SECTION 27

Extracorporeal Blood Purification Techniques Beyond Dialysis

CHAPTER 189

Sorbents: From Basic Structure to Clinical Application

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OBJECTIVES

This chapter will:

1. Describe the nature, the structure, and the composition of sorbent materials.
2. Characterize the mechanisms of the adsorption process.
3. Describe the potential application of sorbents in extracorporeal blood purification techniques.
4. Summarize some of the results achieved by the use of sorbents in specific clinical syndromes.

Solute removal in hemodialysis and other blood purification techniques is achieved mainly 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 adsorption.[1–2] Materials with high adsorptive capacity (sorbents) have been used 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 is summarized in Table 189.1.

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

BASIC PRINCIPLES

The combination of chemicals to form a mixture is a spontaneous and natural process, accompanied by an increase in entropy or randomness. The reciprocal process of separation of a mixture into its constituent species is not a spontaneous process and requires an expenditure of energy. If the mixture comes as two or more immiscible phases, gravity, pressure, or electrical fields can be applied to obtain separation. On the contrary, if it exists in a single homogeneous phase, different processes must be applied, such as the following:

- Separation by phase addition or creation (distillation, crystallization, de-sublimation)
- Separation by barrier (reverse osmosis, dialysis, microfiltration, ultrafiltration)
- Separation by solid agent (adsorption, chromatography, ion exchange)
- Separation by external field or gradient (electrodialysis, electrophoresis)

In clinical settings, blood purification techniques rely mostly on the second and third processes.[5] Membrane separation processes such as hemofiltration or hemodialysis predominantly use diffusion and convection. Diffusion may be limited by the diffusion coefficients of the molecules or by other factors such as temperature, surface area, and thickness of the membrane. On the other hand, convection is limited primarily by the sieving properties of the membrane and the flux of solvent obtained in response to a positive pressure gradient (ultrafiltration). When diffusion and convection are inadequate to remove the target molecules from the patient's blood, the use of sorbents and hemoperfusion may become an additional option for blood purification. In hemoperfusion, 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.

Sorbents can be composed of synthetic or natural materials. In the past, the application of hemoperfusion was limited by the relative bioincompatibility of the sorbent material

TABLE 189.1

Development of Sorbents in Extracorporeal Blood Therapies

1850	First inorganic aluminosilicates (zeolites) used to exchange NH_4 and Ca
1910	Water softeners using zeolites display instability in 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 Amberlyte, 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

and the significant side effects derived from its contact with blood. Hemoperfusion sessions were often accompanied by chills, fever, cutaneous rush, thrombocytopenia, leukopenia, and aluminum leaching.

Today, these reactions have become rare and are prevented in two 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 bioincompatibility reactions are avoided.
- The sorbent material is made bio- or hemocompatible by a specific coating process that covers the particles with biolayers that are well tolerated by blood cells.[6]

There is little debate that the use of sorbents is justified in poisoning or acute intoxications, for which hemoperfusion is the treatment of choice in many instances because of the high affinity of the sorbent for the specific toxic molecule. (This aspect of hemoperfusion 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 is involved when sorbents are used.

The efficiency of membrane separation processes in hemodialysis is limited by membrane permeability. To overcome this problem, high-flux membranes have been introduced. Today, high cutoff membranes are also available, but their efficiency when used in the diffusive mode is limited by the low diffusion coefficients of high-molecular-weight solutes. Adaptations increasing the degree of convection have been made in chronic treatments (online hemodiafiltration) and in continuous therapies (high-volume hemofiltration). In such circumstances, the high rate of ultrafiltration increases significantly the clearance of solutes in the middle-high-molecular-weight spectrum. 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.[7] 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.

However, the process of size-dependent, nonselective adsorption may cause unwanted losses with unexpected removal of antibiotics or other drugs and hormones. The removal kinetics for middle-large molecules during hemoperfusion are distinct in comparison with hemodialysis, and several clinical parameters should be monitored carefully. The basis for safe and efficient application of sorbents in clinical practice resides in a deep knowledge of the materials used and the mechanisms involved in the production and the design of the hemoperfusion device.

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.[8]

Sorbents are present in nature as raw materials, or they can be produced synthetically in the laboratory. Natural sorbents such as zeolites (aluminum silicates) are inorganic polymers with remarkable porosity, deriving from their crystal structure, and can be modified synthetically to control the structure of the internal pore system. Other typical sorbents such as porous carbons are cellulose-derived organic polymers prepared by controlled thermal oxidation (Fig. 189.1).

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, whereas highly functional monomers tend to polymerize in cross-linked structures. Divinyl-benzene is a potent cross-linker frequently used to build polymeric sorbent molecules. Sorbent polymers also can be functionalized with chemical compounds to target specific molecules for adsorption (Fig. 189.2).

Sorbents exist in granules, spheres, fibers, cylindric pellets, flakes, and powder. They are solid particles with single-particle diameters generally ranging from 50 μm to 1.2 cm. Surface area to volume ratio (S/V) is extremely high in sorbent particles with an effective surface area varying from 300 to 1200 m^2/g. They also are classified according to the size of the pores of the inner structure: (1) macroporous: pore size >500 Å (50 nm); (2) mesoporous: pore size 20-500 Å; and (3) microporous: pore size <20 Å.

The S/V generally is described by the following equation:

$$\frac{S}{V} = \pi d_p L \left(\frac{\pi d^2_p L}{4}\right) = 4 d_p \quad (1)$$

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

$$S_g = \frac{4\varepsilon_p}{\rho_p d_p} \quad (2)$$

As an example of a clinically realistic application, if $\varepsilon_p = 0.5$, $\rho_p = 1$ g/cm^3 (1×106 g/m^3), and $d_p = 20$ Å (20×10^{-10} m), $S_g = 1000$ m^2/g. In other words, 1 g of sorbent material provides a potential surface for adsorption of 1000 m^2. Frequently,

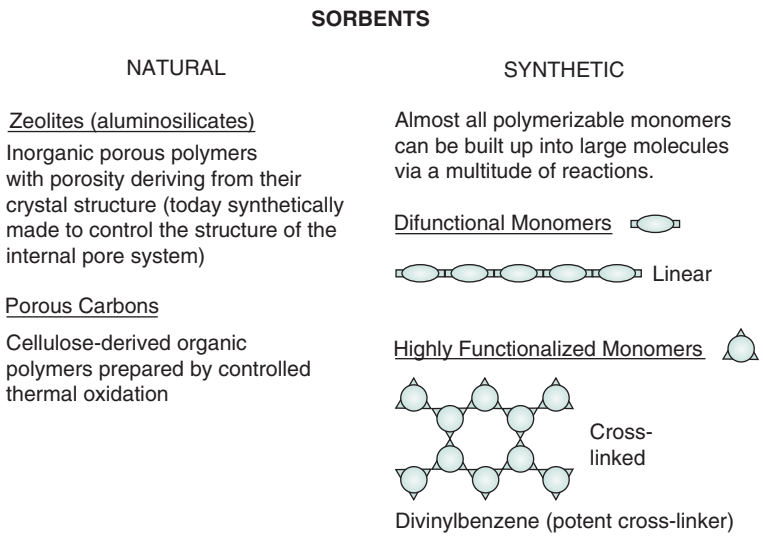


FIGURE 189.1 Description of sorbent characteristics and distinction between natural and synthetic sorbents.

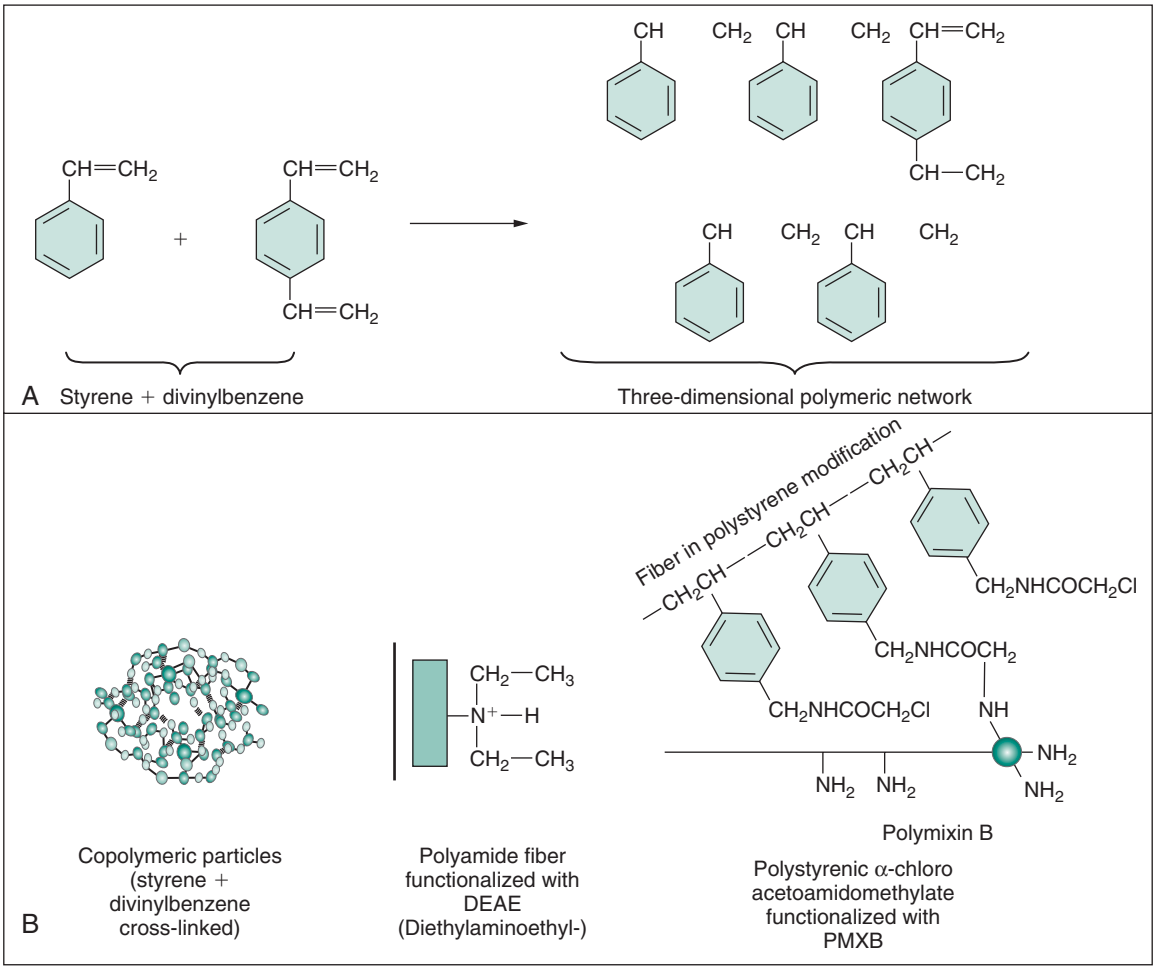


FIGURE 189.2 A, In most synthetic sorbents, styrene is cross-linked by divinylbenzene, forming solid gels in spherical or granular form (40 mm–1.2 cm). Typical characteristics include attachment of ionic functional groups; moisture content (water saturated), 40–65 wt%; particle density, 1–1.5 g/cm^3 (water swollen); bulk density, 0.5–1 g/cm^3 when packed in beds; fractional bed porosity, 0.3–0.4. B, Other forms of synthetic sorbents can be generated beyond the typical styrene-divinylbenzene mixture *(left).* Adsorbent materials can also be represented by polymeric substrates possibly functionalized with specific chemical substances, such as polyamide fibers functionalized with DEAE (diethylaminoethyl-) *(center)* and polystyrenic α-chloroacetamide-methylate functionalized with polymyxin B *(right).*

however, the available surface is not used fully because many factors contribute to limit the fraction of surface truly available for adsorption.

