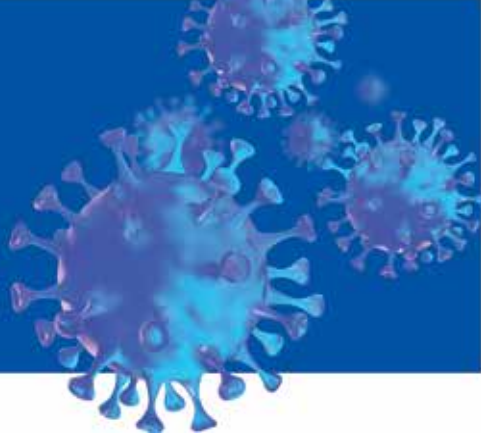
Endotoxemia in critically ill COVID-19 patients
from pathophysiology to advanced targeted complementary therapies



Critically ill COVID-19 patients present a dysregulated host response to infection caused by the primary viral SARS-CoV-2 infection and/or subsequent bacterial superimposed infections. This can lead to unresponsive septic shock with high fatality rate [1]. Gut dysbiosis during COVID-19 is associated with increased risk for bacteremia and translocation of bacterial products [2].

The pathophysiology provides a rationale for the application of Polymyxin B hemoperfusion as additional therapy for the management of critically ill COVID-19 patients with unresponsive endotoxic shock.

Here we review the recent literature on COVID-19 pathophysiology and the application of Polymyxin B hemoperfusion therapy for critically ill COVID-19 patients with unresponsive endotoxic shock.

COVID-19 and superinfections

Critically ill COVID-19 patients present a dysregulated host response to infection caused by the primary viral SARS-CoV-2 infection and/or subsequent bacterial superimposed infections (superinfections). This can lead to conditions of unresponsive septic shock with high fatality rate. Secondary bacterial infections, often of Gram-negative origin, and significantly higher circulating levels of endotoxin are frequently detected in these patients. Gut dysbiosis during COVID-19 has been shown to be associated with increased risk for bacteremia and translocation of bacterial products [2-4]. Endothelial injury and loss of barrier function cause bacterial products to enter the circulation and contribute to the pathophysiology of COVID-19 [5]. In fact, some patients also have gastrointestinal symptoms in addition to the more common fever and respiratory symptoms [6, 7].

Despite the common assertion that COVID-19 is a "cytokine storm"-induced pathogenic process, various published data show clearly that in the case of COVID-19 it is probably more reasonable to talk about a "cytokine drizzle" with significantly lower levels of pro-inflammatory cytokines than in other types of critically ill patients [8-10].

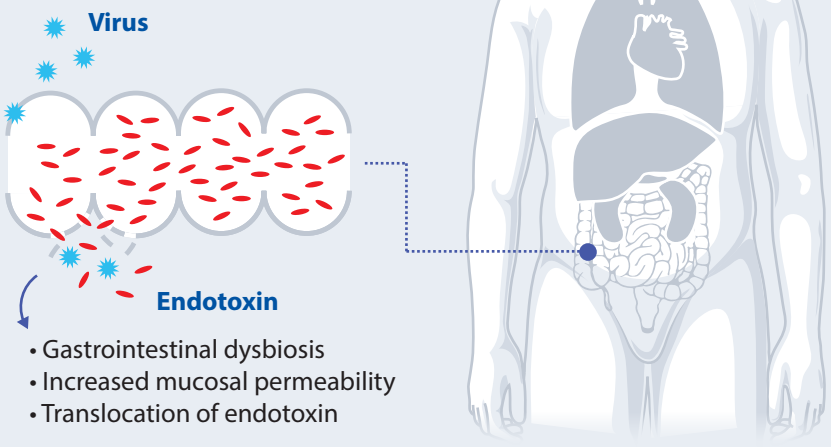
Endotoxemia in critically ill COVID-19 patients

