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Extracorporeal Blood-Filtering Technologies

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24.1 Introduction

To remove toxins from the body, various blood-purification techniques have been used in clinical practice. The general approach of blood purification is to use a semipermeable membrane that selectively removes the solute by diffusion, convection, and, optionally, adsorption. Blood-purification techniques can be broadly divided into two categories: intracorporeal therapies and extracorporeal therapies. In peritoneal dialysis, an example of an intracorporeal therapy, the native peritoneal membrane, which covers most of the intra-abdominal organs and forms the lining of the peritoneal cavity, functions as a semipermeable membrane. In contrast, during extracorporeal therapy, polymer membranes and sorbent cartridges are used to remove toxins and excess body water by concentration-driven, pressure-driven, electrochemical force, and specific antibody-driven operations. Currently, various combinations of hollow-fiber membrane and sorbents support or replace internal organ functions. This chapter focuses on basic principles and clinical applications of extracorporeal blood-purification techniques to provide insights into contemporary and emerging blood-filtering techniques.

24.2 Basic Setup of Extracorporeal Blood-Filtering Techniques

Extracorporeal blood purification requires four main elements: vascular access, blood-filtering unit, dialysis/replacement fluid, and machine for circulation and monitoring (Figure 24.1).

24.2.1 Vascular Access

Vascular access (VA) is the prerequisite and Achilles' heel of extracorporeal blood-purification therapy. VA gives access to the internal milieu of the patient via the bloodstream, permitting blood purification. The patency of VA is of paramount importance for chronic kidney disease (CKD) patient on thrice-weekly long-term hemodialysis therapy.

Depending on the indication of their use, VA may be temporary (acute or midterm) or permanent (chronic) [1]. Acute VA is generally indicated for starting immediate dialysis in an emergency context when a permanent VA has not been created previously, in patients with acute kidney injury who require renal replacement therapy (RRT), in patients with intoxication amenable to removal by extracorporeal blood purification, or for any other indication requiring extracorporeal blood purification. The usual option for acute VA is a central venous catheter (CVC), also called VA catheter. The temporary VA catheters generally used for acute indications are made of semirigid polymer material. Catheter rigidity permits a nontunneled direct percutaneous introduction of the catheter into a large central vein, under local anesthesia. Several types of acute catheters are presently available in the market. Catheters are usually specified by polymer structure, manufacturing design, presence or absence of side holes, single or double lumen, and external extension tubing part.

Bridging VA is considered a temporary solution between acute and permanent VA. This midterm VA is indicated to solve the blood access problem and to ensure the continuity of RRT in a VA failure situation. There are two options available: venovenous angioaccess or arteriovenous (AV) access. Venovenous angioaccess includes two main options: one is the tunneled catheter and the other is the subcutaneous port catheter device. Tunneled catheters differ from nontunneled ones in that they have subcutaneous tunneling and an anchoring system during catheter insertion. They are made of soft biocompatible polymer and have a large-bore lumen to permit a high flow rate, are dual lumen (arterial and venous lumens), are tunneled in the subcutaneous tissue, and are tightly anchored in the subcutaneous tissue, either with a cuff or a U-shaped suture, and their distal tips are usually located in the superior vena cava or in the right atrium. Based on the chemotherapy port concept, venous port catheter devices have also been developed [2,3]. They are a port valve system made of titanium containing one passageway,

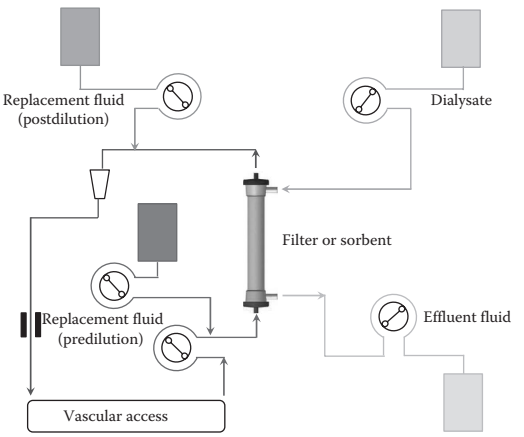

FIGURE 24.1 Main elements of extracorporeal blood-purification therapy.

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subcutaneously implanted and connected to one or two large-bore silicon catheters. As an AV midterm VA, a synthetic polytetrafluoroethylene (PTFE) or polyurethane (PU) AV graft has been used when an autologous AV fistula has failed or cannot be created, or used easily.

As a long-term VA, several types of AV fistula have been described. AV fistula is a surgically created passageway between an artery and a vein. During hemodialysis, the volume of blood is too great for the veins to handle, so a vein must be enlarged. An artery and a vein, usually in the arm above or below the elbow, are sewn together, to create a fistula, and arterial pressure eventually enlarges the vein. The enlarged vein can accommodate a large needle. Both the artery and the vein dilate and elongate in response to the greater blood flow and shear stress, but the vein dilates more and becomes "arterialized" and repeated access by needles is feasible. Though AV graft and in special circumstances, tunneled VA catheters, may also be considered as a permanent VA, AF fistula at this moment is recognized as the most reliable long-term VA [4].