REQUIREMENTS FOR A SORBENT

Sorbent material must have high selectivity/affinity with the 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 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. In addition, the sorbent must be cost effective. The possibility of regeneration should be explored to allow possible reuse. Unwanted losses resulting from adsorption of hormones, proteins, and drugs must be characterized and addressed as potential side effects. An adequate regime of anticoagulation also should be defined to prevent clotting or platelet loss in case of direct contact with blood. All these characteristics are tested carefully in vitro and in animals before approval of use in humans to ensure maximal safety of application in clinical settings.

MECHANISM OF SOLUTE ADSORPTION IN POROUS MEDIA

Different steps and mechanisms can be identified in the process of solute adsorption onto a porous material:

1. External (interphase) mass transfer of the solute by convection from the bulk fluid and then by diffusion through a thin film or boundary layer, to the outer surface of the sorbent
2. Internal (intraphase) mass transfer of the solute primarily by diffusion from the outer surface of the sorbent into the internal porous structure
3. Surface diffusion along the surface of the internal pores
4. Adsorption of the solute onto the porous surface (Fig. 189.3)

The adsorption mechanism involves physiochemical forces of different nature. The overall rate of solute removal is usually controlled by step 2 or 4.[6–8]

The interphase mass transfer is a crucial step because 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 obtained generally 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.[9] Any type of channeling phenomenon may affect the quantity of solute adsorbed per unit of sorbent and influence the saturation process of the unit.

Because 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

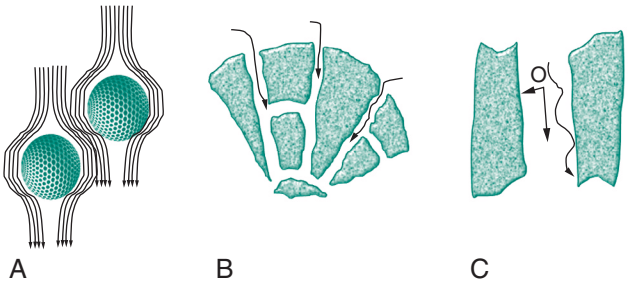


FIGURE 189.3 Mechanisms of mass transport from the bulk solution to the sorbent surface. A, External (interphase) mass transfer of the solute from the bulk fluid by convection through a thin film or boundary layer to the outer surface of the sorbent. B, Internal (intraphase) mass transfer of the solute by 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.

be modeled theoretically 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 (pores) of various diameters (interparticle porosity). The packed bed can simulate a bundle of tortuous capillary tubes. In well-packed beds with relatively constant interparticle 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 as a result of high resistance in areas with small-diameter channels and consequent clotting. On the other hand, areas having large diameter channels offer relatively little resistance to flow and the undesirable phenomena of preferential flow channeling may result, with poor utilization of the sorbent potential, reduction in adsorption performance, and rapid saturation of the unit.[9]

Physical laws and equations governing flow distribution in packed beds go beyond the scope of this chapter. Nevertheless, for the benefit of the reader, a quick summary of governing laws is included in the following section.

FLOW DISTRIBUTION IN PACKED BEDS

The fundamental principle governing the flow of fluids through packed beds is *Darcy's law*, which states that the flow velocity is directly proportional to the pressure gradient and the specific permeability coefficient of a unit whereas it is inversely proportional to the viscosity of the fluid phase and the length of the conduit:

$$v_o = \frac{B_o\,(p_o - p_i)}{\eta L} \qquad (3)$$

In this expression, P_i and P_o are the pressures at the inlet and at the outlet of the cartridge, η is the viscosity, L is the length of the conduit, B^o is the specific permeability coefficient, and v_o is the superficial velocity (the average linear velocity the fluid would have in the cartridge if no packing were present). It is calculated by dividing the flow rate by the cross-sectional area of the empty cartridge (specific permeability coefficient for open tubes is equal to $r^2/8$).

The component of the cross section of the bed available for flow is expressed by the *interparticle porosity* (ε). Random

packing of equal-size particles usually results in $\varepsilon = 0.4 \pm 0.03$. The *total porosity* of beds packed with porous particles is of course larger because of the intraparticle porosity that allows some flow through the particles. The true average fluid velocity (v) is obtained, from Eq. 3 as

$$v = \frac{B^o (p_o - p_i)}{\varepsilon \eta L} \quad (4)$$

The dimension of the specific permeability B^o is cm^2, but it is also given in Darcy units (1 Darcy = 10^{-8} cm^2).

The hydraulic radius concept is frequently used to calculate flow through channels of different geometry. The hydraulic radius r_h is defined in the following way:

$$r_h = \frac{\text{Volume available for flow}}{\text{Surface area of particles in contact with fluid}} \quad (5)$$

and the average flow velocity (v) is expressed as

$$v = \frac{(P_o - P_i) r_h^2}{2\eta L} \quad (6)$$

Several equations have been derived to relate the specific permeability to the particle diameter and the bed porosity. The best-known expression is the *Kozeny-Carman equation,* which gives the specific permeability as

$$B^o = \frac{d_p^2 \varepsilon^3}{180(1-\varepsilon)^2} \quad (7)$$

where d_p is the particle diameter. The average fluid velocity is then given by

$$v = \frac{d_p^2 (P_o - P_i) \varepsilon^2}{180 L \eta (1-\varepsilon)^2} \quad (8)$$

This equation is valid for laminar flow and for beds having porosity less than 0.5.

For packed beds the Reynolds number (Re) is calculated with particle diameter substituted for tube diameter:

$$Re = \frac{\rho v d_p}{\eta} \quad (9)$$

where *Re* is the dimensionless Reynolds number, *v* is the fluid velocity (cm/sec), ρ is the fluid density (g/cm^3), d_p is the particle diameter (cm), and η is the fluid viscosity (poise).

Turbulence and transition from laminar to turbulent flow are not nearly as well defined in packed beds as in open tubes. It is assumed that turbulence in packed beds develops gradually as Re increases from 1 to 100. Actually, even at low Reynolds numbers, in packed tubes there is a lateral movement of the fluid elements because of stream splitting. At high flow velocities, this leads to a substantial "convective diffusivity," analogous to the eddy diffusivity in turbulent flow. The flow profile then can be approximated as plug flow.

The most uniform flow profile can be obtained when beds are packed carefully with spheric particles of equal size. If the ratio of the tube diameter to the particle diameter is less than 100, this ratio may have a significant effect on the flow profile.

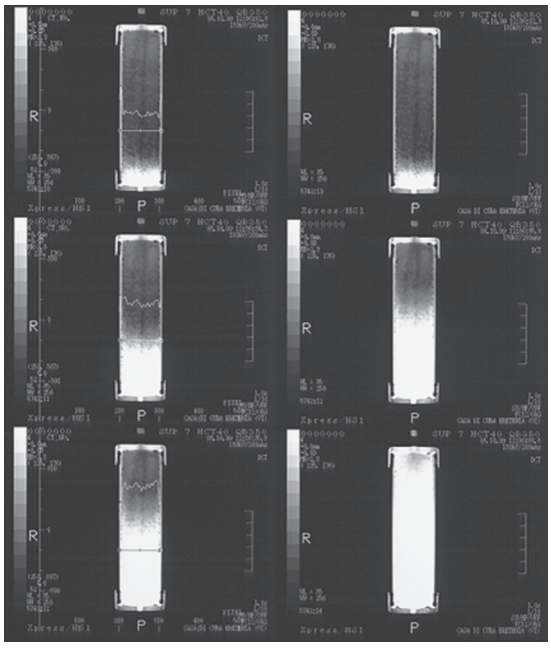


FIGURE 189.4 Computed tomography scans of a sorbent cartridge during injection of blood with contrast medium to study the flow distribution within the packed sorbent bed. Q_b, Blood flow rate.

In commercial cartridges, the tube diameter to particle diameter ratio is far from the above-mentioned ranges; cartridge and particle diameters around 5 cm and 1000 microns, respectively, are common. In some experimental analysis, the flow observed is close to optimal and easily can be assimilated to a plug flow with absence of channeling phenomena (Fig. 189.4). This results in straightforward calculation of the saturation time and the maximal solute removal per unit of sorbent. From these data, the optimal amount of sorbent used in one unit can be calculated according to the treatment duration, the average concentration of the solute at the beginning of the session, and the volume of distribution of the solute in the body.

The internal mass transfer (intraphase) can be seen as a primarily convective transport of the solute through the structure of the sorbent resulting from 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 used only in minimal part because of insufficient permeation of the bulk solution into the structure of the particle.

The physical-chemical mechanisms regulating 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.
- Ionic bonds are generated by electrostatic attraction between positively charged and negatively charged ions; these are typical of exchange ion resins.
- Hydrophobic bonds represent strong binding forces generated by the hydrophobic affinity of the sorbent and the solute molecules (Fig. 189.5).

