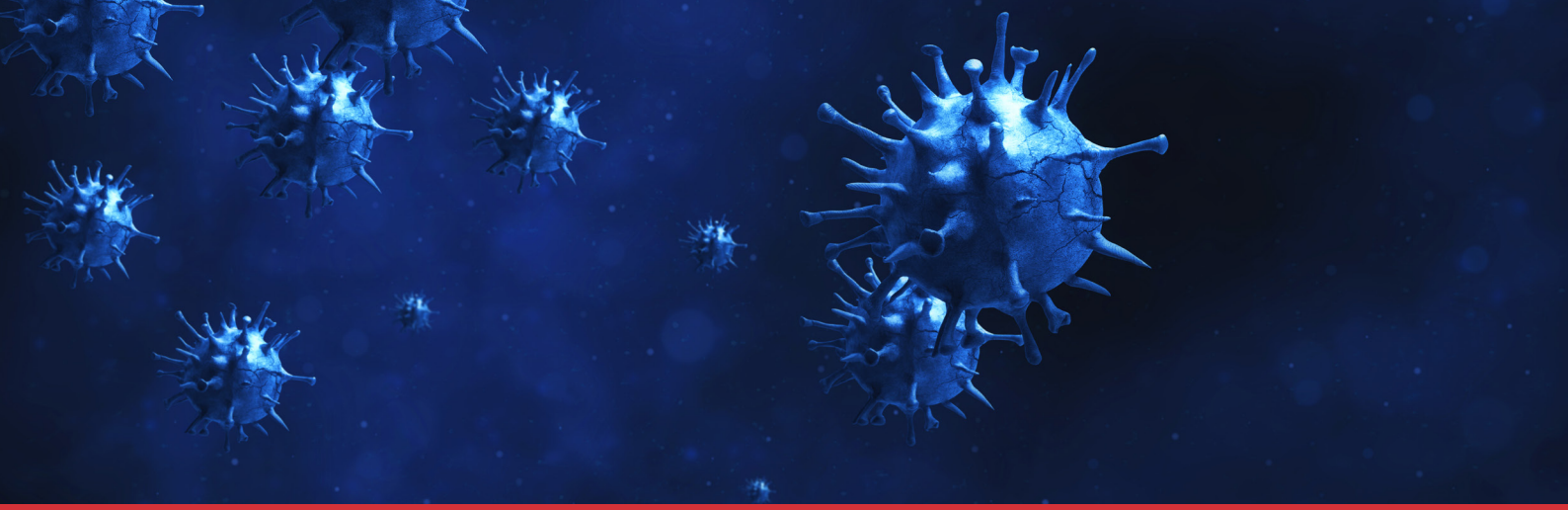


ENDOTOXIN REMOVAL IN COVID-19

Is there a rationale for endotoxin removal in severely ill COVID-19 patients? As a matter of fact, 90% of patients with severe pulmonary forms of COVID-19 have increased endotoxin levels and the level of endotoxin is directly related to the severity of COVID-19.[1,2] Also, these patients are at high risk of sepsis.[3]

Endotoxin triggers cytokine storms

The spike protein in SARS-CoV-2 has been shown to bind to endotoxin, starting the inflammatory signalling and dysregulated immune response.[4] Endotoxin is one of the most potent bacterial inducers of cytokines and can induce a cytokine storm through binding to Toll-like receptor 4 (TLR4).[5,6,7,8]

High risk and prevalence of bacterial infections

Dysregulation of the immune system may be associated with a high risk of developing a secondary bacterial infection. Studies show that up to 60% of COVID-19 patients in the ICU have secondary bacterial infections - most commonly respiratory infections from gram-negative bacteria.[9]

COVID-19 patients with pulmonary superinfections require longer ICU-treatments[10] and are at higher risk of ventilator-associated pneumonia (VAP)[11] - in fact, it is the most frequent hospital acquired infection in these patients, and it is often caused by gram-negative bacteria. Furthermore, VAP has been demonstrated to be the most frequent hospital infection associated with septic shock.[12]

In the absence of a bacterial infection, antibiotic treatment can cause release of endotoxin, triggering endotoxemia and over-production of pro-inflammatory cytokines - an antibiotic-induced inflammatory storm.[13]