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24.2.2 Blood-Filtering Unit

24.2.2.1 Parallel-Plate Dialyzers

In parallel-plate dialyzers, several layers of flat sheet membranes are stacked, supported by thin plates. There were initially some advantages such as lower thrombogenicity and ease of sterilization by ethylene oxide. However, usage of parallel-plate dialyzers has recently declined because hollow-fiber dialyzers are small, efficient, and suitable for reuse.

24.2.2.2 Hollow-Fiber Dialyzers

A contemporary hollow-fiber dialyzer consists of a housing containing a single membrane fiber bundle (Figure 24.2). The bundle is embedded at both ends in polyurethane, which also fixes the bundle within the casing. The end surfaces are covered by end caps, which contain the blood inlet and outlet ports. The two dialysis fluid ports are positioned on the housing. The structural design of both the hollow-fiber hemodialyzer and the dialysis membrane material are of considerable importance. Hollow-fiber membranes are manufactured in wet, dry–wet, or dry-spinning process. Table 24.1 shows a family tree of dialysis membranes. Until the late 1960s, only membranes manufactured from regenerated cellulose were available. In the early 1970s, the interest in removing middle molecules resulted in the search for improved materials and the clinical introduction of new modalities of treatment such as hemofiltration.

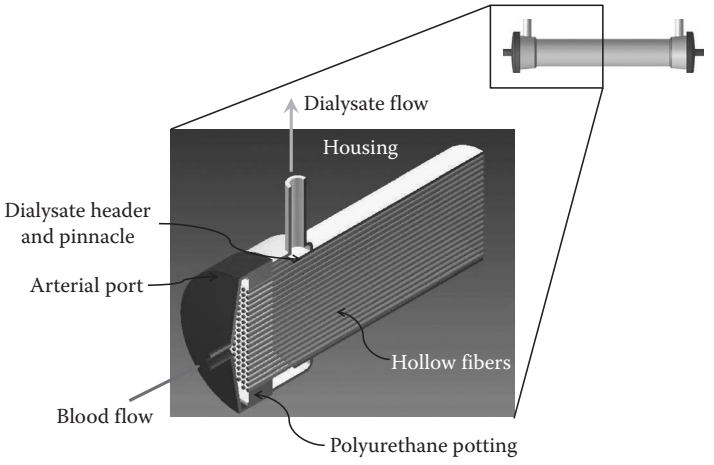

FIGURE 24.2 Structure of hollow-fiber dialyzer and design factors.

TABLE 24.1 Family of Hollow-Fiber Membrane for Hemodialysis

Cellulosic membranes	Substituted/modified cellulose	Hemopheane® SMC® PEG Excebrane®
	Acetylated cellulose	Cellulose acetate Cellulose diacetate Cellulose triacetate
	Regenerated cellulose	Cuprophan® Bioflux® Cuprammonium rayon SCE G-O-P DIAFIL®
Synthetic membranes	Hydrophilized copolymers	PPC Gambrane® PMMA PAN AN69 PAN DX SPAN
	Hydrophilic/hydrophobic copolymers (blended)	PA PS Helixone® APS® Diapes® Arylane® PEPA® Arylane Polyamix™
	Hydrophilic copolymers	EVAL

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These modalities used synthetic membranes prepared from engineered thermoplastics such as polysulfones (PS), polyamides, and polyacrylonitrile (PAN) polymers.

The main performance characteristics of each dialyzer are determined by the size and design of the fiber bundle included. There are some designs that facilitate efficient flow distributions and mass transport by modification in housing structure [5] and fiber structure [6]. The composition of the potting compound has changed over the years. The main motivation was to minimize risks associated with toxic substances, which may evolve after sterilization of the polyurethane resin (PUR). In particular, irradiation with β- or γ-beams may lead to the by-product of carcinogens.

24.2.2.3 Sorbent Cartridges

Since the early 1960s, sorbents have been used in an attempt to increase the efficiency of dialysis, or replace it, in the management of uremia. Additionally, hemoperfusion, a process that allows direct contact of blood from the patient with sorbents has been used to treat drug and chemical intoxication as well as fulminant hepatic encephalopathy. Sorbents used in hemoperfusion devices are activated carbons, ion exchange resins, or nonion macroporous resins. Sorbents can be divided into two large categories (Table 24.2): (i) those that have hydrophobic properties and therefore adsorb the molecules dissolved in the solution in contact with the sorbent and (ii) those that eliminate solutes by chemical affinity. Charcoal and nonionic macroporous resin are within the first category. Charcoal is produced both from biological substances such as coconut shells or peach pits and from nonbiological substances such as petroleum. The charcoal is activated by controlled oxidation in air–carbon dioxide, or steam. Adsorption into charcoal occurs through its pores, and its efficiency depends on the total number of pores and their radius. Activated charcoals are available in many forms, beginning with uncoated granular carbons; most of the available devices now use coated activated charcoal either as granular