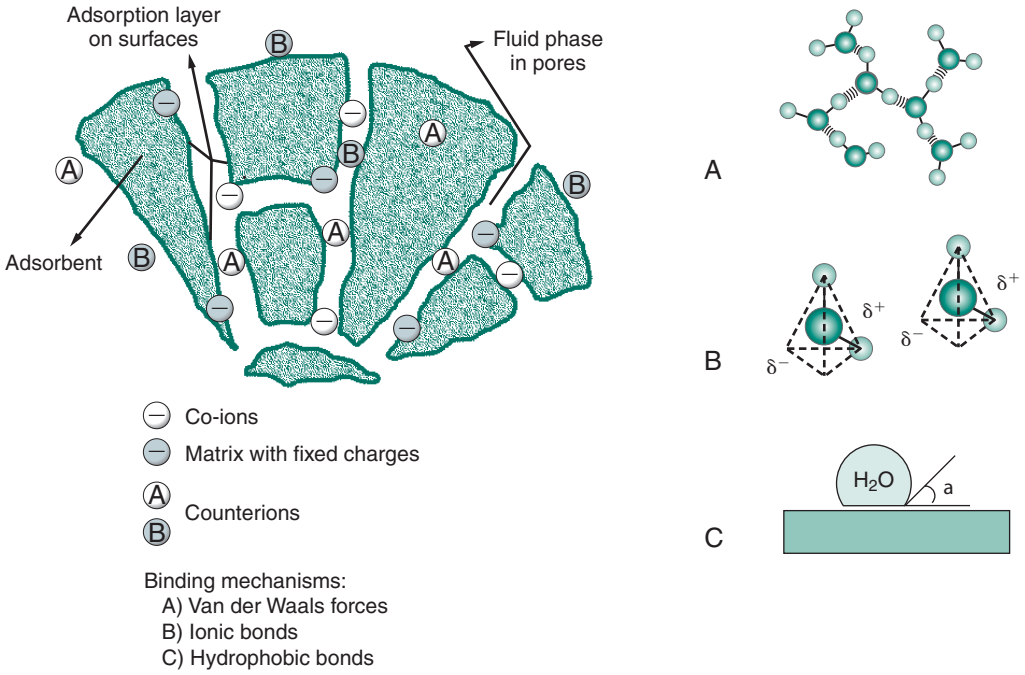


FIGURE 189.5 *Left,* Physicochemical mechanisms regulating molecular surface adsorption. *Right,* Once the molecule is brought to the surface of the sorbent, different chemical and physical forces play the final role: A, Van der Waals forces generated by the interaction between electrons of one molecule 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 exchange ion resins); C, hydrophobic bonds generated by the hydrophobic affinity of the sorbent and the solute molecules.

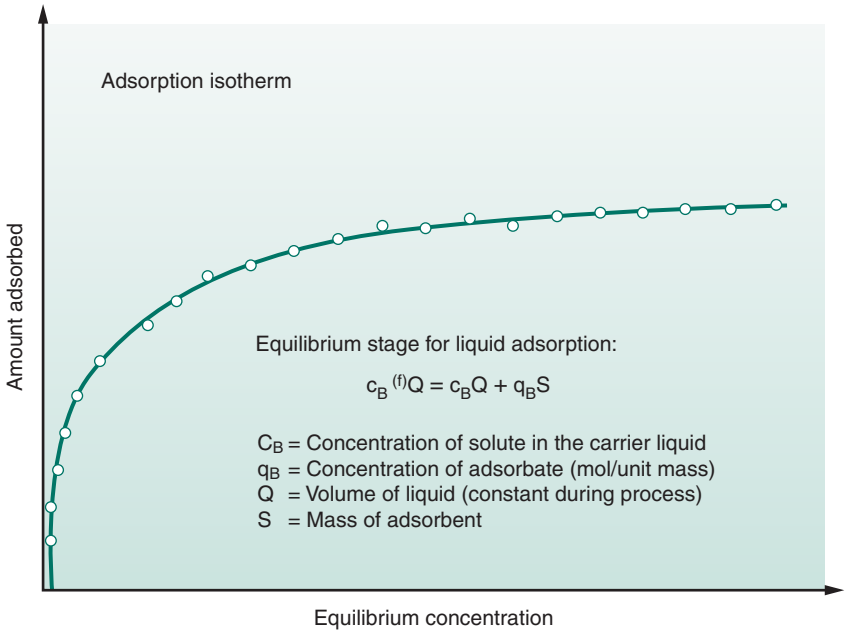


FIGURE 189.6 Typical example of an adsorption isotherm. C_B, Concentration of solute in the carrier liquid; Q, volume of liquid (constant during process); q_B, concentration of adsorbate (mol/unit mass); S, mass of adsorbent.

EFFICIENCY OF ADSORPTION

Porous polymers can be designed and constructed with different internal surface selectivity and various pore sizes. As a consequence, mass separation can be based upon size, geometry, and individual binding properties. To achieve a selective or partially selective adsorption process, the clinician needs to know the properties of the molecules to be separated or removed. If the information is lacking, the properties of the molecules under analysis can be ascertained by combining a number of available analytic measurements to develop a better understanding of the distinctive molecular pattern. A more empiric attempt can be made by trial and error through adsorption isotherms (Fig. 189.6).

When a liquid mixture is brought into contact with a microporous solid, adsorption of certain components in the mixture takes place on the internal surface of the solid. The maximum extent of adsorption occurs when equilibrium is

reached and no further net adsorption occurs. No theory for predicting adsorption curves is embraced universally. Instead, laboratory experiments must be performed at fixed temperature for each liquid mixture and adsorbent, to provide data for adsorption isotherms curves. (Separation processes are energy intensive and affect entropy.) Adsorption isotherms can be used to determine the amount of adsorbent required to remove a given amount of solute from the solvent (within a specific unit) at equilibrium.

Another measure of the efficiency of the unit is obtained by using marker molecules to determine the "mass transfer zones" at different times inside the unit. The mass transfer zone is the portion of the cartridge length that extends from the point at which the sorbent is fully saturated to the point at which the sorbent is completely unsaturated (no solute on the particles). Figs. 189.7 and 189.8 describe graphically the concept of mass transfer zone and different possible profiles occurring in a sorbent unit. Mass transfer zone determination also helps to define the quality of design and performance of the unit along with the expected life span before saturation. The mass transfer zone is a function of packing density and unit design. Poor design and inadequate packing density result in mass transfer zones exceeding the length of the unit and are characterized by a flow-through condition ("breakthrough" of the solute in the fluid phase leaving the unit) even at the beginning of the treatment.

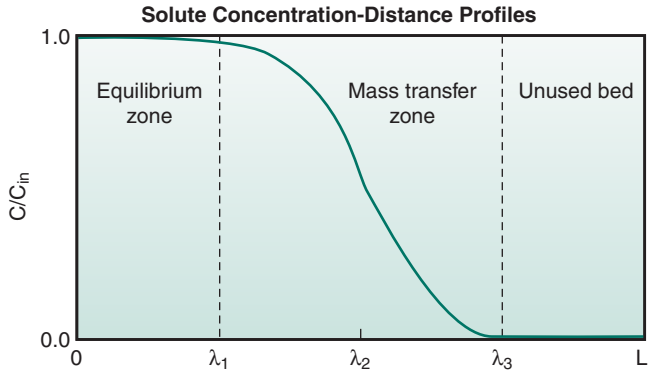


FIGURE 189.7 General concept of mass transfer zone.

BIOCOMPATIBILITY OF SORBENTS

The biocompatibility of a system using sorbents for extracorporeal therapies should be studied considering different aspects. First, the sorbent must be resistant and have sufficient mechanical strength to prevent cracking of the solid component, with release of microparticles 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 (Fig. 189.9). A derivative measure of biocompatibility is given in clinical practice by continuous measure of end-to-end pressure drop in the unit throughout the treatment. Fouling of the screens resulting from cell or albumin adhesion may result in increased resistance to flow and thus in increased pressure drop inside the cartridge. Accelerated clotting of the unit will also cause a sudden increase in end-to-end pressure drop.

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 (Fig. 189.10). When the material is intended for direct contact with blood, biocompatibility should be directed further toward 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 the fibers with a biocompatible material such as polysulfone. In this case, however, the coating may render the sorbent less efficient because the intraphase component of the transport may be negatively affected (Fig. 189.11). The coating acts as a size exclusion barrier

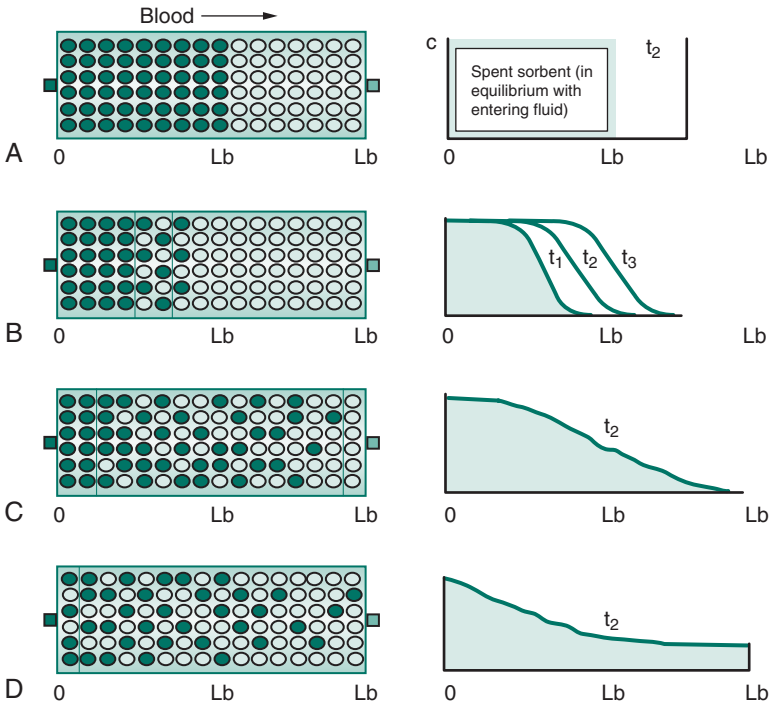


FIGURE 189.8 Evaluation of unit efficiency by determination of mass transfer zones. For this test, concentration of a colored marker molecule (c) is generally used. A, The mass transfer zone is near 0; and this is the ideal stoichiometric front for a fixed bed adsorption. B, Uneven concentration front builds mass transfer zones, but the dimension of each mass transfer zone at each time is less than one third of the length of the unit (Lb). C, The mass transfer zone occupies the entire length of the unit; in this situation, the flow-through condition is obtained immediately after the beginning of the treatment. D, The mass transfer zone is larger than the length of the unit; this condition describes a poor design, the presence of channeling phenomena, or a sorbent material with poor efficiency and leads to typical breakthrough conditions.