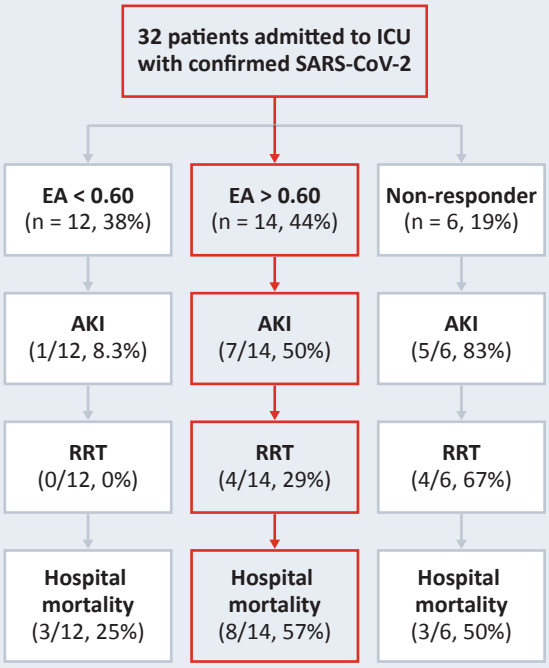
The critically ill COVID-19 patient is often immunosuppressed and prone to superimposed bacterial infections (superinfections) [1]. Superinfections in the critically ill patient are associated with a worse outcome [1]. A recent study published in Science [11] revealed that COVID-19 patients hospitalized in the ICU had significantly higher circulating levels of bacterial DNA and endotoxin and this was correlated with increased levels of inflammatory mediators. These results suggest that the increase in inflammatory mediators is caused by bacterial products in the lung and or in other tissues and organs [11]. Endothelial dysfunction and gastrointestinal translocation of bacteria and bacterial products, such as endotoxin, may significantly contribute to the pathogenesis of severe COVID-19.

Khan et al. evaluated Endotoxin Activity (EA) levels in 32 critically ill patients with COVID-19 pneumonia [5]. A significant proportion of the patients exhibited either elevated EA in the intermediate range (0.40–0.59) (10/32, 31%) or high range (≥0.60) (14/32, 44%) or were non-responders (low neutrophil response) to EA (6/32, 19%). The presence of Gram-negative bacteremia was identified only in 2/32 (6%) patients. Patients with higher levels of endotoxin (≥0.6) showed an higher incidence of Acute Kidney Injury (AKI) and a higher incidence of Renal Replacement Therapy (RRT).

In another study evaluating 19 patients with COVID-19 pneumonia [12], blood samples were analyzed for endotoxin activity (EA), (1→3)-β-D-Glucan (BG), and 16S rRNA gene sequencing to determine the circulating bacteriome. Serum BG is a marker of intestinal barrier dysfunction. Of the 19 patients, 14 were in intensive care and 10 patients received mechanical ventilation, 8 patients (42%) had high EA (≥0.6) and about half of the patients had high serum BG levels. Although only 1 patient had a positive blood culture, 18 of 19 patients were positive for 16S rRNA gene amplification. Gram-negative bacteria were most abundant.
This study shows that high endotoxin activity levels and bacterial DNA are common in the blood of patients with COVID-19 pneumonia, indicating that loss of epithelial barrier function significantly contributes to the pathogenesis of COVID-19.

Gut dysbiosis during COVID-19 is associated with increased risk for bacteremia and translocation of microbial products (mainly endotoxin)





Association between endotoxin activity level and AKI, RRT and hospital mortality in critically ill COVID-19 patients.

Adapted from Khan et al. [5].

Clinical experience with Polymyxin B hemoperfusion therapy in COVID-19 patients with endotoxic shock

Over the last year and a half, various publications have studied the potential role of Polymyxin B Hemoperfusion (PMX-HP - Toraymyxin® - TORAY - Japan) as additional therapy in the management of unresponsive critically ill COVID-19 patients. Here we will summarize the most significant works.

Polymyxin B hemoperfusion in COVID-19 Patients with endotoxic shock: the EUPHAS II registry [13]

De Rosa S. et al. 2020. *Artif Organs*

The study included 12 critically ill patients (median age [IQR] 61.5 years [54.8-68], n=3 (25%) female) with SARS-CoV-2 infection confirmed by RT-PCR, admitted to the ICU between February and May 2020, in 3 Italian and 1 Spanish hospital, and who were affected by septic shock due to secondary Gram-negative infection or endotoxemia and received PMX-HP treatment.