TABLE 24.2 Types of Sorbents and Their Use in Clinical Practice

Sorbent	Type	Applications
Nonselective	Charcoal	Poisoning
	Uncharged resins	Chronic renal failure
Selective	Hydrophobic resins	Rabdomyolysis
	Powdered sorbent	Hepatic failure
	Microsphere-based detoxification system	HIV
	Polymyxin-B	Sepsis
	Polyethyleneimine	Drug overdose and poisoning
		LDL apheresis

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charcoal coated with cellulose nitrate (collodion) polymer and albumin or as heparinized copolymer. Other devices containing charcoals are prepared with extruded charcoal coated with cellulose acetate or with methacrylic hydrogel. Others use spherical charcoals derived from petroleum, coated with polyhema solutions, or derived from pyrrolized inorganic resins. The nonionic resins consist of macroporous cross-linked polystyrene amberlite series; for example, XAD-2 and XAD-4 were available in the United States and Europe for the treatment of poisoning. Recently, a modified divinylbenzene resin coated for hemocompatibility has been used [7]. The nonionic macroporous resins are very similar to charcoal and microsphere agglomerates, which adsorb the toxins they eliminate in their surface. The sorbents that eliminate substances by chemical affinity are fundamentally ion exchange resins, which exchanges one ion for another of the same electrical charge.

24.2.3 Dialysis/Replacement Fluid

In extracorporeal blood-purification therapy, dialysis solution, the so-called, dialysate is used to enhance the removal of low-molecular-weight toxins. Because the goal of dialysis is to restore the composition of the body's fluid environment toward normal, dialysate compositions are set to approximate normal values in the body. Moreover, dialysate composition is a factor strongly affecting cardiovascular stability during treatment. In hemodialysis, 500–800 mL/min of dialysate flow is used generally and depending on the treatment modality, ultrapure dialysate/replacement fluid may be additionally required for infusion or replacement. Water represents more than 95% of dialysate, and a dialysis patient is exposed to 300–400 L of water a week, in contrast to a normal person ingesting 14 L per week. To avoid acute or chronic side effects, quality standards for dialysis water and dialysis fluids have been proposed. AAMI and European Pharmacopoeia standards have been widely used or referenced [8,9]. A standard water treatment system is made of a pretreatment section, including softeners, granular activated carbon, and microfilters, followed by a final treatment section. To polish the pretreated water a deionizer or reverse osmosis (RO) may be used. Usually two RO modules in series are preferred to preserve microbiological quality of the treated water. Recently, with increasing use of ultrapure dialysate, defined as sterile, nonpyrogenic fluid obtained by cold filtration, ultrafiltration of final dialysate is done by installing a polysulfone or polyamide ultrafilter on the dialysate line of the dialysis machine. It is also of importance to assure proper water quality by regular maintenance and a quality control program.

24.2.4 Machine for Extracorporeal Therapy

A machine for extracorporeal blood purification is in charge of blood circulation and monitoring of the treatment system. It is equipped with pumps for blood and dialysate supply, biosensors, and safety system. Because of the paramount importance of safety, international authorities and committees have developed regulations and standards. The basic regulation within the European Union (EU) is Council Directive 93/42/EEC, commonly known as "Medical Device Directive (MDD)." This directive defines

essential requirements now used as the basis for the registration (CE marking) of medical devices within the EU. These essential requirements demand that any risk that may be associated with medical devices must be weighed against the benefit for the patient, and must be compatible with a high level of protection of health and safety. Recently, bio-feedback control systems for blood volume, body temperature, and ultrafiltration have been adopted to improve the tolerance of treatment [10–12].

24.3 Transport Principles in Blood-Filtering Technologies

24.3.1 Diffusion

Diffusion is defined as the migration of molecules by random motion from a region of higher concentration to a region of lower concentration. The rate of diffusion per unit area (J/A) is proportional to the concentration gradient (ΔC), which is the driving force.

$$J/A = -K_0\,(\Delta C)$$

where K_0 is a constant, the overall mass transfer coefficient that characterizes the resistances of layers limiting diffusion of solute across the dialyzer membrane. In hemodialysis, it is useful to use the mass transfer area coefficient (K_0A) to compare diffusion performance of whole dialyzers. K_0A is a property of both the solute and the dialysis membrane with units of mL/min.