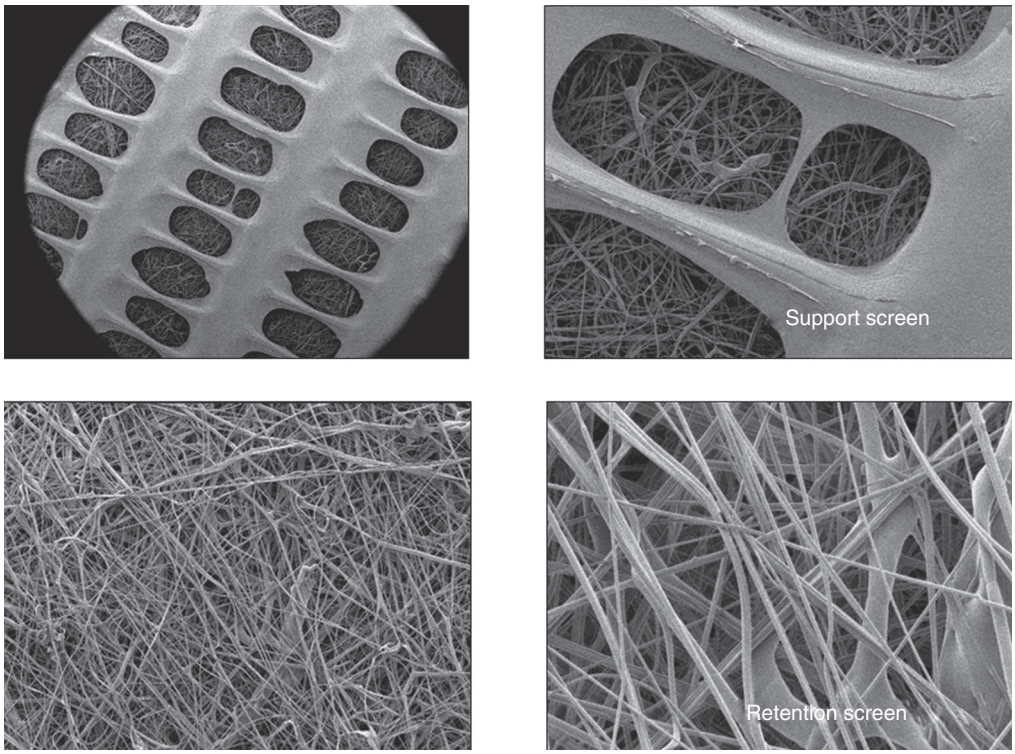


FIGURE 189.9 Screens are used in cartridges to prevent dissemination of sorbent particles and fragments into the circulation. *Top panels* depict support screens, and *bottom panels* depict retention screens. (Images courtesy of Professor P. M. Ghezzi.)

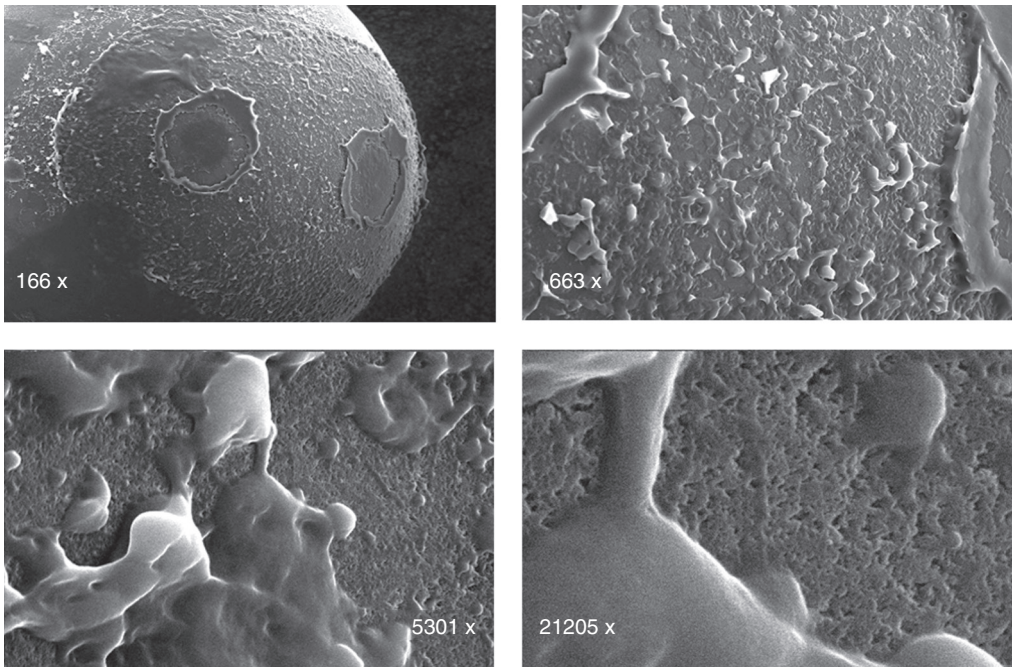


FIGURE 189.10 Electron micrographs showing protein fouling of sorbent beads.

and prevents larger solutes from reaching the intraparticle site of adsorption. The mass transfer considerations for the removal of cytochrome C by a hypothetical coated sorbent is shown in Fig. 189.12.

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 purified plasma with cells.[10–12] 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 also were 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 because of the proposed humoral pathogenesis of these disorders. Assuming there is a humoral disorder with pathologic circulating molecules (e.g., DAMPS: damage-associated molecular patterns; PAMPS: pathogen-associated molecular patterns), extracorporeal therapies designed to remove these molecules would offer potential benefits.[12–15] 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.[15]

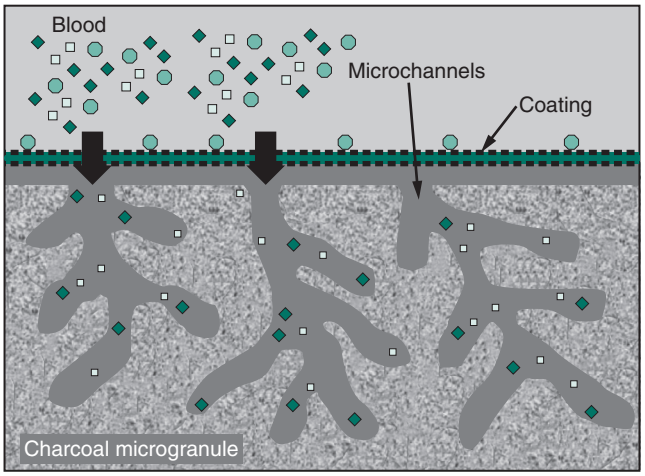


FIGURE 189.11 Conceptualization of size exclusion effect of sorbent coating.

TYPICAL MODALITIES OF UTILIZATION OF SORBENTS

Typical modalities for the utilization of sorbents in extracorporeal therapies are depicted in Fig. 189.13. These techniques have been applied to the management of acute kidney injury and chronic kidney disease.[12–15]

Hemoperfusion

Hemoperfusion (HP) is a technique in which the sorbent is placed in direct contact with blood in an extracorporeal circulation (Fig. 189.13A).[16] A peristaltic pump via blood lines circulates blood through the sorbent cartridge. The HP circuit is simpler than one used for hemodialysis but requires adequate anticoagulation and a very biocompatible sorbent because 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. However, direct contact of blood with charcoal in the absence of a biocompatible coating is not advised. On the other hand, a coating may markedly reduce the adsorptive capacity of the carbon because of the size exclusion effect of the coating layer. More recently, synthetic polymers with remarkable capacity of adsorption have been made available for clinical HP. The pores on the surface of the granules have been widened so that size exclusion has become a minor issue. Because of these recent advances, sorbent units are available for direct HP and have been demonstrated to be efficient in removing poisons, bilirubin, cytokines, or even endotoxin.

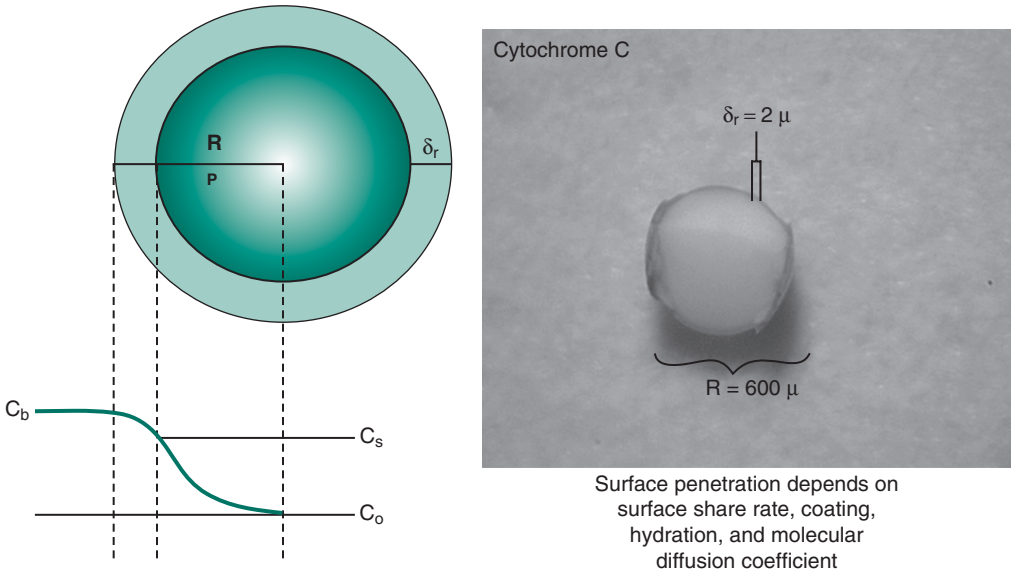


FIGURE 189.12 *Left,* The intraphase or internal mass transfer is described by the difference between the concentration of a solute in the blood (C_B) and the concentration in different internal zones of the sorbent particle (from C_S at the surface to C_O in the innermost zone). δr, Surface penetration; R_P, radius of particle. *Right,* A practical example with cytochrome C in a sorbent particle. Surface penetration depends on surface shear rate, coating, hydration, and molecular diffusion coefficient. (Image on right courtesy of Dr. James Winchester, Beth Israel Medical Center, New York.)