Translocation of bacteria from the gut

Endotoxin in COVID-19 does not originate from the virus itself but is thought to be released from gram-negative bacteria in the gut, due to inadequate blood flow.[14,15,16,17] The gut barrier dysfunction that allows endotoxin to leak out from the gut into the blood, can potentially cause sepsis and multiple organ failure.[18] Also, it can travel to the lungs and affect the immune response as well as the lung microbial composition.[19]

It is argued that comorbidities of COVID-19 such as obesity, type 2 diabetes, cardiovascular diseases, and old age of patients – comorbidities in which increased levels of endotoxin are found – are connected via viral–bacterial interactions, initiated by translocation of bacterial products such as endotoxin from the gut into circulation.[20] In fact, translocation of endotoxin could play a larger role than previously thought in severely ill COVID-19 patients.[21]

Complement activation increases endotoxin levels

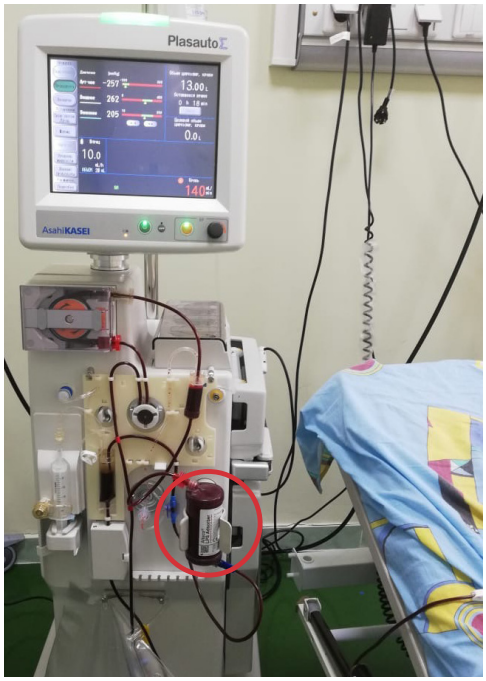
The use of mechanical and hemodynamic support heightens the immune response of the patient. Being on ECMO- and/or a CRRT machine, the patient may have an inflammatory response to extracorporeal circulation (complement activation) resulting in increased endotoxin levels.[22,23,24,25]

Endotoxin removal in COVID-19 - conclusion

Extracorporeal techniques have a possible role in “restoring a balanced immune response by eliminating/deactivating inflammatory mediators”.[26] Binding and clearing endotoxins from circulation could be an appropriate intervention in the fight against COVID-19.

Studies have shown that endotoxin adsorbtion results in clinical improvement in severe COVID-19 patients with elevated endotoxin levels (measured by EAA, Endotoxin Activity Assay).[27]

The Alteco LPS Adsorber removes endotoxin (lipopolysaccharide, LPS) from the patient’s blood as it passes through the device. Based on the significance of endotoxin in COVID-19, the Alteco LPS Adsorber may be of use in COVID-19 patients suspected to have gram-negative bacterial infection, signs of inflammatory response, endotoxemia or sepsis.[28] The removal of endotoxin turns down the exacerbated immune response, helping to stabilize the patient’s hemodynamic parameters.[29]



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10 Bacterial pulmonary superinfections are associated with longer duration of ventilation in critically ill COVID-19 patients
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13 Possible Cause of Inflammatory Storm and Septic Shock in Patients Diagnosed with (COVID-19)
14 COVID-19: it’s all about sepsis
15 “Cytokine storm”, not only in COVID-19 patients. Mini-review
16 Preexisting and inducible endotoxemia as crucial contributors to the severity of COVID-19 outcomes
17 Endotoxin Adsorbent Therapy in Severe COVID-19 Pneumonia
18 Chapter 14 - Contribution of gut microbiota and multiple organ failure in the pathogenesis of COVID-19 infection
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24 Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study
25 Elevated levels of endotoxin, oxygen-derived free radicals, and cytokines during extracorporeal membrane oxygenation
26 Extracorporeal Blood Purification and Organ Support in the Critically Ill Patient during COVID-19 Pandemic: Expert Review and Recommendation
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29 Prolonged Cardiopulmonary Bypass is a Risk Factor for Intestinal Ischaemic Damage and Endotoxaemia