24.3.2 Convection

Convective transport is defined as solute movement that results from bulk movement of solvent, usually in response to differences in hydrostatic pressure. Hydraulic pressure causes molecules to move from a region of high pressure to a region of low pressure. For solutes that are much smaller than the membrane pores, the movement of solvent carries the solute with it at the same rate. For larger solutes, however, movement of solutes may be relatively restricted. The magnitude of this restriction can be expressed as the sieving coefficient (SC).

$$\mathrm{SC} = \frac{C_r}{C_d}$$

where C_r is the mean concentration mass receiving stream (i.e., dialysate compartment) and C_d is the mean concentration mass donating stream (i.e., blood compartment). The fluid transport in hollow-fiber membrane (J_f) is defined as ultrafiltration and can be described as

$$J_f = K_{UF} \cdot \mathrm{TMP}$$

where K_{UF} is the ultrafiltration coefficient that represents the hydraulic permeability of the membrane and $\mathrm{TMP} = P_B - P_D - \pi$ (transmembrane pressure), where P_B and P_D are hydrostatic pressures of blood and dialysate, respectively, and π is the oncotic pressure.

24.3.3 Adsorption

Dialysis membrane may interact with solutes, causing them to adhere or, when present in high concentrations such as serum albumin, to coat the membrane, reducing membrane permeability to other solutes. The albumin coating effect occurs immediately after exposure to blood or serum and accounts

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in part for the lower K_0A [13]. However, because of high blood concentration, adherence of albumin to the membrane does not reduce its overall concentration. On the other hand, solutes present in much lower concentrations may be substantially removed by adsorption to the membrane. For example, the adherence of beta-2 microglobulin and endotoxin to polysulfone membrane during standard dialysis significantly enhances their clearances [14,15]. Sorbents, by taking advantages of large surface area, can be additionally used to adsorb the molecules dissolved in the solution in contact with the sorbent and by the following steps [16]: (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 (interphase) mass transfer of the solute by pore diffusion from the outer surface of the sorbent to the inner surface of the internal porous structure; (c) surface diffusion along the porous surface; and (d) adsorption of the solute onto the porous surface. Physical adsorption may occur thanks to van der Waals forces and chemical adsorption occurs due to chemical affinity.

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24.4 Factors Influencing Solute Transport

24.4.1 Blood Flow

In low-flux hemodialysis, solutes are mostly removed by diffusion. For some easily dialyzed solutes, removal by diffusion is a near-linear function of blood flow. For other solutes, the removal is primarily membrane-dependent, and independent of blood flow (Figure 24.3). When membrane permeability is high, solutes are removed quickly, in the proximal part of the hollow fiber. Increase in blood flow enhances solute removal by extending the gradient further. Blood flow distribution in hollow-fiber bundle could also influence solute transport in a dialyzer. Blood flow distribution is determined by arterial port design of the dialyzer and blood flow rate [17].

24.4.2 Hematocrit and Blood Water Content

The nonaqueous fraction of whole blood is not dialyzable, so, as the patient's hematocrit increases, solute clearance falls, due to the decrease in flow of "blood water" through the dialyzer. An expression can be derived for blood water flow:

$$Q_{BW} = Q_B[0.72\gamma(hct) + 0.93(1 \boxtimes hct)]$$

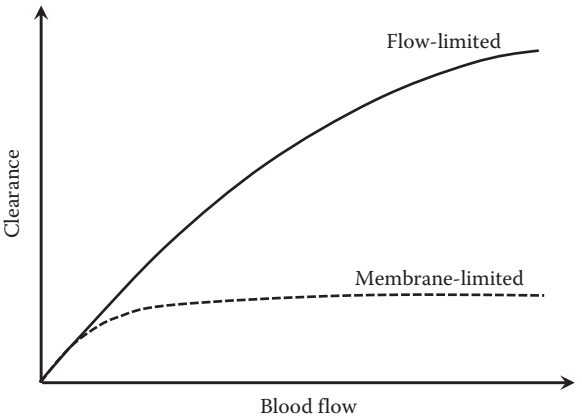

FIGURE 24.3 Relationship between blood flow and solute clearance in hollow-fiber dialyzer.

where Q_B is whole blood flow into the dialyzer, Q_{BW} is blood water flow, *hct* is the fractional red cell volume of whole blood, 0.93 is the water fraction of plasma, and 0.72 is the effective water fraction of the red cell. To completely account for the hematocrit effect, the fraction of red cell volume available for dialysis (γ) must be added to the formula. For urea, γ has been measured at 1.11 due to a reversely bound pool of urea within the red cell [18]. For creatinine, γ is approximately 0.50, and for phosphorous, γ is essentially zero.

24.4.3 Dialysate Flow

The flow of dialysate enhances solute removal by maintaining the concentration gradient across the dialysis membrane. When blood and dialysate flow are countercurrent, solute removal is maximal and the relationship between dialysate flow and clearance is similar to that of blood flow as mentioned earlier. However, in contrast to blood side, stagnation and channeling of dialysate flow lead to nonuniform dialysate flow distribution. Fiber structure, fiber packing density, and flow baffle design influence dialysate flow distribution in a dialyzer [6,19].