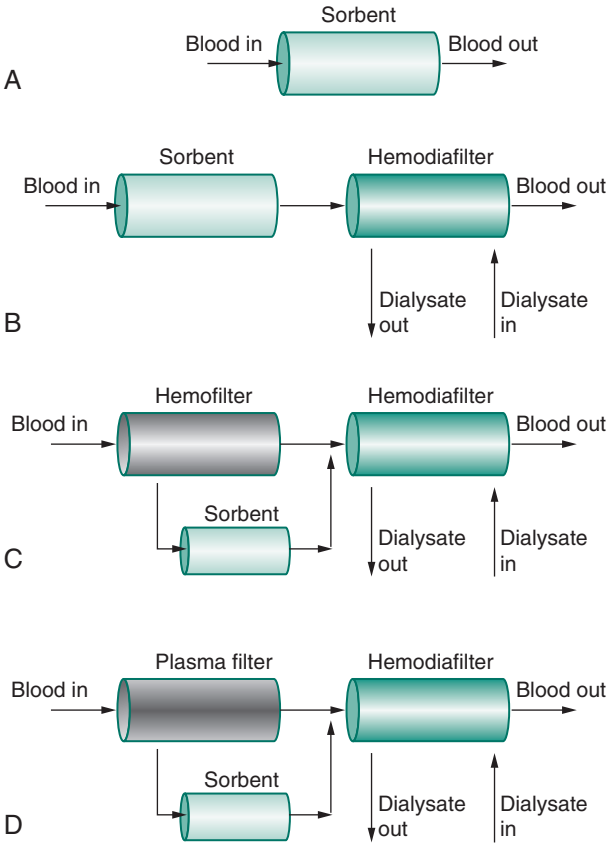


FIGURE 189.13 Possible modes of sorbent application. A, Hemoperfusion. B, In hemoperfusion-hemodialysis, the sorbent unit is placed in series before the hemodialyzer. C, The sorbent unit is placed online in the ultrafiltrate produced from a hemofilter. The hemofilter is placed in series with the hemodialyzer. The system, used for online hemodiafiltration in patients undergoing long-term treatment, is called paired filtration dialysis with sorbent. D, The sorbent unit is placed online in the plasma filtrate produced from a plasma filter. The plasma filter is placed in series with the hemodiafilter. The system, which is used for critically ill patients with septic shock, is called coupled plasma filtration adsorption.

A typical HP circuit is represented in Fig. 189.14 together with some examples of sorbent cartridges.

Hemoperfusion Coupled with Hemodialysis

Sorbents have also been used in conjunction with hemodialysis (hemoperfusion-hemodialysis, HPHD, Fig. 189.13B). In this case the sorbent unit is placed in series with the dialyzer.[17–18] The sorbent unit sometimes is placed before the dialyzer because the dialyzer can correct temperature or other abnormalities induced by the sorbent (e.g., acidosis). In other configurations, the sorbent is placed after the hemodialysis filter to maximize duration and avoid early saturation of the sorbent bed. In this technique, sorbents must be hemocompatible because of direct contact with blood. The HPHD technique is used mostly in an attempt to augment removal of molecules (e.g., β-2 microglobulin) that are poorly removed by dialysis. Recently, however, with the introduction of online hemodiafiltration, convective removal of β-2 microglobulin has been improved significantly, and the need for this additional mechanism is definitely less pronounced.

Furthermore, some dialysis membranes such as polymethyl methacrylate (PMMA) present a modified surface that allows for significant adsorption of different molecules during hemodialysis. This mechanism opens a new dimension in dialysis membrane characterization and it is likely to be used in acute patients because it has been used successfully in chronic hemodialysis. Other options are under evaluation, including the possibility to add sorbent particles in the dialysate compartment of a hemodialyzer, or to co-extrude two different polymers to obtain a fiber with enhanced filtration and adsorption properties.

Another approach combining a hemodialyzer with a sorbent unit involves use of sorbents in "uncoated" form for online regeneration of ultrafiltrate or plasma filtrate. Because such sorbents cannot be placed in direct contact with whole blood, a preliminary separation process generating ultrafiltrate or plasma filtrate is performed and sorbents are applied on these cell-free fluid phases. This is the case for double chamber hemodiafiltration (paired filtration-dialysis or HFR [hemodiafiltration with endogenous reinfusion of ultrafiltrate]) or coupled plasma filtration adsorption (CPFA), in which ultrafiltrate or plasma filtrate is produced in a separate unit before the dialyzer and then regenerated by a sorbent. After this process, blood is reconstituted before being delivered to a high-flux dialyzer.

Double-Chamber Hemodiafiltration

In double-chamber hemodiafiltration (HFR, Fig. 189.13C), plasma water (ultrafiltrate) is separated from whole blood and, after passing through the sorbent, is reinfused into the blood circuit, reconstituting whole blood (see Fig. 189.14).[16] This technique is used mostly in chronic dialysis as a particular form of hemodiafiltration. Chronic methods called DCHDF (double-chamber hemodiafiltration), PFD (paired filtration dialysis), and HFR (hemodialysis with ultrafiltrate regeneration) are still used in Europe in chronic dialysis patients.

Coupled Plasma Filtration-Adsorption

CPFA is a modality of blood purification in which plasma is separated from whole blood by a plasma filter and circulated in a sorbent cartridge (Fig. 189.13D). 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 (Fig. 189.15).[17–18] The aim of this approach is to attempt to achieve adequate removal of molecules, typically hydrophobic in nature, that are not removed appreciably by hemofiltration or hemodialysis techniques. The advantage is to exclude the blood cells from contact with the sorbent and to reinfuse endogenous plasma after nonselective simultaneous removal of different sepsis-associated mediators, without the need of donor plasma. This technique has been used mostly in septic patients[18] showing specific advantages of blood purification, restoration of hemodynamics, and immunomodulation.

Derivative Techniques

Plasma filtration combined with adsorption (PFAD) also has been used to remove bilirubin and albumin-bound toxins in the case of liver failure. In this condition, several variants

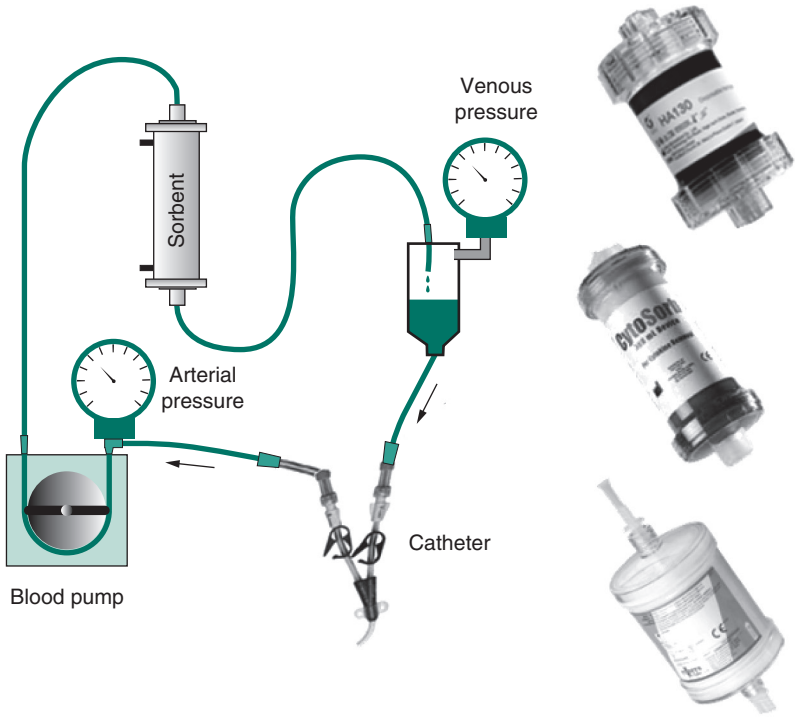


FIGURE 189.14 Typical hemoperfusion circuit.

have been proposed. Conjugated bilirubin cannot be removed effectively by hemofiltration and thus plasma filtration membranes are used to separate plasma and allow direct contact of bilirubin with the sorbent for more effective removal.

Other techniques are based on a specific albumin circuit created to attract lipophilic molecules, which subsequently are removed by adsorption in a secondary circuit.[19] This is the case of the MARS therapy and also the "Prometheus" therapy for liver support and acute intoxication (Figs. 189.16 and 189.17).

In another technique using uncoated sorbents (detoxification plasma filtration, DTPF HemoCleanse, Inc., West Lafayette, IN), a hemodiabsorption mechanism is associated with a push-pull plasma filtration system involving a suspension of powdered sorbents surrounding a 0.5 μm plasma filter membranes.[20] Bidirectional plasma flow (at 80–100 mL/min) across the plasma filtration membrane provides direct contact between plasma proteins and powdered sorbents, resulting in measurable clearance of cytokines (tumor necrosis factor-α, interleukin-1β, and interleukin-6).[19] Finally, specific sorbents are created to target-defined molecules such as LPS or cytokines, opening the perspective of clinical applications to a wider spectrum of disorders.

A major criticism may be raised concerning the removal of beneficial substances or drugs by the mechanism of adsorption. By using specific experimental conditions,[21] we assessed the different adsorptive properties of a hydrophobic resin for the most commonly used antibiotics. Except for vancomycin, for which a modest removal can be observed, the levels of other antibiotics such as tobramycin or amikacin tended to remain stable over time.[21]

Efficiency and adequacy of treatment, established criteria in the extracorporeal treatment of chronic kidney disease, now are reconsidered in critical care nephrology. However, the complex scenario of sepsis makes these criteria even more difficult to establish and interpret. Even 20 years after the original descriptions, the incidence of sepsis continues to increase and mortality remains unacceptably high. Dedicated, multipurpose extracorporeal systems in which renal replacement for acute kidney injury is just one organ support system offered hold promise for the future of sepsis management.

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.[22] The cellular and humoral response of the host to bacterial invasion results in a series of symptoms and organ derangements that 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 the 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 high cutoff membranes have been proposed. The latter are still under investigation 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 two 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 because of technical complexity and high costs.