Median SAPS II score at admission was 57.5 [52.8-75.1] and APACHE II was 23.0 [21.5-26.3].
Septic shock (vasopressors use and blood lactate levels > 2mmol/l) was diagnosed in 9 patients (75%), Gram-negative bacteria was identified in most of the microbiological cultures (n=17, 65%), followed by Gram-positive bacteria in (n=4, 15%), fungi (n=3, 12%) and no growth (n=2, 8%), while baseline median Endotoxin Activity (EA) level was 0.78 [0.70-0.92].
SOFA score progressively improved over the 120 hours following PMX-HP (median [IQR] SOFA score was 14 [12-15] at T0 and 10 [6-11] at T120, p = 0.001) and was associated with median EA level decrease from 0.78 [0.70-0.92] at T0 to 0.60 [0.44-0.72] at T120 (p = 0.245). In addition, a direct correlation was observed between SOFA score reduction and EA level trend over time.

Lung Injury Score (LIS) decreased from 2.88 [2.5-3.31] at T0 to 2.5 [1.5-2.67] at T120 (p = 0.02), and septic shock markers over the same period improved with Vasopressor Dependency Index (VDI) from 28.6 [24.4-39.5] at T0 to 0 [0-4.23] at T120, p < 0.001; and lactates from 3.4 [2.33-4.3] at T0 to 1.6 [1-2] at T120, p<0.001). Nine out of 12 patients (75%) required CRRT because of AKI.

In this series of critically ill COVID-19 patients with endotoxic shock, PMX-HP therapy was associated with organ function recovery, hemodynamic and shock markers improvement and reduction of EA levels over time.

No PMX-HP related complications were observed.

Polymyxin B hemoperfusion therapy and extracorporeal CO2 removal in a patient with COVID-19: A case report [14]

Monastra L. et al. 2021. *Case Reports International*

A 54-year-old man with a medical history of obesity and hypertension developed fever, cough and diarrhoea presented at the emergency department with fever and severe respiratory failure. The patient was asthenic and dyspnoeic and was immediately intubated and transferred to the ICU. Critical care management was initiated, including mechanical ventilation and vasopressors. A swab test for SARS-CoV-2 infection resulted positive. Tocilizumab and antibiotics therapy were initiated. Blood cultures resulted positive for multi-resistant Gram-negative infection (*Acinetobacter Baumanii*). Endotoxic shock was suspected (EA = 0.92), and two treatments with PMX-HP were performed in 48h. After two sessions the patient's clinical condition improved, EA, procalcitonin, CRP and IL-6 decreased. Hemodynamic parameters also improved with increase in mean arterial pressure (MAP) and noradrenaline was suspended. However, a week later the patient's conditions deteriorated.
The patient became hypercapnic and in order to facilitate ultraprotective ventilation, extracorporeal CO_2 removal (ProLUNG® System - ESTOR - Italy) was initiated and continued for 6 days resulting in improved $PaCO_2$ and increase of pH. The patient was hospitalized in the ICU for 113 days and was then admitted to a rehabilitation facility.

Tocilizumab and PMX-DHP have efficacy for severe COVID-19 pneumonia [15]

Shinomiya S. et al. 2021. *SAGE Open Med Case Rep*

A 52-year-old man presented with fever and dyspnea and was diagnosed with COVID-19 pneumonia confirmed with PCR test. Mechanical ventilation and favipiravir administration were started for respiratory failure. However, favipiravir could not be continued due to hepatic dysfunction. Consequently, tocilizumab was administered, and continuous hemodiafiltration and PMX-HP were performed for acute renal failure. C-reactive protein decreased from 44 to 3.52 mg/dL, and the patient's respiratory status improved over time, enabling mechanical ventilation to be withdrawn.

Polymyxin B haemoperfusion treatment for respiratory failure and hyperferritinaemia due to COVID-19 [16]

Ishiwari M. et al. 2021. *Respirol Case Rep*

A 69-year-old man with a history of type 2 diabetes and high blood pressure was diagnosed with COVID-19. He had hyperferritinaemia and respiratory failure. Despite the initiation of favipiravir and high-dose corticosteroid and ceftriaxone, his respiratory failure progressed and serum ferritin levels increased. After PMX-HP therapy, there was improvement of the respiratory parameters and hyperferritinaemia.

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Take home messages

- Critically ill COVID-19 patients present a dysregulated host response to infection
- Viral infection is often followed by bacterial superinfections
- Gut dysbiosis may lead to bacteremia (often of Gram-negative origin) and translocation of bacterial products
- Endotoxemia is common in critically ill COVID-19 patients and correlates with a worse outcome
- Polymyxin B hemoperfusion can be used as complementary therapy in critically ill COVID-19 patients with endotoxic shock
- Published data show an improvement in hemodynamics, organ function and reduction in EA, lactate, PCT and CRP levels

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