24.4.4 Membrane Properties

Dialysis membranes manufactured in the past were composed of a thin uniform meshwork of modified cellulose fibers with an effective pore size that depended on the density of fibers. Modern synthetic membranes are often asymmetric; that is, they are constructed from a highly porous, relatively thick polymer that offers little resistance to diffusion to the overlying thin layer that constitutes the diffusion barrier. For small dialyzable solutes, the rate of diffusion across a porous membrane depends on the number and geometry of pores as well as the charge and surface area of membrane [20,21]. During extracorporeal blood purification using hollow-fiber membrane, blood-membrane surface interection, swelling of the membrane and membrane surface potential affect the effective surface area for solute transport.

24.4.5 Solute Properties and Protein Binding

The transport of solute across dialysis membranes depends on the interaction of the solute with the membrane, so properties of both must be considered. The most important property of solute is molecular size, but water solubility, charge, and molecular shape also influence transport. Serum albumin serves as a transport protein for hydrophilic solutes such as fatty acids that are poorly soluble in aqueous solutions. Just as binding to serum proteins may affect removal of drugs by dialysis, binding of uremic toxins to albumin can inhibit the therapeutic effectiveness of dialysis, causing even small toxins to behave like larger poorly dialyzable compounds [22].

24.4.6 Convection

In addition to solute permeability, membrane porosity can be measured in terms of water permeability. The latter is usually expressed as an ultrafiltration coefficient (K_{UF}), the filtration flow rate per unit of applied hydraulic pressure:

$$K_{UF} = Q_f / \Delta P$$

Removal of solute by filtration (convection) during dialysis slightly augments removal by diffusion. In reality, during extracorporeal therapy, both diffusion and convection occur simultaneously along the same membrane. The decrease in solute concentration due to diffusion means the capacity for solute removal by convection falls along the dialyzer length. Conversely, the fall in blood flow rate due to filtration along the dialyzer length interferes with diffusion. A simple model proposed for this phenomenon is [23]

$$K_D = K_{D0} + Q_f T$$

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where *T*, termed the transmittance, represents the mL/min increase in clearance for each mL/min of filtration. During filtration, on the other hand, concentration polarization and cake layer formation on the surface of dialysis membrane impair the effectiveness of filtration. High blood flow rate may serve to reduce the thickness of the secondary layer by increasing shear forces at the membrane surface.

24.5 Clinical Applications

24.5.1 Blood Filtering in Kidney Diseases

There are various extracorporeal renal replacement techniques using hollow-fiber membranes (Figure 24.4).

24.5.1.1 Low-Flux Hemodialysis

Conventionally, hemodialysis membranes are classified according to water permeability. The ultrafiltration coefficient K_{UF} is a general parameter that represents water permeability of dialyzers. Low-flux dialyzers have ultrafiltration coefficient less than 8–10 mL/h/mmHg [24]. Low-flux hemodialysis focuses on removal of low-molecular-weight solutes by diffusion. During low-flux hemodialysis, fluid transport across dialysis membrane does not influence hematocrit level in hollow fibers and the probability of backfiltration is low.

24.5.1.2 High-Flux Hemodialysis

High-flux membranes are more porous due to larger pore size, increased surface area, and higher pore number. Generally, dialyzers that have an ultrafiltration coefficient of more than 20 mL/h/mmHg are