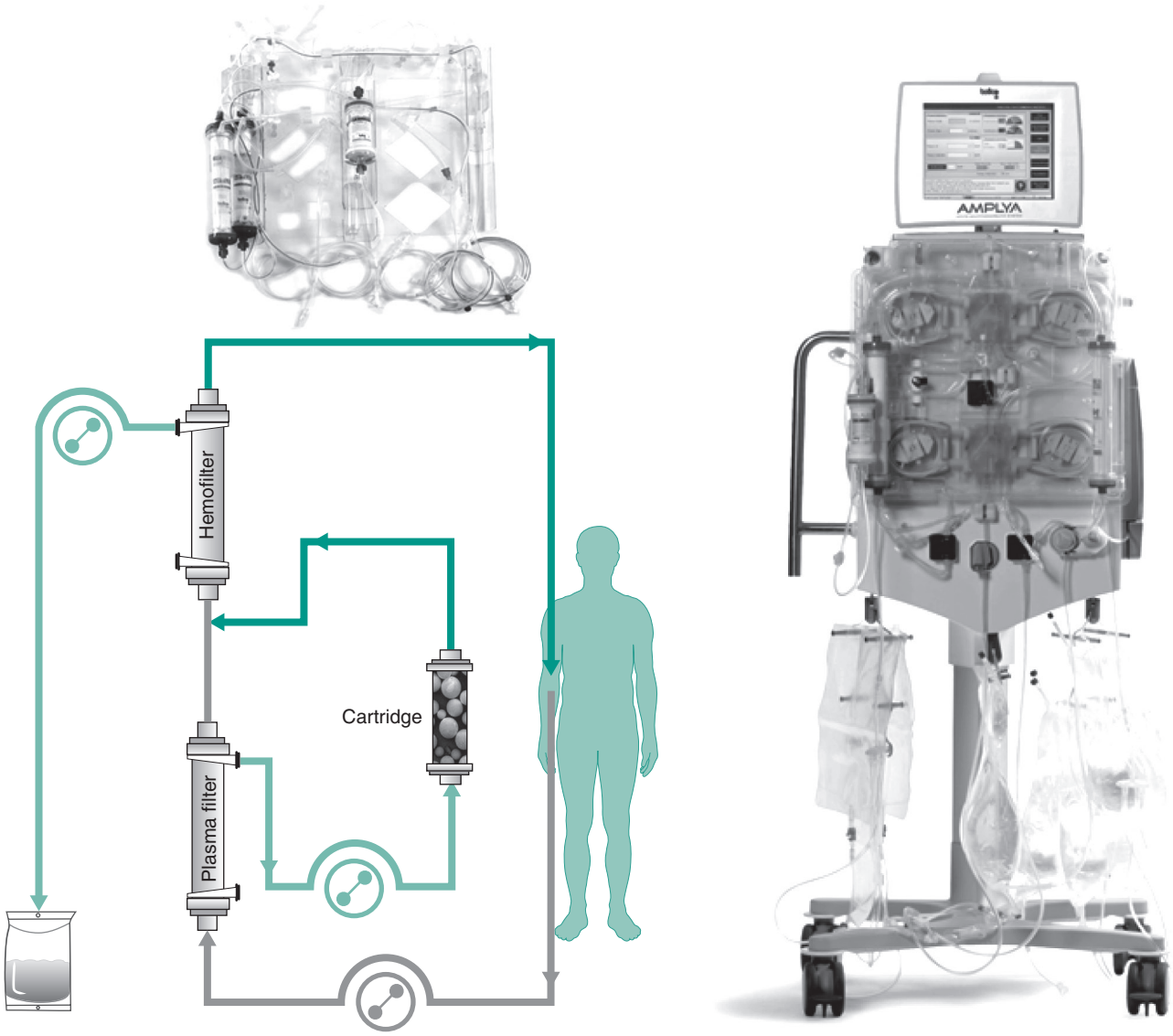


FIGURE 189.15 Coupled plasma filtration adsorption system.

Coupled Plasma Filtration-Adsorption

Sorbents may address the clinical requirement that a CRRT-type treatment with high capacity to remove large molecules also have the ability to eliminate sepsis-associated mediators in a relatively selective manner. CPFA has represented the initial experience with sorbents in sepsis, with the rationale of reinfusing endogenous plasma after nonselective simultaneous removal of different sepsis-associated mediators without need of donor plasma. In vitro studies demonstrated removal rates of cytokines were different according to varying sorbents tested, ranging from marginal efficiency to nearly complete elimination from plasma in association with significant reductions in circulating concentrations.

In experimental studies, CPFA resulted in a significantly increased ($p = .0041$) survival (85%) at 72 hours in treated animals injected with lipopolysaccharide compared with controls injected but not treated with CPFA.[23] The overall net effect on survival could be due to the removal of not only TNF and PAF but also many other mediators not measured in the study.

In a prospective randomized crossover trial aimed at comparing clinical and biologic effects of CPFA versus continuous venovenous hemofiltration (CVVH) in critically ill septic patients, significant hemodynamic improvement was observed after 10 hours of CPFA.[24] The circuit adsorbed almost 100% of the cytokines in the plasma filtrate. In all patients, the sepsis-induced impairment in TNF-α production by circulating monocytes incubated in vitro with exogenous lipopolysaccharide was restored after 10 hours of treatment and reached values close to normal. Co-incubation experiments with a monoclonal antibody directed against IL-10 could abrogate (60%) monocyte unresponsiveness. In CVVH, improvement of monocyte responsiveness was only partial as compared with CPFA and significantly delayed. At the hemodynamic level, all patients treated with CPFA (APACHE score >20) showed increased peripheral vascular resistance that allowed a significant reduction in the dose

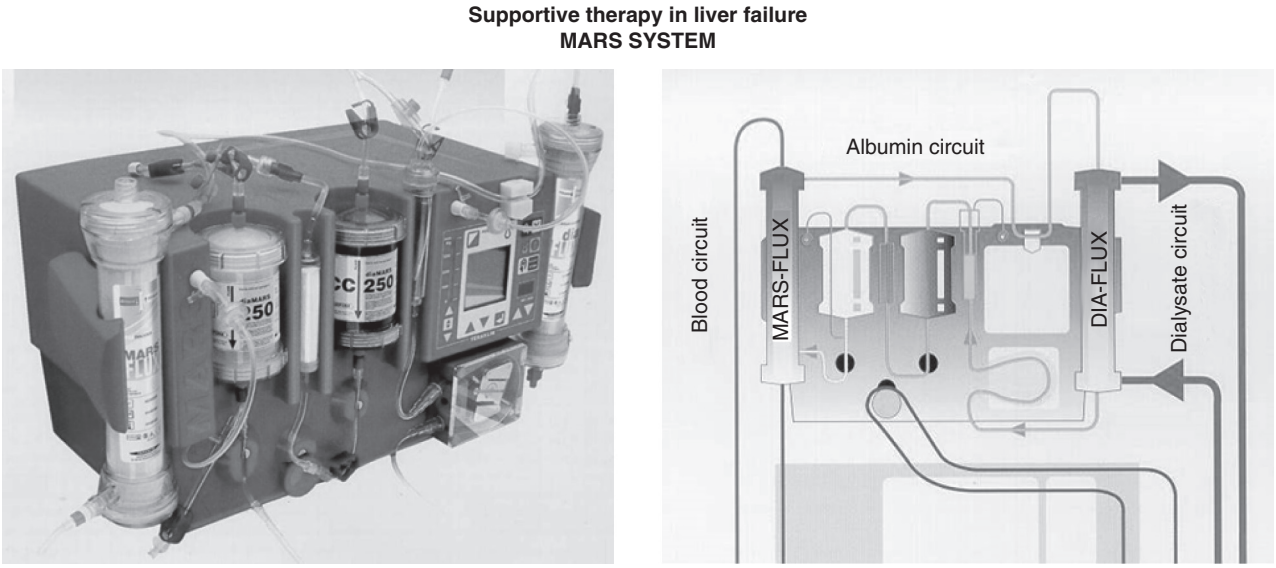


FIGURE 189.16 MARS device for treatment of liver failure.

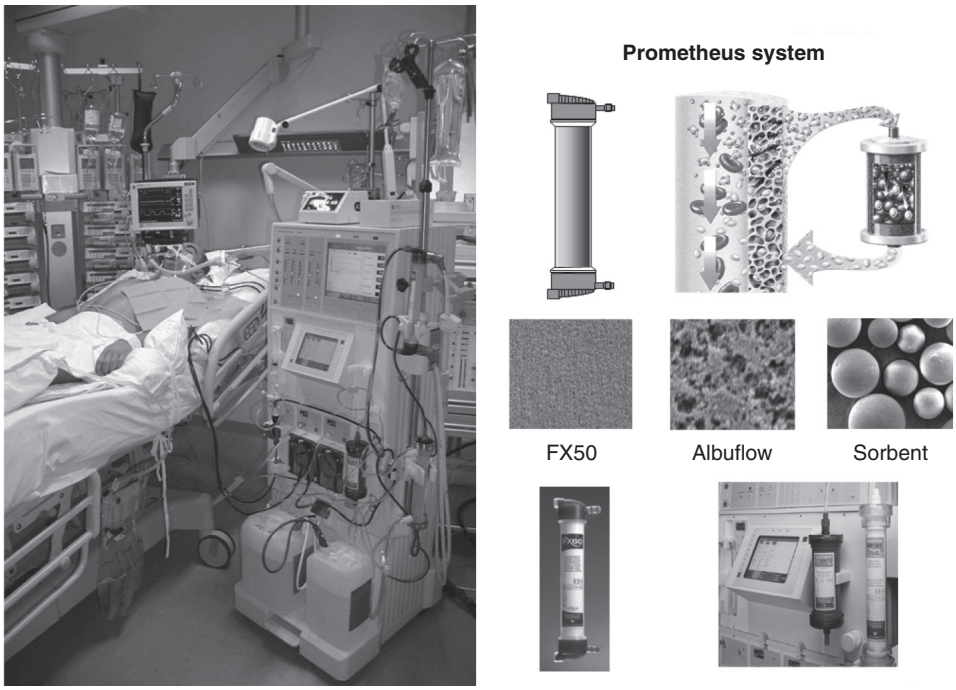


FIGURE 189.17 Prometheus device for treatment of liver failure.

of vasopressor drugs at 5 hours and remained steadily low after a 10-hour treatment. The reduction of vasopressor drugs was not observed during CVVH. These data suggest that CPFA may induce significant hemodynamic improvements in highly unstable patients. Because CPFA may be used in conjunction with conventional CRRT, the system may allow for adequate fluid and electrolyte balance while providing enhanced blood purification and restoration of immunohomeostasis.

