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New Targets for Extracorporeal Blood Purification Therapies in Sepsis

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Abstract
As highlighted by the last international consensus definition for sepsis and septic shock (sepsis-3), sepsis comes from a complex relationship between a pathogen and a dysregulated host response. To date, the treatment of sepsis is based on antimicrobial treatment, source control, and organ support. Extracorporeal blood purification therapies have been proposed as adjuvant therapies to modulate the dysregulated inflammatory response. These therapies aim mostly at removing inflammatory mediators (cytokines) and endotoxins from the blood. However, so far, they failed to clearly demonstrate an improvement in patient survival when evaluated in randomized trials. Recently, new devices directly targeting the primary determinants of sepsis, e.g., the pathogen itself and the host immune cells, have been developed. This short review aimed at presenting new blood purification devices that have recently been developed to target pathogens and immune cells. For each, we will present the mechanism of action of the therapy and discuss the related literature.

Introduction

As highlighted by the last international consensus definition for sepsis and septic shock (sepsis-3), sepsis comes from a complex relationship between a pathogen and a dysregulated host response [1]. To date, the treatment of sepsis is based on antimicrobial treatment, source control, and organ support [2].

In the near future, the growing incidence of extensive drug-resistant pathogens and the paucity of novel antimicrobial drugs may leave few pharmacologic options to treat patients infected with resistant pathogens [3]. Therefore, scientists are currently developing and testing other therapeutic approaches, of which new blood purification therapies aiming at removing the pathogen itself from the blood. Additionally, these therapies may also participate in the immune homeostasis recovery. Indeed, the early removal of the pathogen could avoid the trigger of the immune cascade and the development of the subsequent cytokine storm and its deleterious consequences [4].

Extracorporeal blood purification therapies have been proposed as adjuvant therapies to modulate the dysregulated immune response. These therapies primarily aimed at removing inflammatory mediators (cytokines) or pathogen-associated molecular patterns (PAMPs) (endotoxins) from the blood. However, they failed to demon-

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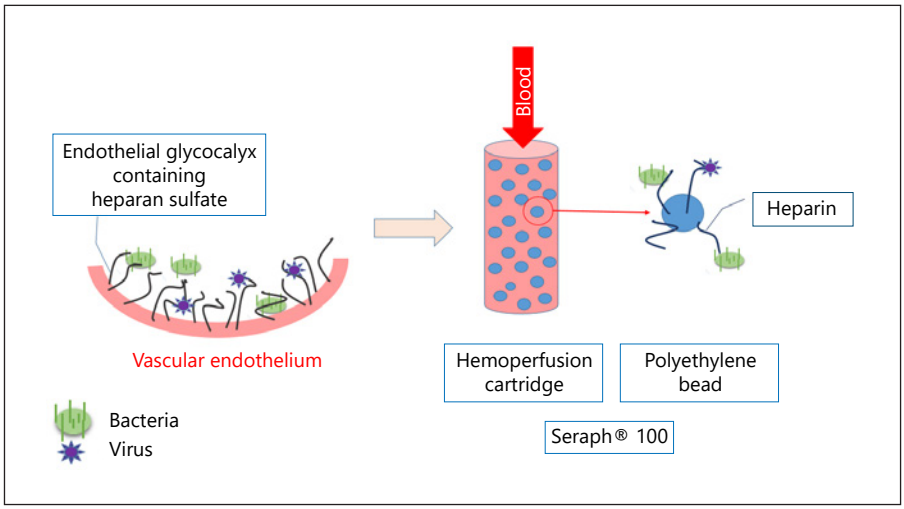

Fig. 1. Schema of the Seraph® 100. The hemoperfusion cartridge is filled with polyethylene beads coated with heparin. Heparin is able to adsorb pathogens, such as the heparan sulfate contained in the glycocalyx at the endothelium surface.

strate an improvement in survival when evaluated in randomized trials [5]. Pitfalls for the success of these therapies could be the inadequate timing for treatment initiation, inadequate patient selection due to the lack of efficient immunomonitoring methods, and also the selection of an inadequate target to remove. Instead of the removal of cytokines that are downstream mediators in the immune cascade, the removal of key players, such as the pathogen or selected host immune cells, could be a more suitable target for blood purification therapies.

Removing the Pathogens

Removing the pathogens from the blood at the early phase of sepsis could decrease the trigger of the immune cascade and the subsequent cytokine storm. It could also be considered for the treatment of bacteremia with extensive drug-resistant pathogens. Different hemoperfusion devices aiming at removing the pathogens from the blood are currently developed.