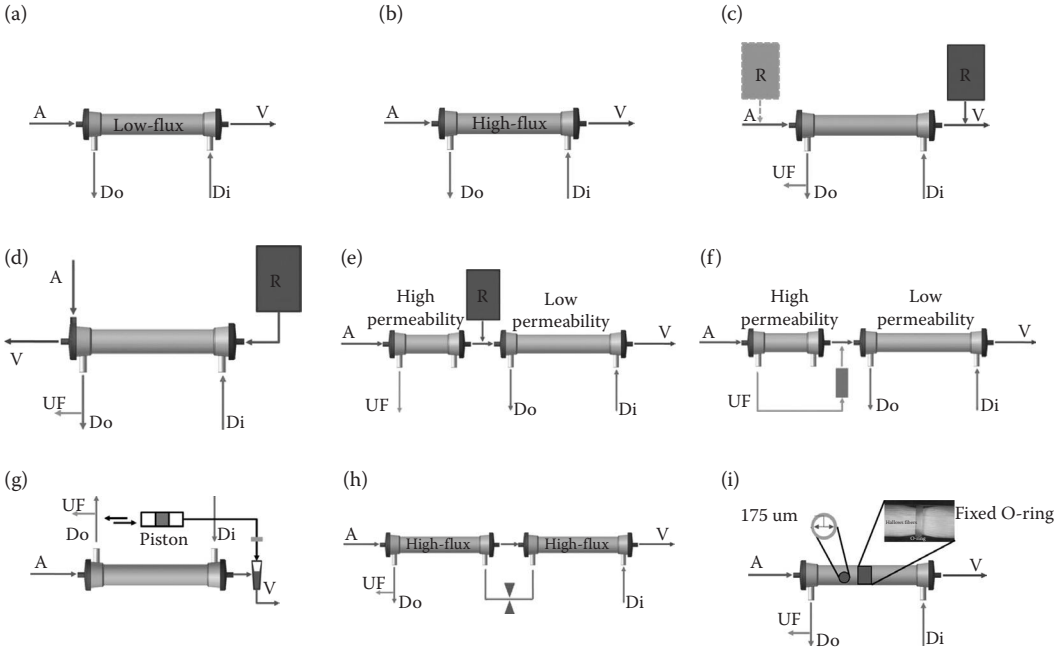

FIGURE 24.4 Various extracorporeal RRT using hollow-fiber dialyzers. (a) Low-flux hemodialysis, (b) high-flux hemodialysis, (c) hemodiafiltration, (d) middilution hemodiafiltration, (e) paired filtration dialysis, (f) hemodiafiltration with reinfusion, (g) push/pull hemodiafiltration, (h) double high-flux dialysis, and (i) enhanced internal filtration dialysis.

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called high-flux dialyzers, which allow more fluid transport across dialysis membrane by convection. During high-flux hemodialysis, direct filtration, fluid transport from blood compartment to dialysate compartment occurs in the proximal part of hemodialyzer while backfiltration occurs in the distal part. Volumetric ultrafiltration control contributes to increase in dialysate pressure. Both low- and middle-molecular-weight solutes are removed by diffusion and convection during high-flux hemodialysis.

24.5.1.3 Hemodiafiltration

Owing to advances in dialysis membrane, ultrafiltration control system and online production of large amounts of ultrapure dialysate, hemodiafiltration (HDF) is becoming popular to enhance middle-molecular-weight solute removal [25]. HDF allows high filtration volume (5–20 L/session) necessitating infusion or replacement. Dialysis membranes that have an ultrafiltration coefficient of more than 50 mL/h/mmHg are adopted in this dialysis modality.

24.5.1.4 Middilution Hemodiafiltration

To reduce spontaneous BF in a hollow-fiber module, middilution hemodiafiltration (MD-HDF) uses a specially designed filter with a blood header cap that contains fibers arranged in outer annular and inner core region [26]. Blood enters the side port of the blood header and flows down to the outer annular region of fibers and mixes with the replacement fluid at the other end, where blood flow is countercurrent to dialysate. The diluted blood then flows back along the central core of fibers to exit at the central port of the blood header, where blood flow is cocurrent to dialysate.

24.5.1.5 Paired Filtration Dialysis

Paired filtration dialysis (PFD) involves high-permeable membrane and low-permeable membrane to separate diffusion and convection [27]. The first filter allows hemofiltration via a high-permeable membrane followed by the infusion of sterile replacement fluid before blood flow through the second filter to undergo dialysis across a low-permeable membrane.

24.5.1.6 Hemofiltration with Reinfusion

HFR is modified from PFD to avoid exogenous reinfusion. The ultrafiltrate from the hemofilter is passed through a sorbent cartridge to retain uremic solutes and is reinfused as a replacement fluid. Endogenous reinfusion avoids losses of nutrients, amino acids, hormones, and vitamins during dialysis [28].

24.5.1.7 Push/Pull Hemodiafiltration

To enhance DF and BF, a double-cylinder piston pump is attached to the dialysis outlet pathway at one end and the venous chamber at the other [29]. As this pump pulls out the dialysate from the dialysis pathway, it creates a negative TMP and effects the filtration in the hemodiafilter. It simultaneously lowers the air–fluid level in the venous air chamber. As the pump pushes the dialysate back into the dialysate outlet pathway, it creates a positive TMP and affects BF in the hemodiafilter. It simultaneously elevates the air–fluid level in the air chamber. Since the time taken for the extracorporeally circulating blood to pass the hemodiafilter is approximately 40 s, the blood is concentrated and diluted many times before it leaves the hemodiafilter (approximately 25 times) and body fluid replacement volume will exceed 120 L during a 4-h session. The synchronized lowering and elevation of air–fluid level in the venous chamber with the filtration and BF, respectively, is to circumvent the variation in the blood flow returned to the patient's body.

24.5.1.8 Double High-Flux Dialysis

To shorten treatment time, two high-flux dialyzers are placed in series. A flow restrictor in the dialysate pathway between the two dialyzers allows a low dialysate pressure in the proximal dialyzer favoring DF. The high dialysate pressure, generated upstream to the flow restrictor, in the distal dialyzer favors BF,

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which thus acts as the replacement fluid. The high dialysate compartment pressure of the distal dialyzer favors BF, which thus acts as the replacement fluid [30].

24.5.1.9 Enhanced Internal Filtration Dialysis

By various modifications in filter or fiber geometry, higher convection transport is achieved during enhanced internal filtration dialysis (EIFD). The dialyzer may be modified by the introduction of an O-ring to enhance the dialysate pressure differentials between the proximal and distal parts of the dialyzer [31]. A lower dialysate pressure in the proximal part favors filtration, while a higher dialysate pressure in the distal part of the dialyzer favors BF. Minor alterations in the fiber diameter can accentuate the pressure drop along the fiber and hence favor DF in the proximal part and BF in the distal part [32]. Higher fiber density ratio and housing structure with a wholly surrounding baffle and a slope facilitate the uniform diffusion of the dialysate [33].