In the concept of using extracorporeal therapies for sepsis, there has been a widespread tendency to focus on "bad humors" rather than to attempt to achieve restoration of balance of physiologic factors. Often too much emphasis has been placed on individual markers. The results obtained with CPFA suggest that treatments should focus more carefully on a "balancing hypothesis" trying to restore a correct equilibrium between immunologic suppression and activation of immune response.

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.[25] The unselective but continuous diminution of the peak concentrations of pro- and antiinflammatory mediators in fact may lead to a type of immunomodulation with partial restoration of immunohomeostasis.

CytoSorb

Recently, new sorbent devices have been studied and are undergoing clinical validation in sepsis. In particular, the

FIGURE 189.18 CytoSorb hemoperfusion device.

CytoSorb cartridge has demonstrated a substantial capacity for mediator removal in sepsis[26] (Fig. 189.18). Originally designed as a β-2 microglobulin removal unit to be used in series with a filter in chronic hemodialysis patients, the new device initially has demonstrated significant reductions in IL-1 and TNF-α from the plasma of septic patients studied in vitro.

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 approximately 10 to 50 kDa range. The goal is to reduce toxic cytokine levels to prevent or mitigate organ failure and immune suppression, thereby improving clinical outcome.

CytoSorb is being evaluated in a randomized, controlled, multicenter study in Germany in 43 patients with septic shock and respiratory failure (predominantly ARDS). In the trial, cytokine removal with CytoSorb plus standard of care (SOC) therapy is being compared with SOC therapy alone. These clinical findings will be evaluated in the context of CytoSorb's ability to reduce the concentrations of a broad spectrum of cytokines in this approximately 10 to 50 kDa range. Further clinical trials are undergoing 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.[27]

The major advantages of sorbent therapy in sepsis can be summarized from the interesting results achieved so far. Sorbent therapy appears to

- restore cell responsiveness, as measured by capacity to respond to external stimuli;
- reduce circulating cytokine levels;
- improve pathologic apoptosis, HLA-DR expression, and phagocytosis capacity; and
- increase systemic vascular resistance, reducing the dose of norepinephrine required to maintain stable hemodynamics in the patient.

Sorbent therapy may be modular with conventional CRRT platforms, and the two modalities can be carried out in series or in sequence. The combined mechanisms of membrane separation and adsorption may ensure adequate blood purification, accurate fluid balance, and enhanced removal of various molecules involved in immunoresponse regulation.

Polymyxin-B Hemoperfusion

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.[28–32] This direct HP technique uses 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 LPS (lipopolysaccharide), 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. One treatment consists of whole-blood perfusion for a limited duration (typically 2 hours) per day through the PMX cartridge, obtaining appreciable removal of endotoxin.[33–38] The treatment may be repeated on subsequent days.

From a historical perspective, the PMX device (Toraymyxin: Toray Industries, Japan) for extracorporeal removal endotoxin removal was introduced in Japan several years ago and is intended to represent an adjuvant sepsis therapy. The treatment is indicated particularly in septic shock from gram-negative bacteria with high levels of circulating endotoxin assessed by specific assays. Because of the high affinity of PMX for endotoxin, the rationale of the extracorporeal therapy is to prevent the evolution of the biologic cascade of sepsis.[39,40]

The PMX cartridge has been studied in vitro (Fig. 189.19) in animals and humans. Several papers have demonstrated an efficient removal of endotoxin from the blood passing through the sorbent bed. At the same time, flow distribution in the cartridge has been shown to be homogeneous with efficient utilization of the surface area available for adsorption.[38]

An early paper from Nemoto et al.[29] presented some important clinical evidence for a positive impact of the device on outcome of septic patients. Moreover, although several subsequent studies often have produced confusing or even conflicting results,[35,41] PMX is used routinely in Japan since 1995, and more than 50,000 septic patients have been treated. Additional evidence has emerged, suggesting a clear role of PMX in the therapy of sepsis and particular attention has been placed on safety, because PMX is a toxic substance. Concerns for a possible release of PMX into the circulation clearly were solved by several safety-biocompatibility reports. Nevertheless, PMX is to be used with caution in patients with bleeding tendency as a result of the required heparinization of the circuit.

Besides the biologic rationale and apparently excellent performance of the cartridge, an intriguing question arises about the timing of applying this technology in septic patients. In the time course of sepsis, a biologic clock and a clinical clock can be discussed. The first starts when infection begins and fragments of gram-negative bacteria invade the host. At this point, an immediate intervention with a system designed to remove the initiator substance of sepsis could result in a blockade of the humoral response and the ensuing biochemical cascade. On the contrary, the clinical clock starts only after the first signs and symptoms

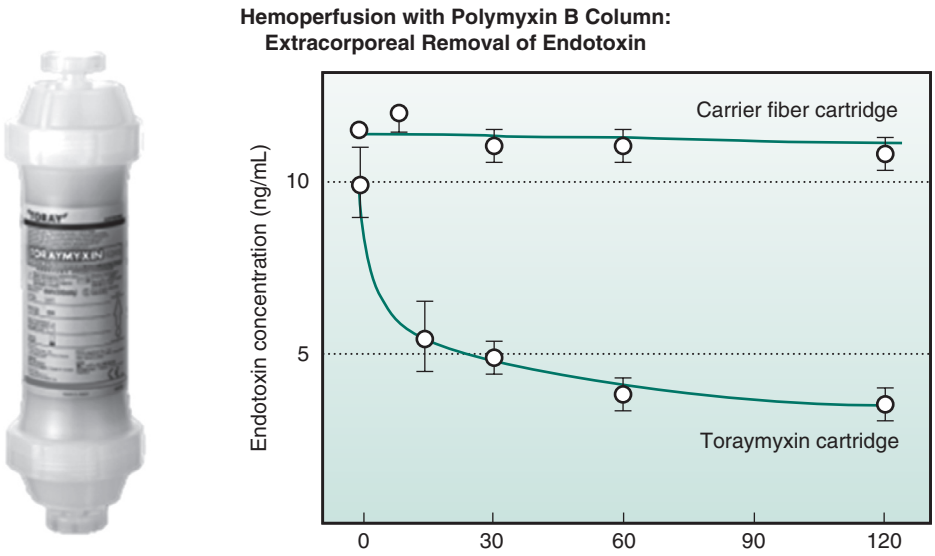


FIGURE 189.19 Endotoxin concentration changes with polymyxin-B hemoperfusion cartridge.

appear and the patient displays the initial sepsis syndrome. At this point, the humoral and tissue derangement already has begun and organ damage may occur promptly, if not already present. In these circumstances, intervention with an extracorporeal therapy can result only in possible organ protection from further insults but not in an effective blockade of the syndrome.[39]

The goal should be to set the biologic and the clinical (diagnostic) clocks at the same time and at the same speed. To achieve this, early gram-negative sepsis markers that may identify high-risk patients most likely to benefit from early application of PMX therapy should be identified. Gene polymorphism for different molecule expression may be one avenue to explore. Furthermore, each sepsis episode must be subtyped – for example, cases of peritonitis are almost inevitably caused by gram-negative bacteria. In these cases, the therapy could be applied earlier on the assumption of a logical rationale. The latter approach has been undertaken by a group of investigators coordinated by two centers, including our hospital, in the study called EUPHAS (Early Use of Polymyxin-B Hemoperfusion in Abdominal Sepsis). 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.[42]

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 polymyxin-B-based direct hemoperfusion (PMX-DHP) for endotoxin removal.[43] 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. Septic shock was diagnosed in 305 (85.4%) patients. The most common source of infection was abdominal (44.0%) followed by pulmonary (17.6%). Gram-negative bacteria represented 60.6% of the pathogens responsible for infection. After 72 hours from initiation of PMX-HP, several SOFA score components significantly improved with respect to baseline: cardiovascular (2.16 ± 1.77 from 3.32 ± 1.29, p <.0001), respiratory (1.95 ± 0.95 from 2.40 ± 1.06, p < .001), and renal (1.84 ± 1.77 from 2.23 ± 1.62, p = .013). Overall 28-day survival rate was 54.5% (60.4% in abdominal and 47.5% in pulmonary infection). Patients with abdominal infection treated within 24 hours from the diagnosis of septic shock had a 28-day survival rate of 64.5%. Patients showing a significant cardiovascular improvement after PMX-DHP had a 28-survival rate of 75% in comparison with the 39% of patients who did not (p < .001). Cox regression analysis found cardiovascular, respiratory, and coagulation SOFA scores to be independent covariates for 28-day survival. A higher 28-day (58.8 vs. 34.5%, p = .003), intensive care unit (ICU) (59 vs. 36.7%, p = .006) and hospital survival rate (53.2 vs. 35 %, p = .02) was observed in European patients than in Asian patients. However, the two populations were highly heterogeneous in terms of source of infection and severity scores at admission. The EUPHAS2 is the largest registry conducted outside Japan for the purpose of assessing the clinical use of PMX-DHP.

Finally, a large prospective randomized, double-blind, controlled trial called EUPHRATES has been conducted in Canada and North America.[44] 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.

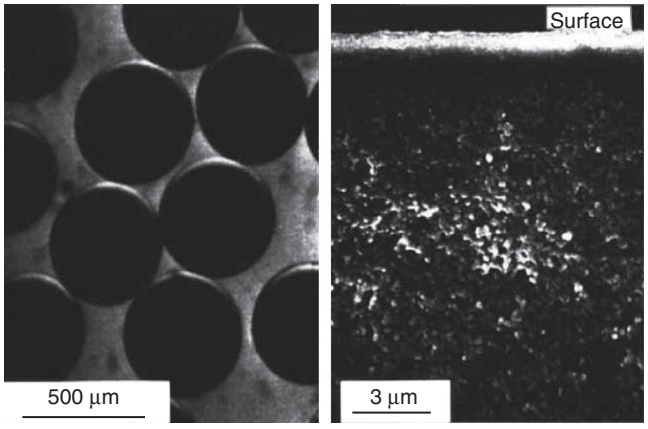
NOVEL APPLICATIONS OF SORBENTS

Lixelle β-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[45] (Fig. 189.20). Peptides and proteins of molecular weight less than 20,000 daltons are able to permeate the bead pores and attach to the ligand by hydrophobic interactions. The U.S. Food and Drug Administration (FDA) approved the column by a humanitarian device exemption in 2015 with an indication of dialysis-related amyloidosis in ESRD patients; it currently is being evaluated in a postapproval trial.

