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Extracorporeal Sorbent Technologies: Basic Concepts and Clinical Application

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Abstract

Limitations imposed by the characteristics of some solutes and the structure of dialysis membranes have spurred new interest in the use of mechanisms beyond diffusion and convection for extracorporeal solute removal. Sorbents have been utilized for more than 50 years in extracorporeal blood treatments for specific purposes, and better understanding of their basic aspects may further expand the potential for their clinical application. In this chapter, the basic principles applying to sorbents are discussed, including composition and structure, along with the fundamental mechanisms of solute removal. The critical importance of sorbent biocompatibility is also highlighted. With these basic principles in mind, the clinical application of sorbents is discussed, with an emphasis on the use of hemoperfusion and coupled plasma filtration-adsorption for sepsis-related disorders. Finally, new sorbent-based clinical approaches for acute conditions and end-stage renal disease are presented, emphasizing that sorbent technologies may assume a larger role for a variety of clinical disorders in the future.

Introduction

Solute removal in hemodialysis and other blood purification techniques is mainly achieved by diffusion and convection. However, the limitations imposed by the characteristics of some solutes and the structure of dialysis membranes have spurred new interest in the use of further mechanisms of solute removal such as

Table 1. Development of sorbents in extracorporeal blood therapies

1850	First inorganic aluminosilicate (zeolites) used to exchange NH_4 and Ca
1910	Water softeners using zeolites display instability in the presence of mineral acids
1935	Adams and Holmes synthesize the first organic polymer ion exchange resin
1950	Application of synthetic porous polymers (styrene or acrylic acid based) (spherical beads: trade names of Amberlite, Duolite, Dowex, Ionac, and Purolite)
1960	Manipulation of physiochemical characteristics (commercial use)
1970	Application in blood purification techniques such as hemoperfusion
1980–2000	Improved design and coating for better hemocompatibility of adsorbent materials
2000 and beyond	Search for new sorbent materials and new possibilities of application

adsorption [1, 2]. Materials with high adsorptive capacity (sorbents) have been utilized for more than 50 years in extracorporeal blood treatments for specific purposes. The evolution in knowledge and clinical use of sorbents has been significant over the years and can be summarized in Table 1.

The analysis of the molecular structure of sorbents, as well as the study of the physiochemical mechanisms involved in the process of adsorption, are fascinating. A better understanding of these basic aspects may further expand the potential for the clinical application of sorbent materials [3, 4].

Basic Principles

In clinical settings, blood purification techniques achieve molecular separation primarily by membrane-based and adsorptive processes [5, 6]. When the former techniques using diffusion and convection are inadequate to remove the target molecules from the patient's blood, the use of sorbents and hemoperfusion (HP) may become an additional option for blood purification. In HP, blood is circulated through a unit (cartridge) containing the solid sorbent material. Solute removal and blood purification are obtained by absorption (binding) of molecules onto the sorbent particles.

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Sorbents can be composed of synthetic or natural materials. In the past, the application of HP was limited by the relative bio-incompatibility of the sorbent material and the significant side effects derived from its contact with blood. HP sessions were often accompanied by chills, fever, cutaneous rush, thrombocytopenia, leukopenia, and aluminum leaching. Today, these reactions have become rare and can be prevented in 2 ways:

- In some techniques, plasma is separated from cells before being circulated through the sorbent bed. After the sorbent cartridge, blood is reconstituted so that red cells, white cells, and platelets never come in contact with the sorbent surface, and bio-incompatibility reactions are avoided.
- The sorbent material is made bio- or hemo-compatible by a specific coating process that covers the particles with bio-layers that are well tolerated by blood cells [7].

There is little debate that the use of sorbents is justified in poisoning or acute intoxications, for which HP is the treatment of choice in many instances due to the high affinity of the sorbent for the specific toxic molecule. (This aspect of HP is not the focus of this chapter.) However, the use of sorbents in chronic or acute blood purification techniques is still a matter of discussion. In particular, the additional value offered by adsorption must be counterbalanced by the increase in costs that are involved when sorbents are utilized. Nevertheless, the relative selectivity of adsorptive processes and the possibility of placing the sorbent in direct contact with blood may be seen as a further step toward increasing the efficiency and specificity of the blood purification process for certain types of solutes [8]. In particular, specific molecules can be targeted for removal by selective adsorption mechanisms. Furthermore, solutes with molecular size larger than the pore dimensions of membranes can be removed by direct adsorption onto the surface of the sorbent particles.

