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What's New in Shock? March 2016

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In this edition of *Shock*, there are many high quality and interesting reviews, as well as outstanding research reports. The preface by Drs. Kellum and Gomez (1) elaborates on a series of papers in this issue of *Shock* which are dedicated to the understanding and exploration of the mechanisms by which sepsis induces organ dysfunction. These papers are the result of the Fourteenth International Consensus Conference of the Acute Disease Quality Initiative (ADQI).

Along other reports, Chawla *et al.* (2) review the latest findings and discoveries that associates epithelial dysfunction with organ dysfunction in sepsis. This occurs when cell death is not obvious, but the function of organs profoundly altered. The authors elegantly discuss modalities that might enable clinicians to determine prognosis, therapeutic targets, or response to therapy in this group of patients. Although these studies mainly remained experimental, there is hope that targeted therapy of epithelium will improve outcome of septic patients.

Kellum et al. (3) report on the effort to develop a consensus for blood purification in patients with sepsis-induced organ dysfunction by using a modified Delphi method. This is a major movement since there is no common consensus on how extracorporeal blood purification therapy might be applied or studied in patients with sepsis. The morbidity and modalities involved with sepsis show a very wide range of clinical and molecular phenotypes from patient to patient, mainly due to pathogen and/or the host-specific factor. As such, it is difficult to have a common consensus on how extracorporeal blood purification therapy may be use for these patients. While we can't discuss all aspects of this consensus here, we leave it up to the reader and strongly recommend to dive into these papers. We believe, that these papers can open a dialogue to substantially advance the knowledge in the field and improve our clinical practice for these patients.

On same topic of sepsis, Ince *et al.* (4) review and discuss another cell type involved in sepsis, which are the endothelial cells. The authors discuss endothelial cell-associated hemostatic responses to sepsis and their response to inflammation. By highlighting the differences between endothelial cells lining in different organs and their responses to sepsis, the authors delineate the response of these cells in the three key organs: kidney, liver and lungs. Despite the new insights, the authors acknowledge that assessing endothelial cells lining function is yet to be advanced at the bedside and that specific targeting of these cells remains a challenge.

Sepsis is a complex, yet mysterious entity with a broad clinical phenotype. This phenotype cannot be limited to one cell type or one system. Although at a cellular level, alterations in

vascular biology such as endothelial dysfunction and coagulopathy, as well as epithelial dysfunction and immune system dysregulation has been studied during sepsis, some intracellular organelles like mitochondria are less well studied. Pinsky *et al.* (5) raised five crucial questions about the role of mitochondria in sepsis. While all the questions are interesting to expand on, we found that the first question asking whether mitochondria are initiators, victims or innocent bystanders in the organ dysfunction in sepsis, was the essential platform to discuss more in detail. Understanding the answer will enlighten our approach in early diagnosis and management of patients with sepsis. The authors refer to this histopathological observation where a normal cellular morphology has been observed, despite organ dysfunction. They suggest that signals from mitochondria could be responsible for deficient cellular function in these cases of patients. However, they highlight that tissue damage may be the underlying mechanism for mitochondrial dysfunction. But as every good study and as we always say, a good study asks more questions than providing answers, this report really opens the door for various questions: Is it mitochondria or tissue specific? Is this really organ/tissue dependent? What comes first and what is the consequence?

Moving to the immune system and its dysfunction during sepsis, Rimmele *et al.* (6) discussed various changes in different components of the immune system during sepsis. Due to the accessibility of different cellular and extra cellular components of the immune system through peripheral blood, our knowledge has advanced, yet to be complete. Indeed, leukocytes may serve as an indicator of failure in systemic responses during sepsis, some associated with poor outcomes. Summarizing the techniques for studying the circulating leukocytes during the sepsis, the author highlighted several surface markers that modulate during sepsis in neutrophil and monocyte. Can a marker or a combination of markers serve as a predictive platform for early diagnosis or sepsis? What about a platform for prognosis evaluation? While new reports tried to address this, further attempts with larger sample size might enlighten this matter. The author discussed this by raising the question of “can immune cells serve as biopsy?”

On this subject, Maslove *et al.* (7) in the “clinical aspect” section of this edition of *Shock*, report on their systemic analysis on 22 separate gene expression studies of whole blood (15 studies) or leukocyte fraction (7 studies) of septic patients. The data was obtained from Gene Expression Omnibus (GEO) database. The authors partitioned samples using clustering methods based on the gene expression level. Comparing the whole blood with leukocyte isolates, the author conclude the whole blood generated greater specificity for the diagnosis of sepsis and more cohesive clusters. The authors also report that when using this method, pediatric cohorts show higher specificity for diagnosis of sepsis compared with adult cohorts. While the authors discussed the limitation of their report in detail, we also believe that combining different microarray platforms is a confounding factor as they discussed, more specifically the significant difference in silhouette widths which is reported here for one of the platforms.

In an elegant, well designed study, Zhang *et al.* (8) provided multiple line of evidence that show phosphatidylserine (PS) role during inflammation-associated coagulopathy in sepsis. The authors show an important role for PS in augmenting coagulation in sepsis when it exposed to microparticles, blood cells and endothelium. This is in line with their previous

work (9), which shows reduction in neutrophil PS decreased mortality in mouse model of sepsis. The next logical step would be to study their novel and exciting data in a clinical system.

Hayakawa *et al.* (10) reported on the predictive value of High D-dimer level on arrival of trauma patients. The study included 519 adult patients with severity score of 16, in a multicentre retrospective study. The authors reported a lower survival in the high D-dimer group of patients regardless of their fibrinogen level. This led them to conclude that high D-dimer is a predictor of early death or a predictor of requiring massive transfusion in severe trauma.

Moving to prognostic markers, Zhao *et al.* (11) presented data that showed tight junction associated proteins level in the plasma might serve as a prognostic marker for sepsis in emergency departments. As discussed, sepsis is partly an endothelial cell dysfunction entity and it is presumable that damage in endothelial cells can lead to disruption in tight junction, hence releasing tight junction protein in circulation. Analysing occludin (OCLN), claudins, zonula occludens (ZO-1), procalcitonin and lactate level, the author found that the level of ZO-1 and OCLN can serve as the early prognostic marker in sepsis patients.

Radiocontrast media (RCM) is routinely administered during Computed Tomography (CT) scanning with reported adverse reactions of 1-3% upon administration. What are the risk factors associated with RCM-induced anaphylactic shock? Kim *et al.* (12) evaluated 154 patients retrospectively whom admitted to the emergency department with clinical manifestation of anaphylaxis due to administration of RCM. Using multivariate analysis, the authors showed that age, neurological manifestations, and allergy history were associated with the development of shock. The median time between RCM exposure and the development of shock was very short, at only 11 min, emphasizing a careful attention to the elderly patients and patients with neurologic manifestations.

Again on predicting variables, Siren *et al.* (13) report on predictive value of admission Heme oxygenase-1 (HO-1) for predicting mortality and Cerebral Performance in patients who resuscitated from out-of-hospital cardiac arrest. Measuring HO-1 at admission and on day 1, they showed that admission HO-1 has a reasonable predictive value for 90 days mortality (AUC ~0.623) and for 12-month Cerebral Performance Category (AUC~0.611). While it might be useful to use HO-1 as a general marker of disease severity, its specificity, in particular for specific organ damage diagnosis should be studied and addressed carefully in future.

We hope you will enjoy reading through this issue of Shock and anticipate our annual meeting which will have a lot of great science and research and a chance to interact with a lot of the current authors.

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