Seraph® 100 Microbind® Affinity Blood Filter

The Seraph® 100 Microbind® Affinity Blood Filter, Seraph® 100 (ExThera Medical, Martinez, CA, USA) is an hemoperfusion treatment using heparin to adsorb pathogens (shown in Fig. 1). The device can be placed within a renal replacement therapy (RRT) circuit, between the blood pump and the hemofilter, or used as a standalone hemoperfusion treatment. This hemoperfusion cartridge contains polyethylene beads on which heparin has been covalently immobilized. Many pathogens use heparan sulfate as a receptor for invasion on the surface of human cells [6]. Because heparin and heparan sulfate share a similar structure, they have similar properties, and heparin is also able to bind the microorganisms. Binding process relies on charge and electrostatic interactions as heparin is negatively charged and can attract the positively charged amino acids on the pathogen's surface.

In vitro studies have confirmed that heparinized beads like the ones contained in the Seraph® 100 are able to bind various pathogens such as viruses (Zika virus, cytomegalovirus, adenovirus), both Gram-negative and Gram-positive bacteria, drug-resistant bacteria, and also positively charged cytokines [7–9]. Recently, a first-in-human safety study was completed in Germany on 15 patients with septic shock requiring RRT. No adverse events occurred during the treatment and 14 days thereafter. Among the 4 patients with bacteremia, a significant increase in time to positivity of the blood cultures was demonstrated, reflecting a reduction in pathogen load [10]. An international multicenter randomized, controlled trial is ongoing. This post-market study includes patients with suspected bacteremia and confirmed organ dysfunction to receive the standard of care or the standard of care plus hemoadsoprtion with Seraph® 100 (NCT 04260789).

Lately, the Seraph® 100 was tested during the COVID-19 pandemic. Indeed, previous studies found that Seraph® 100 was able to bind viruses, and it was also demonstrated that the spike proteins of SARS-CoV-2 could bind to heparan sulfate on the cells' surface and thereby on heparin [11]. Because COVID-19 viremia is associated with disease severity and mortality, removal of SARS-CoV-2 using hemoperfusion with Seraph® 100 was proposed for the most severe patients. Numerous patients infected with SARS-CoV-2 and hospitalized in ICU have

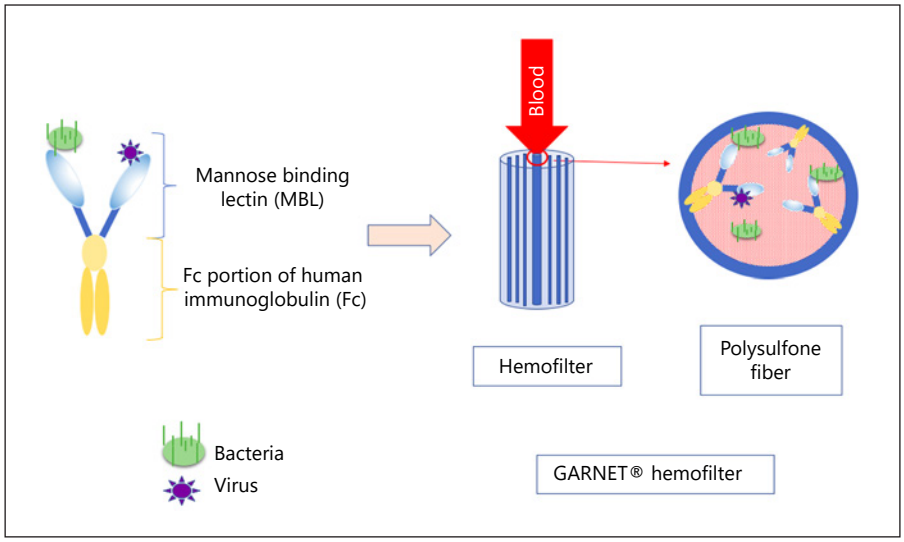

Fig. 2. Schema of the GARNET® hemofilter. The inner surface of the polysulfone fibers contained in this hemofilter is coated with an engineered protein (FcMBL) able to bind pathogens.

already been treated with Seraph® 100. No adverse events were observed (except for one transient hypotension at treatment initiation), and the results suggest an improvement in organ dysfunctions and oxygenation parameters [12–14]. Preliminary analysis of an international registry reporting data of COVID-19 patients treated with Seraph® 100 suggests a lower mortality when patients are treated early after ICU admission (before 60 h) [15]. A randomized, controlled trial is ongoing, including patients with COVID-19, acute respiratory distress syndrome, and one additional organ dysfunction, to receive either standard treatment or standard treatment plus Seraph® 100 (NCT04547257). In 7 patients infected with SARS-CoV-2 and treated with Seraph® 100, Kielstein et al. [16] reported a posttreatment decrease of the viral nucleocapsid protein in blood, confirming an effective clearance by the device.