Sorbent Materials and Structure

To deliver an adequate adsorbent-based therapy, some important requirements must be fulfilled: (1) an effective, biocompatible, and safe sorbent material; (2) a sorbent cartridge with adequate design and structure; and (3) operating conditions allowing for optimal utilization of the available surface of the sorbent [9].

Sorbents are present in nature as raw materials or they can be synthetically produced in the laboratory. Natural sorbents such as zeolites (aluminum silicates) are inorganic polymers with remarkable porosity, deriving from their crystal structure, and can be synthetically modified to control the structure of

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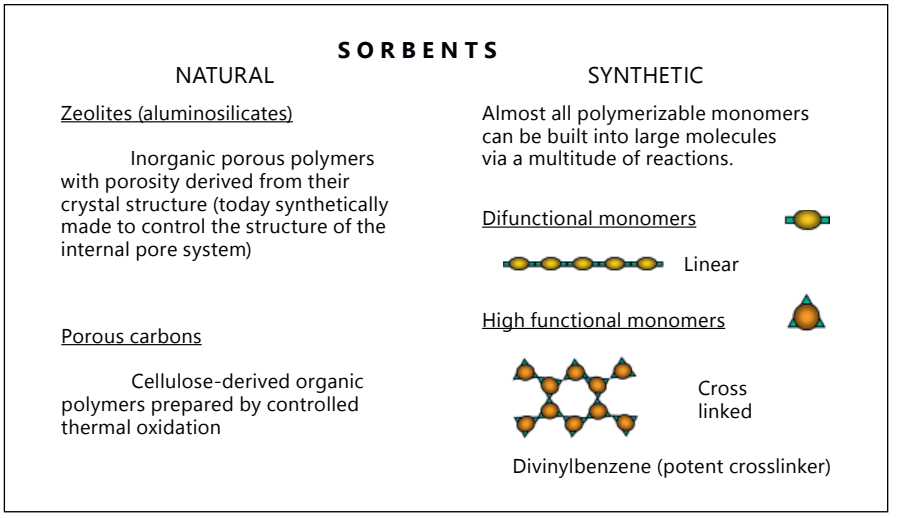

Fig. 1. Description of sorbent characteristics and distinction between natural and synthetic sorbents.

the internal pore system. Other typical sorbents such as porous carbons are cellulose-derived organic polymers prepared by controlled thermal oxidation (Fig. 1).

Different polymers of synthetic origin constitute the other class of sorbents. Almost all monomers susceptible to cross-linking can be transformed into large polymeric molecules via a multitude of reactions. Bifunctional monomers tend to aggregate in linear polymeric structures while highly functional monomers tend to polymerize in cross-linked structures. Divinylbenzene is a potent cross-linker frequently utilized to build polymeric sorbent molecules. Sorbent polymers can also be functionalized with chemical compounds to target specific molecules for adsorption.

Sorbents exist in granules, spheres, fibers, cylindrical pellets, flakes, and powder. They are solid particles with single particle diameters generally ranging between 50 μm and 1.2 cm. The surface area to volume ratio (S/V) is extremely high in sorbent particles, with an effective surface area varying from 300 to 1,200 m^2/g. They are also classified according to the size of the pores of the inner structure: (a) macroporous: pore size >500 Å (50 nm); (b) mesoporous: pore size 20–500 Å; and (c) microporous: pore size <20 Å.

The surface to volume ratio (S/V) is generally described by the following equation:

$$S/V = \pi d_p L \, (\pi d^2_p L/4) = 4 d_p \quad (1)$$

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where d_p is the pore diameter and L is the pore length. Considering fractional particle porosity (ε_p) and particle density (ρ_p), the specific surface area per unit of mass (S_g) is:

$$S_g = 4\,\varepsilon_p/\rho_p\,d_p \quad (2)$$

As an example of a clinically realistic application, if $\varepsilon_p = 0.5$, $\rho_p = 1$ g/cm^3 (1×10^6 g/m^3), and $d_p = 20$ Å (20×10^{-10} m), $S_g = 1{,}000$ m^2/g. In other words, 1 g of sorbent material provides a potential surface for adsorption of 1,000 m^2. Frequently, however, the available surface is not fully utilized since many factors contribute to limit the fraction of surface actually available for adsorption.

