoxicity related to intracellular oxidative stress and inflammation. In this manuscript, the authors sought to determine changes in autophagy in response to N-acetylcysteine administration after gentamicin. N-acetylcysteine attenuated histopathologic changes associated with gentamicin and ameliorated gentamicin-induced decreases in autophagy proteins. Importantly, N-acetylcysteine may help reduce the inflammatory response following gentamicin treatment, and offers a potential therapeutic option to prevent acute kidney injury.

Finally, an exciting novel therapeutic potential in the treatment of shock involves gene transfer. In this work, Shang et al. (13) sought to determine whether inhibition of G-protein coupled receptor kinase 2 by adenoviral β-ARKct cardiac gene transfer could reduce post-resuscitation myocardial injury in pigs with cardiac arrest. Here the authors induced ventricular-fibrillation cardiac arrest in control pigs and those pre-treated with the gene transfer vector, noting that the β-ARKct treated group had better cardiac output, ejection fraction, lower troponin I and CK-MB, and decreased lactate after resuscitation. β-ARKct treated pigs also had upregulation of beta-1 adrenergic receptors. This novel work shows the potential for gene transfer to result in significant cardiac remodeling and improved outcomes following devastating cardiac arrest, highlighting future areas of gene transfer study in the recovery from shock.

In summary, this issue of *Shock* contains many exciting manuscripts encompassing a wide array of clinical and basic science research from international sources. The manuscripts collectively broaden our understanding of shock, suggest potential new prognostic markers, and raise the possibilities of novel therapeutics and promising new lines of research.

## References


1. Yepuri N, Dhawan R, Cooney M, Pruekprasert N, Meng Q, Cooney RN. Sparstolonin B: A unique anti-inflammatory agent. Shock 52:____-____, 2019.
2. Li S, Wan X, Laudanski K, He P, Yang L. Left-sided ventricular-arterial coupling and volume responsiveness in septic shock patients. Shock 52:____-____, 2019.
3. Kahn F, Tverring J, Mellhammar L, Wetterberg N, Bläckberg A, Studahl E, Hadorn N, Kahn R, Nueesch S, Jent P, Ricklin ME, Boyd J, Christensson B, Sendi P, Akesson P, Linder A. Heparin-binding protein as a prognostic biomarker of sepsis and disease severity at the emergency department. Shock 52:____-____, 2019.
4. Chen T, Pan T, Luo X, Wang D. High central venous-to-arterial $CO_2$ difference is associated with poor outcomes in patients after cardiac surgery: A propensity score analysis. Shock 52:____-____, 2019.
5. Cha J-J, Wi J. Vitamin D deficiency and neurologic outcome after sudden cardiac arrest. Shock 52:____-____, 2019.
6. Green TL, Leventhal SM, Lim D, Cho K, Greenhalgh DG. Lipopolysaccharide stress induces cryptic exon splice variants of the human glucocorticoid receptor. Shock 52:____-____, 2019.
7. Baek SD, Kang J-Y, Shin S, Park H- S, Kim M- S, Kim SM, Lee EK, Chang JW. Predictive factors of duration of continuous renal replacement therapy in acute kidney injury survivors. Shock 52:____-____, 2019.
8. Wang AW, Cauvi DM, Hawisher D, Reyes T, Coimbra R, Bickler S, De Maio A. The contribution of the omentum to the outcome from sepsis: An experimental animal study. Shock 52:____-____, 2019.
9. Suresh MV, Balijepalli S, Zhang B, Singh VV, Swamy S, Panicker S, Dolgachev VA, Subramanian C, Ramakrishnan SK, Thomas B, Rao TC, Delano MJ, Machado-Aranda D, Shah YM, Raghavendran K. Hypoxia-inducible factor (HIF)-1α promotes inflammation and injury following aspiration-induced lung injury in mice. Shock 52:____-____, 2019.
10. Makrecka-Kuka M, Korzh S, Vilks K, Vilskersts R, Circule H, Dambrova M, Liepinsh E. Mitochondrial function in the kidney and heart, but not the brain, is mainly altered in an experimental model of endotoxaemia. Shock 52:____-____, 2019.
11. Li Z, Jia Y, Feng Y, Cui R, Wang Z, Qu K, Liu C, Zhang J. Methane-rich saline protects against sepsis-induced liver damage by regulating the PPAR-γ/NF-κB signaling pathway. Shock 52:____-____, 2019.
12. Cui J, Tang L, Hong Q, Lin S, Sun X, Cai G, Bai X-Y, Chen X. N-acetylcysteine ameliorates gentamicin-induced nephrotoxicity by enhancing autophagy and reducing oxidative damage in miniature pigs. Shock 52:____-____, 2019.
13. Shang D, Zhu F, Tan Q, Hu B, Liu D, Cong M, Song J, Li T, Ji X. Adenoviral βARKct cardiac gene transfer ameliorates postresuscitation myocardial injury in a porcine model of cardiac arrest. Shock 52:____-____, 2019.