Last but not least, a previous in vitro study suggested that, except for aminoglycosides, no relevant reduction of the anti-infective agents concentrations were observed during treatment with Seraph® 100 [17]. Similar results were obtained in vivo with immunosuppressive drugs (mycophenolic acid and tacrolimus), and the plasma concentrations were not affected by the Seraph® 100 hemoperfusion [18]. Seraph® 100 already received a CE-mark and is therefore one of the first pathogen apheresis devices that can be used routinely.

GARNET® Hemofilter

The mannose-binding lectin (MBL) is a human opsonin which plays a major role in the innate immune system. This opsonin is able to recognize and bind with multiple carbohydrate patterns that are present on the surface of all pathogens (bacteria, viruses, fungi, parasites) [19]. The binding between a pathogen and an opsonin such as MBL is the first step for the phagocytosis of the pathogen; it is called "opsonization."

The FcMBL is a genetically engineered recombinant protein derived from the MBL and further linked to the Fc portion of a human immunoglobulin. The FcMBL was first used as a coating on magnetic nanobeads to be mixed with the blood of an infected individual and then removed from the blood using a magnet [20]. More recently, a new device was developed and consisted of an hemofilter containing hollow polysulfone fibers subsequently coated with the FcMBL. This new hemoperfusion device, the GARNET™ hemofilter (BOA™ Biomedical, Cambridge, MA, USA), could remove pathogens from the blood of infected patients (shown in Fig. 2). This enhanced hemofilter may provide RRT and blood purification for sepsis together.

Didar et al. [21] conducted the first animal study evaluating this new device. During a treatment with bactericidal antibiotics in septic rats, they observed a major increase in PAMPs in the blood. These PAMPs were removed from the blood with the FcMBL hemoperfusion device. They also observed a clinical improvement in vital signs when the septic rats were treated with antibiotics and FcMBL hemoperfusion as compared to antibiotics alone [21]. PAMPs are known to trigger the immune cascade in septic patients. Thus, removing PAMPs from the blood at the early phase of sepsis could limit the develop-

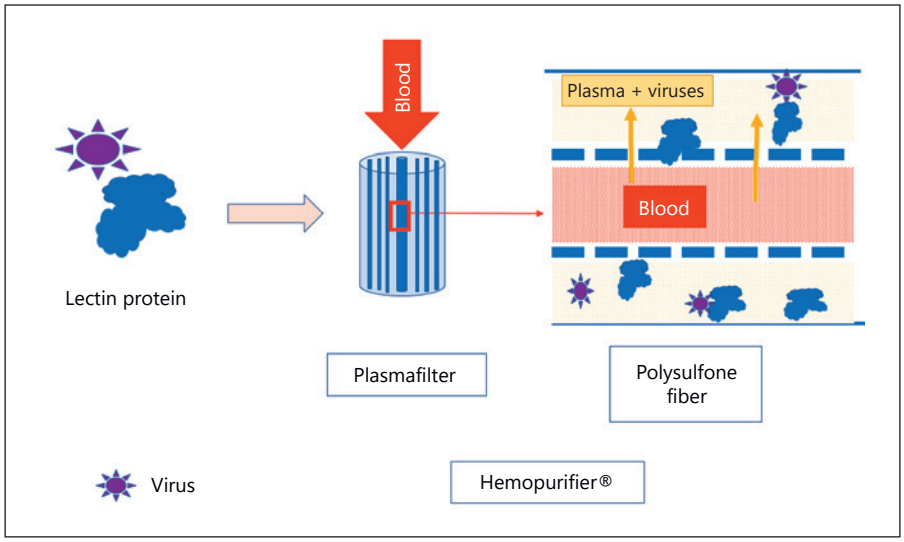

Fig. 3. Schema of the Hemopurifier®. The outer surface of the polysulfone fibers contained in this plasmafilter is coated with lectin proteins able to bind viruses.

ment the cytokine storm. A prospective single arm, multicenter, human study has recently been launched to evaluate the security and feasibility of hemodialysis with the GARNET™ device in chronic hemodialysis patients with a bloodstream infection (NCT 04658017).