Requirements for a Sorbent

Sorbent materials must have high selectivity/affinity with a capacity to enable sharp separation and minimize the amount of sorbent required to make a suitable commercial product. The sorbent should have favorable kinetics and transport properties for the rapid adsorption of target solutes, chemical and thermal stability, low solubility in the contacting fluid, and high mechanical strength to prevent crushing or erosion.

In a sorbent cartridge used for clinical purposes, the material must allow free flow of blood or plasma (fluid phase) and easy filling and emptying of the packed bed. Other requirements are high resistance to fouling to permit long cartridge life span and maximal biocompatibility with no tendency to promote undesirable chemical reactions or side effects.

Mechanism of Solute Adsorption in Porous Media

Different steps and mechanisms can be identified in the process of solute adsorption onto a porous material: (a) external (inter-phase) mass transfer of the solute by convection from the bulk fluid and by diffusion through a thin film or boundary layer, to the outer surface of the sorbent; (b) internal (intra-phase) mass transfer of the solute by convection from the outer surface of the sorbent into the internal porous structure; and (c) surface diffusion along the surface of the internal pores and adsorption of the solute onto the porous surface (Fig. 2). The adsorption mechanism involves physiochemical forces of different nature [7–9].

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The interphase mass transfer is a crucial step since it brings the solution (fluid phase) and the molecules to be removed in contact with the sorbent. The cartridge in which the sorbent is contained must promote uniform distribution of internal flow of the fluid phase (plasma or whole blood). Uniform flow distribution profiles are generally obtained using granules or spherical beads of equal size. Packing density between 40 and 60% is considered optimal to prevent preferential channeling of the flow with undesired loss of performance. Any type of channeling phenomenon may affect the quantity of solute adsorbed per unit of sorbent and influence the saturation process of the unit.

Since blood is a non-Newtonian fluid, accurate analysis of the flow distribution in different conditions of flow and viscosity should be made. Flow distribution in packed beds can be theoretically modeled using equations of physical chemistry and transport. The packing structure is usually complex, and the resulting flow pattern is complicated. There are tortuous paths through the interstitial space of the bed, which consists of channels of various diameters (inter-particle porosity). The packed bed can simulate a bundle of tortuous capillary tubes. In well-packed beds with relatively constant inter-particle porosity, the variation of flow velocity among individual channels is relatively small. However, if packing is not homogeneous, channels of different size can be present with significant variation of fluid phase velocity, leading potentially to blood stagnation due to high resistance in areas with small-diameter channels and consequent clotting. On the contrary, areas having large diameter channels offer relatively little resistance to flow and the undesirable phenomenon of preferential flow channeling may result, with poor utilization of the sorbent potential, reduction in adsorption performance and rapid saturation of the unit.

The internal mass transfer (intra-phase) can be seen as a convective transport of the solute through the structure of the sorbent due to flow of the fluid phase inside the sorbent particle. This once again depends on the packing density, the pressure gradient, and the permeability coefficient of the particle. Often this mechanism is far from being optimized and the sorbent is generally utilized only in minimal part due to insufficient permeation of the bulk solution into the structure of the particle.

The physiochemical mechanisms regulating the surface adsorption are multiple. Once the molecule is brought to the surface of the sorbent, different chemical and physical mechanisms are involved:

- van der Waals forces are generated by the interaction between electrons of one molecule and the nucleus of another molecule; these are weak and generally reversible.