Virus Removal by Lectin Affinity Plasmapheresis

The Hemopurifier device (Aethlon Medical; San Diego, CA) is a plasma filter that 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 and binds viral particles in the plasma filtrate produced in the proximal third of the filter. Based on the transmembrane pressure profile, the filtrate reenters 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.[46]



Micrograph of adsorbent beads | Scanning electron micrograph of a cross-section of the adsorbent

FIGURE 189.20 Lixelle adsorbent beads.

Hemoperfusion for Sepsis-Induced Acute Lung Injury

The HA300 device (Jaffron 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 kDa to 60 kDa, it is well suited for the removal of many inflammatory mediators that are relevant in sepsis (Fig. 189.21). The device has been evaluated prospectively in 46 patients with acute lung injury related to extrapulmonary sepsis.[47] Patients in the intervention group (n = 25) received treatment on 3 consecutive days plus standard care. In comparison with the control group, hemodynamic and respiratory parameters were significantly improved at day 7. Moreover, ICU and 28-day mortality were significantly lower in the HP group.

Sorbent Technology in Wearable Artificial Kidney Devices

Finally, because of limitations of currently available ESRD therapies, substantial interest now exists in applying the principles of miniaturization to the development of wearable/implantable dialysis devices.[48] In a recently

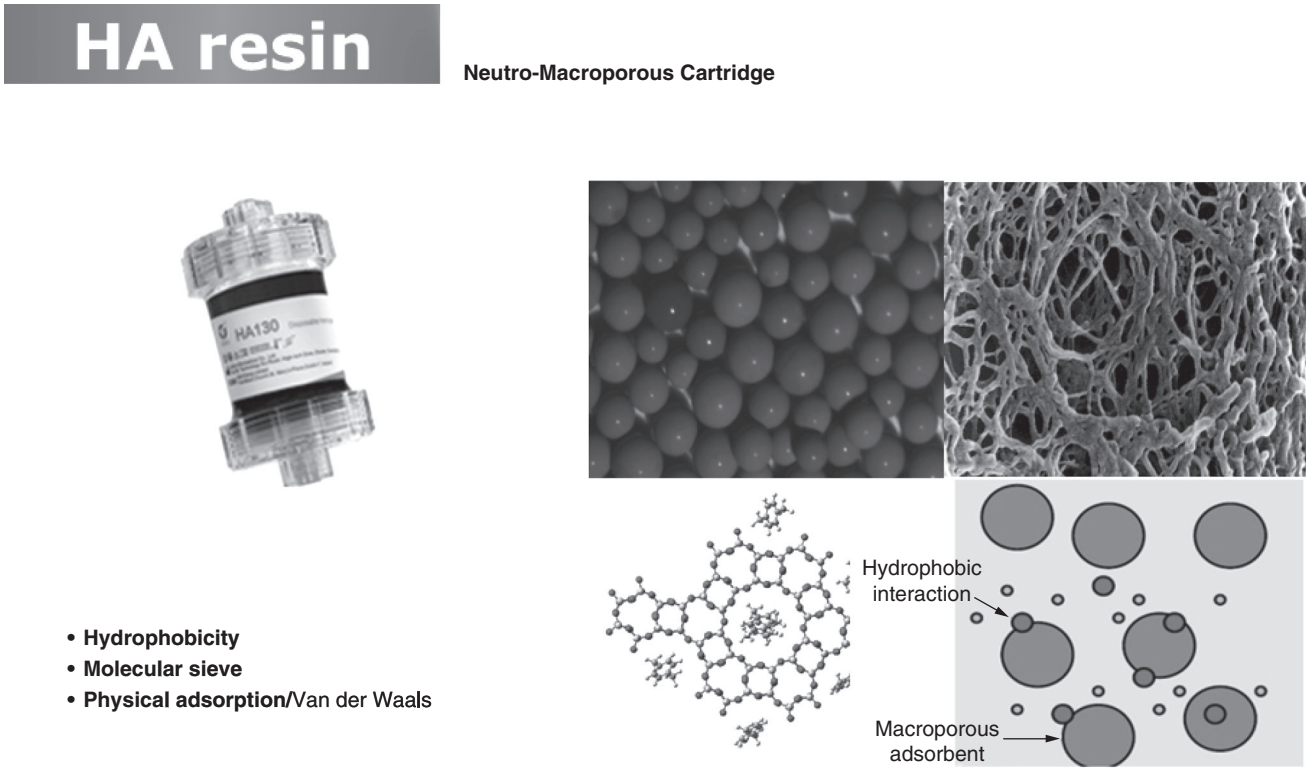


FIGURE 189.21 Jaffron neutral macroporous hemoperfusion cartridge.

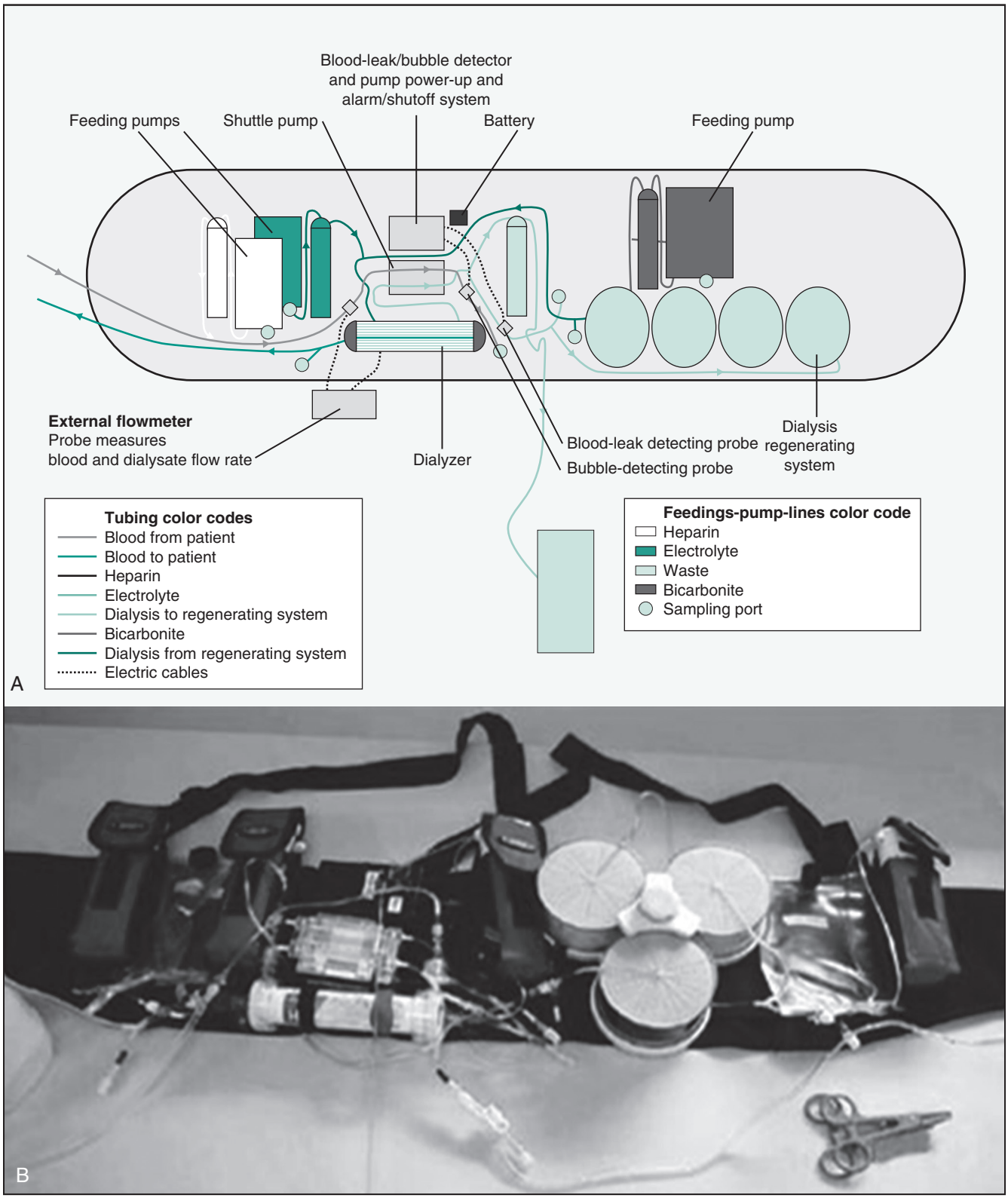


FIGURE 189.22 Dialysate regeneration system. (From Davenport A, Gura V, Ronco C. A wearable haemodialysis device for patients with end-stage renal failure: a pilot study. *Lancet.* 2007;370:2005-2010.)

developed version,[49,50] spent dialysate is regenerated using a sorbent-based system that includes urease, zirconium phosphate, hydrous zirconium oxide, and activated carbon (Fig. 189.22). It is expected that continued advancements in this area will occur in the future.

CONCLUSION

Although adsorbent materials have been employed routinely 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.

Key Points

1. Conventional extracorporeal treatments using diffusion and convection have limitations in capacity to remove hydrophobic/protein-bound compounds or solutes in the molecular range beyond the membrane cutoff. For this reason, adsorption can be a useful mechanism for the removal of certain solutes from the circulating blood.
2. Natural and synthetic sorbents are used in clinical practice. They must have high selectivity/affinity to enable sharp separation, high and rapid capacity of adsorption, chemical and thermal stability, low solubility in the contacting fluid, mechanical strength to prevent crushing and erosion, resistance to fouling, and good biocompatibility.
3. Different chemical and physical forces are involved in adsorption, including van der Waals forces generated by atomic and molecular interactions, ionic bonds generated by electrostatic forces, and hydrophobic bonds.
4. Sorbents can be applied in different modes depending on the technique: (a) HP, in which there is direct contact of the sorbent with blood; (b) HPHD, in which the sorbent unit is placed in series before the hemodialyzer; (c) paired filtration dialysis with sorbent, in which the sorbent unit is placed online in the ultrafiltrate obtained from a hemofilter; and (d) CPFA, in which the sorbent unit is placed online in the plasma filtrate produced from a plasma filter.
5. Sorbent therapy represents an additional option for blood purification. It offers additional benefits when used alone or in conjunction with classic dialysis techniques.

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