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24.5.2 Blood Filtering in Acute Liver Failure

Acute liver failure (ALF) or acute chronic liver failure is associated with a high mortality of 28%. The prognosis of ALF has been substantially improved by orthotopic liver transplantation (OLT). However, the scarcity of organs and the lifelong need for immunosuppression and its attending adverse effects precludes OLT as an option in all cases. Moreover, 40% of the episodes of ALF may recover, with medical therapy and the regenerative ability of the liver, thereby making an irreversible treatment like OLT redundant.

The main metabolic functions of the normal liver are detoxification, biotransformation, excretion, and synthesis. Therefore, ALF is characterized by the accumulation of several toxic substances, including bilirubin, ammonia, glutamine, glutamate, aromatic amino acids, free fatty acids, lactate, phenols, mercaptans, endogenous benzodiazepines, and proinflammatory cytokines. These toxins are responsible for the clinical manifestations of cerebral edema, hepatic encephalopathy, jaundice, pruritis, sepsis, and so on. On the other hand, decreased synthesis of coagulation factors and proteins can cause coagulopathy, ascites, immune disorders, and so on. Cerebral edema leading to raised intracranial pressure and brain herniation is the principal cause of mortality in patients with ALF and is attributed to be secondary to hyperammonemia. Ammonia produced by the urease-producing bacteria in the colon is normally broken down into urea by the liver. In cases of ALF, there is inadequate conversion of ammonia to urea and there is extracellular and intracellular hyperammonemia. Intracellular ammonia is converted to glutamine, in the brain astrocytes, leading to increased intracellular osmolality and brain edema. Similarly, the conversion of extracellular ammonia to glutamate eventually triggers nitric oxide synthase release and cerebral vasodilatation. It has been observed that hyperammonemia precedes brain herniation by 1–2 days, allowing an opportunity for extracorporeal detoxification [34].

Extracorporeal liver assist may be offered to patients as a support to the recovery of injured liver with medical therapy or as a bridge to a more definitive treatment like OLT. Based on the previous discussion, liver assist should essentially involve two components—first, detoxification of blood and second, the replacement of the more important metabolic functions of the liver. Consequently, liver-assist devices can be classified into two broad categories:

1. *Artificial liver (AL)*: Involves the detoxification of blood by circulating it extracorporeally against physical/chemical gradient involving albumin or through sorbents.
2. *Bioartificial liver (BAL)*: In addition to the detoxification of blood, it involves the circulation of plasma through a hepatocyte-housing bioreactor to replace the metabolic functions of the liver. These are cellular-based techniques for supporting liver function and are in various phases of clinical evaluation. For further information, the reader should consult textbooks on liver diseases.

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24.5.2.1 Artificial Liver

The toxins involved in the pathogenesis of liver failure represent both water-soluble (ammonia, uremic toxins) and albumin- or protein-bound toxins (bilirubin, bile acids, aromatic amino acids, free fatty acids, benzodiazepines) [35]. Thus, unlike in renal failure where the toxins are mainly water soluble, modifications in dialysis or other additional techniques to enhance the clearance of protein-bound toxins have to be implemented in patients with ALF. Second, the available AL devices incorporate multiple removal techniques in conjunction, either in series or in parallel, for effective detoxification of blood. The commonly applied techniques of toxin removal include [36]:

1. *Plasmapheresis or plasma exchange*: Separation of plasma by the centrifugation method or via membrane filtration facilitates a nonselective removal of all noncellular components of blood.
2. *Plasma fractionation*: Filtration of plasma through very high-permeability membranes (molecular weight cut-off of >70–100 kDa); removes high-molecular-weight substances.
3. *Hemofiltration*: Filtration through medium- to high-permeability membranes (molecular weight cut-off between 15 and 70 kDa).
4. *Hemodialysis*: Removal of water-soluble, low-molecular-weight substances by diffusion across a low-permeability membrane.
5. *Albumin dialysis or aided transfer*: Albumin in the dialysate or bound to the filter membrane enhances the clearance of albumin-bound toxins.
6. *Adsorption*: Circulating blood over a sorbent material like charcoal, neutral resin, or anion-exchange resin removes protein-bound toxins.

The two commercially available and more extensively used AL devices are the molecular adsorbent recirculating system (MARS; Gambro Lundia, Lund, Sweden) and the Prometheus system (Fresenius Medical Care, Bad Homburg, Germany).