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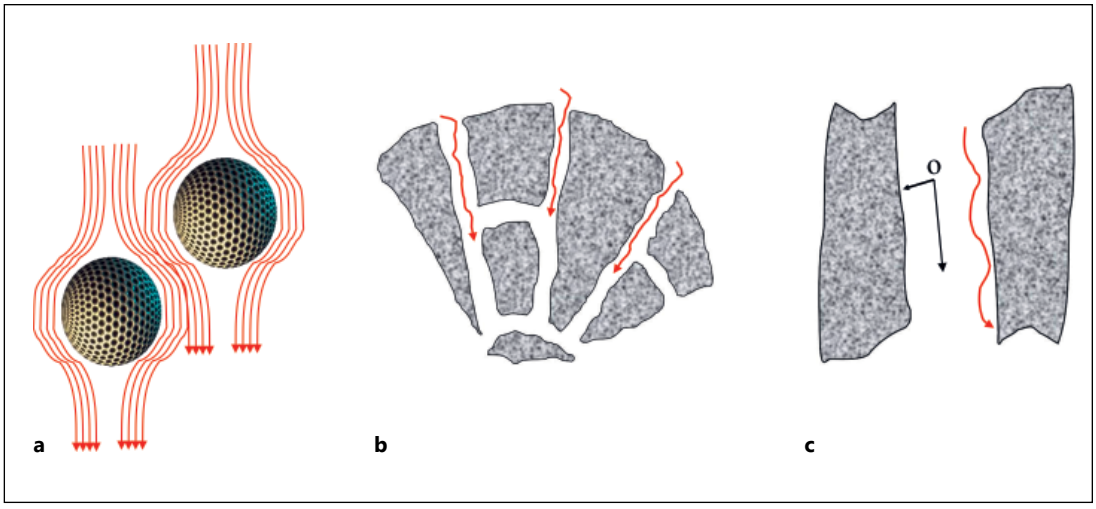

Fig. 2. Mechanisms of mass transport from the bulk solution to the sorbent surface. **a** External (interphase) mass transfer of the solute by convection from the bulk fluid by diffusion through a thin film or boundary layer to the outer surface of the sorbent. **b** Internal (intraphase) mass transfer of the solute by pore convection from the outer surface of the adsorbent to the inner surface of the internal porous structure. **c** Surface diffusion along the porous surface and adsorption of the solute onto the porous surface.

- Ionic bonds are generated by electrostatic attraction between positively charged and negatively charged ions; these are typical of ion exchange resins.
- Hydrophobic bonds represent strong binding forces that are generated by the hydrophobic affinity of the sorbent and solute molecules (Fig. 2).

Biocompatibility of Sorbents

The biocompatibility of a system utilizing sorbents for extracorporeal therapies should be studied considering the different aspects. First, the sorbent must be resistant and have sufficient mechanical strength to prevent cracking of the solid component, with release of micro-particles and fragments to the systemic circulation. To further prevent this unwanted effect, cartridges are provided with a screen that allows free passage of blood but retains particles or their fragments. A derivative measure of biocompatibility is given in clinical practice by the continuous measure of end-to-end pressure drop in the unit throughout the treatment. Fouling of screens due to cell or albumin adhesion may result in increased resistance to flow and thus increased pressure drop inside the cartridge. Accelerated clotting of the unit will also cause a sudden increase in end-to-end pressure drop.

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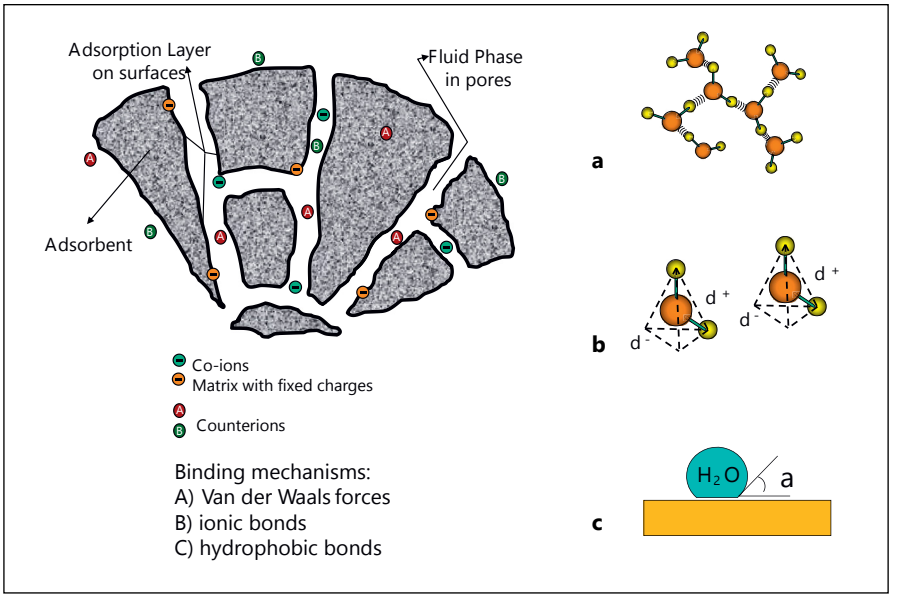