Hemopurifier®

The Hemopurifier® (Aethlon Medical, San Diego, CA, USA) combines a plasmapheresis and an adsorption mechanism to remove viruses from the blood (shown in Fig. 3). The adsorption agent is a lectin protein from the common snowdrop (*Galanthus nivalis agglutinin*). It has a strong affinity for the ubiquitous glycoproteins (GPs) present on the surface of enveloped viruses such as the coronaviruses and the filoviruses. These GPs can also be shed from virus-infected cells, and the device could bind these soluble GPs.

The Hemopurifier® consisted of a plasmafilter with a pore size of 200 nm. The affinity agent is fixed in the extracapillary spaces of the filter. When the blood flows through the plasmafilter, the pressure gradient allows the plasma, viruses, and soluble GPs to be filtered to the extracapillary space, where the virus and GPs are captured via the immobilized affinity agent (lectin proteins). At the end of the filter, the cleared plasma is returned to the whole blood [22].

This therapy was proposed as a treatment option for viral infections lacking of effective treatments and associated with a high risk of mortality or a high transmissibility. Thus, the Hemopurifier® was used as an add-on treatment during hemodialysis sessions (3 times/week) in end-stage renal diseases patients with hepatitis C virus infection. The combination of the Hemopurifier® plus dialysis decreased hepatitis C virus viral load by 57% in 1 week [23]. This therapy was also successfully used to treat a patient with a severe Ebola virus disease [24]. In vitro studies confirmed a significant reduction of the viral load of a coronavirus (MERS-CoV) and Marburg virus [22]. This therapy could be an interesting option for the COVID-19 disease, and a clinical trial should start recruiting patients soon (NCT04595903).

Targeting the Host Immune Cells

Finally, because immune cells are key players of sepsis pathogenesis and are producing the cytokines, another approach consists of modulating the activity or removing from the blood the activated leukocytes [25, 26].

Selective Cytopheretic Device

To replace the renal function in patients with AKI or end-stage renal disease, Humes et al. [27] have developed an extracorporeal cell therapy, the renal assisted tubule device (RAD). The RAD was composed of primary renal cells seeded on the inner surface of an hemofilter fibers. During a phase II study evaluating the RAD, a higher survival was observed in the patients treated with a sham RAD, without the renal cells [27]. Moreover, this improvement in survival was observed only in patients receiving regional citrate anticoagulation. Subsequent studies demonstrated an ability of this new device to adsorb

activated leukocytes and to modulate their activity. This new device was referred to as the selective cytopheretic device (SCD) [28].

The SCD (SeaStar Medical, Inc, Denver, CO, USA) is composed of a cartridge containing polysulfone hollow fibers similar to the ones used in RRT hemofilters. To develop its properties, the SCD must be included in an extracorporeal circuit with regional citrate anticoagulation. Unusually, the blood enters the SCD through the side port and flows in the extracapillary space of the hemofilter (usually designed for dialysate or ultrafiltrate).

The exact mechanism of action of the SCD is getting better understood with preclinical studies and is probably due to the association of activated leukocytes adsorption (mainly neutrophils and monocytes) and a decrease of leukocytes activation, both promoted by local shear stress conditions and low calcium levels. It is hypothesized that the activated leukocytes are adsorbed along the outer walls of the polysulfone fibers because the shear stress between the fibers is similar to the one in the capillary system. The low level of ionized calcium also promotes the transition of the adsorbed activated leukocytes to more reparative subsets [29].

A multicenter RCT included 134 adults ICU patients with AKI and multiorgan dysfunction to receive CRRT alone or CRRT plus SCD. It confirmed the safety of the device but failed to find a mortality reduction. However, a nonsignificant decrease in mortality and reduction in dialysis dependency was observed in the subgroup of SCD-treated patients with an ionized calcium in the circuit maintained <0.4 mMol/L 90% of the therapy time [30]. In critically ill children with AKI and multiorgan dysfunction, the SCD therapy was feasible and safe with 75% survival and 100% renal recovery in the survivors [31]. A trial including adult patients with SARS-CoV-2 infection and AKI is ongoing (NCT04395911).

