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From the Desk of the Editor

Opportunities and Challenges of Application of Cytosorb Therapy in Sepsis Management

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Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection. In 2017, an estimated 48·9 million incident cases of sepsis were recorded worldwide, and 11·0 million sepsis-related deaths were reported, representing 19·7% of all global deaths.[1] Though overall data related to sepsis is poor but it is also a major health care challenge for resource limited countries. Severe sepsis is a significant & common health problem in ICU patients of Bangladesh[2]. A continuum of severity from sepsis to septic shock and multi-organ dysfunction syndrome (MODS) exists. MODS is a clinical syndrome characterized by the development of progressive and potentially reversible physiologic dysfunction in 2 or more organs or organ systems that is induced by a variety of acute insults, including sepsis. Sepsis leads to malignant intravascular inflammation, coagulopathy, circulatory derangement, tissue hypoxia, cytotoxicity and apoptosis. As a result, dysfunction of vital organ systems occur. Host response and other factors influenc outcome. Patients with sepsis must be treated with-timely, appropriate antibiotics, intravenousfluids, vasopressor and inotropic support & oxygen therapy.[3] Other additional treatments including extracorporeal blood purification techniques (BPT). These techniques include hemofiltration, hemoperfusion, intermittent or continuous high-volume hemofiltration (HVHF), plasmapheresis or adsorption.[4] The rationale behind such an approach is to achieve “immune homeostasis” which theoretically reduces the potential damage caused by dysregulation of the host response to infection. Given the pivotal role of cytokine production in sepsis, it follows that removal of these substances, through such BPT, may attenuate the response particularly in the early phase of sepsis.[5] Indications include 1) Rhabdomyolysis resulting from Reperfusion syndrome, Trauma, Malignant Hyperthermia. 2) External injuries including Sepsis / Septic shock, Hemorrhagic shock, Trauma, Ruptured aortic aneurysm, Post-Cardiac Arrest Syndrome, Cardio-pulmonary resuscitation, Extensive surgery, Organ transplantation, Cardiosurgical intervention, Severe skin and soft tissue damage, Burns, Necrotizing fasciitis, Post-Cardiotomy Syndrome, Acute Respiratory Distress Syndrome. 3) Diseases: Pancreatitis, Liver insufficiency, Renal insufficiency, Stroke, Myocardial infarction, Cardiogenic shock / Heart failure, Tumor Lysis Syndrome, Hemophagocytosis Syndrome. Liver failure / Hyperbilirubinemia bridging to transplant or to recovery, Life-threatening bleeding under Direct Oral Anticoagulants (DOAC)[6].

Substances removed by Cytosorb therapy include Pro inflammatory cytokines: IL 2, IL3, IL6, IL8, IL9, IL18, TNF-α, IFN-γ. Anti-inflammatory cytokines: IL4, IL13, IL10 etc., Hormones: T3, Cortisol, Drugs: Antibiotics: Aminoglycoside, Linezolid, Clindamycin, Meropenem, Glycopeptide, Piperacillin etc. Other drugs: Digoxin, Rivaroxaban, Dabigatran, phenobarbital, Tacrolimus etc. Metabolic products: Bilirubin, Bile acid, Ammonia, Triglyceride etc.

COVID-19 is characteristically sepsis due to viral infection[7]. So, there is basis of cytokine removal therapy as some patients showing cytokine storm. To date, more than 5,750 critically ill patients with COVID-19 infection have been treated with Cytosorb in over 30 countries. On 10 April 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization for emergency use of Cytosorb to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure by reducing pro-inflammatory cytokine levels, which may ameliorate a cytokine storm due to the overabundance of pro-inflammatory cytokines and, in turn, provide clinical benefit to such patients.Worldwide over 221,000 single treatments of Cytosorb therapy have been performed to date.[8]

Despite having some promising data but to date, there is not enough data to provide any kind of evidence-based recommendations for the use of sorbent technologies, but the following points have been considered as most important unanswered questions which may aid further recommendations. They are as follows.

1: Which patient would benefit the most from cytokine removal?

2: When to start cytokine removal therapy in sepsis?

3: How long should cytokine removal therapy last and how long should it be continued?

4: Which patient population should be studied in the future?

5: What severity of sepsis would be the most appropriate to include in a study looking at cytokine removal therapy in patients with sepsis?

6: Which biomarker should be the most appropriate to include in a study looking at cytokine removal therapy in patients with septic shock?

For the time being, clinical results with the use of cytokine adsorbent therapies are scarce. More studies should be performed to have a precise idea of adsorption properties (kinetics, saturability, potential mediator release, drug

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removal) of the adsorbent. Plasma cytokine levels before and after treatment of various cytokines should be provided to clearly demonstrate the adsorptive properties.

Though it is a newer therapy and require advance setup, in recent years dialysis facilities have gradually increased among both Government and Private hospitals in Bangladesh. At present 187 dialysis facilities are available in the country.[9] So, there is a scope of application of Cytosorb therapy, and it is available since 2018 in Bangladesh. Due to lack of data, it is difficult to assess its outcome. The challenges include cost affordability, device (cartridge) availability, expert consensus for its use and indications, and availability of skilled therapist and technician.Similarly, it is also used in India and Sri Lanka to treat sepsis, selective cases of COVID-19 infection, Dengue etc. Data has shown some promising outcome in terms of reduced mortality, morbidity, decrease need of vasopressor and early hospital discharge.Cytosorb therapy is widely used in European and Middle east countries in comparison to resource limited countries. Data also has shown some promising outcome in terms of early liberation from vasopressor, less ICU days and reduce hospital stay.

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