Fig. 3. Left: physicochemical mechanisms regulating molecular surface adsorption. Right: once the molecule is brought to the surface of the sorbent, different chemical and physical forces play the final role: (**a**) van der Waals forces generated by the interaction between electrons of one molecule and the nucleus of another molecule (weak and generally reversible); (**b**) ionic bonds generated by electrostatic attraction between positively charged and negatively charged ions (typical of ion exchange resins); (**c**) hydrophobic bonds generated by the hydrophobic affinity of the sorbent and solute molecules.

The second aspect is the intrinsic structure of the sorbent material. The inner surface of the sorbent should be compatible with blood to avoid cell and protein deposition that may occupy the adsorption sites and impair the sorbent capacity. When the material is intended for direct contact with blood, biocompatibility should be further directed towards preventing unwanted reactions in circulating blood (from complement activation to cytokine release), leukopenia, thrombocytopenia, development of antibodies, and significant adsorption of albumin. All these effects can be mitigated by coating the surface of the granules or fibers with a biocompatible material such as polysulfone. In this case, however, the coating may render the sorbent less efficient because the intra-phase component of the transport may be negatively affected. The coating acts as a size exclusion barrier and prevents larger solutes from reaching the intra-particle site of adsorption.

To obviate the need for coating the sorbent, some techniques separate plasma from cells and circulate cell-free plasma through the sorbent bed, avoiding direct contact with cells. Downstream in the circuit, blood is reconstituted by mixing

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purified plasma with cells [10]. In some cases, only plasma water ultrafiltrate is regenerated by exposing it to the sorbent bed and subsequently reinfusing it downstream into the circuit.

Rationale for the Use of Adsorption in Clinical Settings

For many years, the use of sorbents was mostly proposed for chronic hemodialysis patients to remove molecules that were not easily removed by hemodialysis. Sorbents were also indicated in case of drug intoxication and poisoning where toxin removal had to be obtained rapidly and efficiently. More recently, a rationale for the use of sorbents in critical illness, sepsis, and acute kidney injury has emerged due to the proposed humoral pathogenesis of these disorders. Assuming there is a humoral disorder with pathologic circulating molecules (e.g., damage-associated molecular patterns; pathogen-associated molecular patterns), extracorporeal therapies designed to remove these molecules would offer potential benefits [11]. There is a possibility to employ selective sorbents to target specific molecules. In clinical practice, however, although the use of sorbents may offer some interesting advantages, all other aspects such as hemocompatibility, unwanted solute losses, or alteration of anticoagulation requirements in the extracorporeal circuit should be considered [11].

Most Common Modalities of Utilization of Sorbents

Sorbent-based techniques have been applied to the management of both acute kidney injury and chronic kidney disease [10–12].

Hemoperfusion

HP is a technique in which the sorbent is placed in direct contact with blood in an extracorporeal circulation [8]. A peristaltic pump via blood lines circulates blood through the sorbent cartridge. HP has a circuit simpler than hemodialysis, but requires adequate anticoagulation and a very biocompatible sorbent since there is a direct contact between blood and sorbent material. Charcoal has a high adsorbing capacity, especially for relatively hydrophobic, low molecular weight solutes that are retained in case of kidney or liver failure. Direct contact of blood with charcoal in the absence of a biocompatible coating, however, is not advised. On the contrary, a coating may markedly reduce the adsorptive capacity of the carbon due to the size exclusion effect of the coating layer. More recently, synthetic polymers with remarkable capacity of adsorption have been made avail-

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able for clinical HP. The pores on the surface of the granules have been enlarged such that size exclusion has become a minor issue. Due to these recent advances, sorbent units are today available for direct HP and have been demonstrated to be quite efficient in removing poisons, bilirubin, cytokines or even endotoxin.