Immune Cells as Side Targets for Cytokine and/or Endotoxins Adsorption Devices

Interestingly, it has been suggested that blood purification devices primarily designed to remove cytokines and/or endotoxins could also have other targets. Thus, Peng et al. [32] observed an improvement in the clinical outcomes of septic rats treated with CytoSorb®, even in the absence of changes in plasmatic levels of the measured cytokines. An in vitro experiment using blood withdrawn from septic patients found that polyethylene beads (CytoSorb®), and also in a lesser extent highly adsorbing hemofilter (oXiris®), could adsorb leukocytes (mainly activated monocytes and neutrophils) in addition to their designated targets (cytokines and/or endotoxins). Alongside with leukocytes adsorption, they observed a decrease in CD11b expression, which means a decrease in neutrophils activation. Also, although lymphocytes were not captured by the devices, T-cell activity (both CD3+ and CD4+) was decreased with hemoadsorption, participating in the modulation of the immune response at a cellular level [33].

Polymyxin-B is an antibiotic immobilized on columns inside an hemoperfusion cartridge, whose purpose is the adsorption of endotoxins. This blood purification device is proposed at the early phase of a septic shock due to Gram-negative bacteria, in order to decrease the activation of inflammation. Srisawat et al. [34] have suggested that polymyxin-B could also act at the cellular level of the immune modulation, by improving the expression of the monocyte human leukocyte antigen (HLA-DR) at the surface of leukocytes in septic ICU patients. Because a low HLA-DR level is associated with an immunosuppressive state, hemoadsorption may have an impact not only on the proinflammatory phase of the septic shock but also on the late immunosuppressive phase. So far, randomized controlled trials have failed to demonstrate a reduction in mortality associated with polymyxin-B use in septic shock patients [35, 36].

Conclusion

We presented herein three devices designed to remove pathogens through mechanisms that are inspired by nature. The Seraph® 100 uses the ability of the pathogens to bind to heparan sulfate for cells adhesion; the GARNET™ hemofilter uses the interaction between the human opsonin and the pathogen for the first step of immune defense (opsonization); and the Hemopurifier® exploits the natural affinity of the snowdrop lectin for the viruses' GPs. Except for the Seraph® 100, these devices are not yet commercialized; however they seem promising as adjunctive treatments for infections with few therapeutic options.

Removing or reprogramming certain host immune cells could be a possible pathway to treat the immune dysregulation associated to sepsis. The SCD is designed for this purpose only, but other hemoperfusion devices such as the CytoSorb® or the polymyxin-B columns have demonstrated unexpected properties for immune cells adsorption. This last observation suggests that blood purification techniques remain not fully understood, and different mechanisms of action may be involved and should be further explored.

All these therapies are currently under assessment in clinical trials, but many questions are still to be answered for each of them: what are the best patients to receive the therapy, what is the best timing for initiation, for how long should the device be used, does these treatments adsorb active molecules (antibiotics, vitamins), what are their exact effects on inflammation and immune mediators? When used during an RRT session, the anticoagulation should also be questioned as it could interfere with the blood purification treatment. As an example, the SCD therapy requires a low level of ionized calcium, whereas the Hemopurifier® should not be used with regional citrate anticoagulation as the virus-binding process requires calcium. Most of these therapies can be used as add-on treatments during the RRT session. However, in the absence of need for RRT, the hemoperfusion device could be used as a standalone therapy, inside an extracorporeal circuit. In this particular situation, the expected benefits of the treatment should be balanced with the complications of the extracorporeal circulation. These complications are mainly associated with the catheter insertion, the anticoagulation of the circuit, and the inflammation induced by the circulation of blood in an extracorporeal circuit.

Conflict of Interest Statement

Céline Monard has received speaker honoraria from Fresenius Medical Care and bioMerieux. Paul Abraham has no conflict of interest to declare. Antoine Schneider has received speaker and/or consulting honoraria from Fresenius Medical Care, CytoSorbents SA, Jafron, Medtronics, and B. Braun Avitum. Thomas Rimmelé has received speaker and/or consulting honoraria from Astute, Fresenius Medical Care, Baxter Healthcare Corp, Biomérieux, Jafron, Medtronic, Nikkiso, and B. Braun. He is the principal investigator of the ECRO trial, comparing the effects of the oXiris® membrane to a standard membrane on endotoxins and cytokines levels during peritonitis-induced septic shock (NCT 03426943).

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Author Contributions

Celine Monard drafted the manuscript. Paul Abraham, Antoine Schneider, and Thomas Rimmelé critically revised it and approved the final version.

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