Coupled Plasma Filtration-Adsorption

Continuous plasma filtration-adsorption (CPFA) is a modality of blood purification in which plasma is separated from the whole blood by a plasma filter and circulated in a sorbent cartridge. After the sorbent unit, plasma is returned to the blood circuit and the reconstituted whole blood undergoes hemofiltration or hemodialysis. Today, specific ready-to-use disposable kits are prepared for easy application of the technique [10]. The aim of this approach is to attempt to achieve adequate removal of molecules, typically hydrophobic in nature, that are not removed appreciably by other hemofiltration or hemodialysis techniques. The advantage is to exclude blood cells from contact with the sorbent and to reinfuse endogenous plasma after non-selective simultaneous removal of different sepsis-associated mediators, without the need of donor plasma. This technique has been mostly used in septic patients [13] showing specific advantages of blood purification, restoration of hemodynamics, and immunomodulation.

The results obtained in clinical practice were in fact the basis to formulate the "peak concentration hypothesis" and to offer a possible explanation of the beneficial effects of sorbents in septic patients [14]. The unselective but continuous diminution of the peak concentrations of both pro- and anti-inflammatory mediators may in fact lead to a type of immune-modulation with partial restoration of immuno-homeostasis.

Sorbent-Based Adjunctive Therapies for Sepsis

This wider approach to the concept of blood purification opens new perspectives in a revisited strategy for the application of sorbents and extracorporeal therapies, especially in the area of sepsis [14]. The cellular and humoral responses of the host to bacterial invasion result in a series of symptoms and organ derangements, which are mediated by the presence of chemical substances found in the plasma and tissue. Continuous renal replacement therapies (CRRT) have gained increased popularity for their ability to facilitate the removal of excess fluid and waste products in septic patients with acute kidney injury. However, removal rates and clearances of different proinflammatory cytokines (IL-1, TNF) and lipid mediators (PAF) are hindered by insufficient membrane permeability. To overcome such limitations, high volume hemofiltration and use of

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high cut-off membranes have been proposed. The latter are still under investigation, both for potential benefits and also possible drawbacks (e.g., excessive leakage of albumin). Plasma filtration techniques (plasmapheresis and plasma exchange) have shown an increase in TNF clearance by 2 orders of magnitude relative to standard CRRT and have demonstrated some possible survival benefits in septic animals. However, plasmapheresis cannot be considered a routine therapy, due to technical complexity and high costs.

In addition to CPFA, the following are commonly applied adsorptive therapies for sepsis:

CytoSorb™

CytoSorb™ is the first-in-class therapy specifically CE marked as an extracorporeal cytokine cartridge in the European Union. Its use is broadly indicated for clinical conditions in which plasma cytokine concentrations are elevated. The unit contains a biocompatible, highly porous polymer bead designed to capture and adsorb cytokines in the ~10–50 kDa range [15]. The goal is to reduce toxic cytokine levels to prevent or mitigate organ failure and immune suppression, thereby improving the clinical outcome. Clinical trials are underway in septic patients to establish the real clinical influence of this device on short- and long-term outcomes. Another use of this cartridge is the intended removal of cytokines from the extracorporeal circulation in the case of extracorporeal membrane oxygenation applied in the context of cardiac surgery.

Polymyxin-B-HP

In the area of sorbents applied to blood purification, the technique of polymyxin-B (PMX) HP for endotoxin removal has gained important evidence and results [16, 17]. This direct HP technique utilizes a unit in which polystyrene-based fibers are functionalized with covalently bound PMX. This compound is a potent antibiotic that acts as an avid scavenger of circulating lipopolysaccharide S, the major component of bacterial endotoxin. Because endotoxin is the trigger of many humoral and cellular reactions in sepsis leading to organ damage and dysfunction, there is a clear rationale for endotoxin removal in sepsis.

From a historical perspective, the PMX device (Toraymyxin: Toray Industries, Japan) for extracorporeal removal of endotoxin was introduced in Japan several years ago and is intended to represent an adjuvant sepsis therapy. The treatment is particularly indicated in septic shock from Gram-bacteria with high levels of circulating endotoxin assessed by specific assays. Due to the high affinity of PMX to endotoxin, the rationale of the extracorporeal therapy is to prevent the evolution of the biological cascade of sepsis. Although studies have often pro-

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duced confusing or even conflicting results [18–22], PMX is routinely used in Japan since 1995 and more than 50,000 septic patients have been treated to date.

A group of investigators was coordinated by 2 centers including our hospital in the study called Early Use of Polymyxin-B Hemoperfusion in Abdominal Sepsis (EUPHAS). This multicenter randomized controlled study provided the first evidence that PMX can achieve a significant reduction in mortality for patients with abdominal septic shock, after a careful analysis of the literature had reported a similar retrospective result [20].

In 2010, the EUPHAS2 project created a registry with the purpose of recording data from critically ill septic patients affected by severe sepsis and septic shock, and treated with PMX-based direct HP (PMX-DHP) for endotoxin removal [21]. The aim of the registry was to characterize the application of PMX-DHP in daily clinical practice. The registry involved 46 European and 11 Asian hospitals, collecting retrospective data of 357 patients (297 in Europe and 60 in Asia) from 35 centers between January 2010 and December 2014. Finally, EUPHRATES (evaluating the use of polymyxin B hemoperfusion in a randomized controlled trial of adults treated for endotoxemia and septic shock) was conducted in Canada and North America [22]. The initial results from the trial have been announced recently and further analysis of the potentially beneficial effects of PMX-DHP in specific subgroups of septic patients with high endotoxin levels is ongoing.

Novel Applications of Sorbents

Lixelle Beta 2-Microglobulin Apheresis Column

The Lixelle column (Kaneka Co., Tokyo, Japan) contains 350 mL of porous cellulose adsorbent beads (diameter ~460 μm) to which are attached a ligand containing a hydrophobic hexadecyl group [23]. Peptides and proteins of molecular weight less than 20,000 Da are able to permeate the bead pores and attach to the ligand by hydrophobic interactions. The US FDA approved the column by a humanitarian device exemption in 2015 with an indication of dialysis-related amyloidosis in end-stage renal disease (ESRD) patients, and it is currently being evaluated in a post-approval trial.

Virus Removal by Lectin Affinity Plasmapheresis

The hemopurifier device (Aethlon Medical, San Diego, CA, USA) is a plasma filter which exploits the known ability of certain lectin-based compounds to bind viral particles. In this device, a resin to which an agglutinin ligand is attached acts as an affinity matrix for the binding of virions and viral glycoproteins. The resin comprises the non-blood compartment of the plasma filter

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and binds viral particles in the plasma filtrate produced in the proximal third of the filter. Based on the transmembrane pressure profile, the filtrate re-enters the blood compartment at a more distal stage through a Starling's flow mechanism. Successful treatment with this device (in series with a CRRT filter) of a critically ill patient infected with the Ebola virus has been reported recently [24].

HP for Sepsis-Induced Acute Lung Injury

The HA330 device (Jafron Biomedical, Zhuhai, China) is a novel HP column containing neutral macroporous beads. With an approximate pore size distribution corresponding to a molecular weight range of 10–60 kDa, it is well suited for the removal of many inflammatory mediators that are relevant in sepsis. The device has been evaluated prospectively in 46 patients with acute lung injury related to extrapulmonary sepsis [25]. Patients in the intervention group (n = 25) received treatment on 3 consecutive days plus standard care. In comparison to the control group, hemodynamic and respiratory parameters were significantly improved at day 7. Moreover, both ICU and 28-day mortality were significantly lower in the HP group.

Sorbent Technology in Wearable Artificial Kidney Devices

Finally, due to limitations of currently available ESRD therapies, substantial interest now exists in applying the principles of miniaturization to the development of wearable/implantable dialysis devices [26]. In a version developed by Gura et al.[27], spent dialysate is regenerated using a sorbent-based system that includes urease, zirconium phosphate, hydrous zirconium oxide, and activated carbon. It is expected that continued advancements in this area will occur in the future.

Conclusions

Although adsorbent materials have been routinely employed in clinical medicine for poisoning and intoxication, their use for other clinical applications has been relatively rare. An improved knowledge of the manufacturing processes and the possibility of designing new sorbents with improved characteristics of biocompatibility offer new opportunities with enormous potential. A new series of studies has demonstrated the feasibility, safety, and clinical benefits of using sorbents alone or in combination with other techniques. Therefore, sorbent technologies may assume a larger role for a variety of clinical disorders in the future.

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