24.5.2.2 Molecular Adsorption Recirculating System

MARS essentially is a modification of a normal dialysis circuit, with the interposition of a closed albumin dialysate circuit between the blood (flowing in dialyzer 1) and the bicarbonate-based dialysate (flowing in dialyzer 2) (Figure 24.5a). The MARS platform is a single pump platform that circulates albumin dialysate in a closed loop. The MARS monitor is mounted onto a hemodialysis or CRRT machine that maintains the blood and bicarbonate dialysate flows. Blood exits the patient via a central vein vascular access and flows through a high-flux albumin-coated polysulfone hemodialyzer (dialyzer 1; membrane thickness 100 nm; pore size 50 kDa; surface area 2.1 m^2). The dialysate side of dialyzer 1 is bathed by the albumin dialysate that is continuously pumped by the MARS monitor. Thus, in dialyzer 1, there is an effective exchange of protein-bound toxins in blood with the albumin in the dialysate and dialysis of water-soluble toxins across the membrane. The toxin-rich or "spent" albumin dialysate leaves dialyzer 1 and then flows across the "blood" compartment of a low-flux polysulfone hollow-fiber dialyzer (dialyzer 2). The dialysate compartment of dialyzer 2 is bathed by the bicarbonate dialysate pumped by the HD or CRRT machine. The water-soluble uremic toxins are dialyzed across the gradient established by the bicarbonate dialysate, which is discarded. The removal of water-soluble toxins in dialyzer 2 constitutes the first step in the regeneration of the "spent" albumin dialysate. The next step in the regeneration of albumin dialysate is by adsorption and involves its flow through an activated charcoal column followed in series by its flow across an anion exchange resin. This regenerated albumin dialysate is now available for the next cycle of flow through the dialysate compartment of dialyzer 1. As is evident, the albumin dialysate flows in a "closed" circuit and its capacity to remove protein-bound toxins in the blood is dependent upon the regenerating ability of the activated charcoal column and anion exchange resin. The typical intermittent MARS treatment session is implemented for 6–8 h with the blood flow and albumin dialysate flow rates set between 150 and 200 mL/min and the bicarbonate buffered dialysate flow rate set between 300 and 500 mL/min. Heparin is used to maintain circuit anticoagulation with a targeted

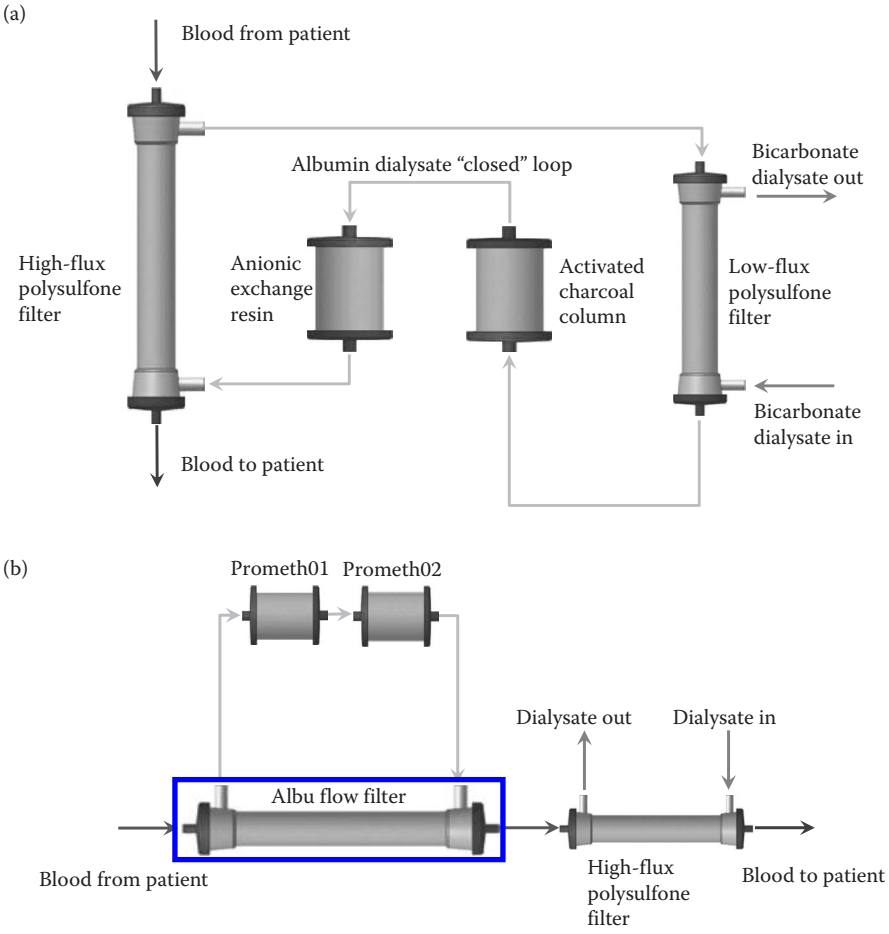

FIGURE 24.5 Schematic diagrams of (a) molecular adsorbent recirculating system (MARS) and (b) Prometheus system.

activated clotting time between 160 and 190 s. In select cases, it is possible to run the circuits heparin free [37]. MARS appears to be a safe procedure though it carries the potential of adverse effects including inherent risks of catheterization for vascular access, mild thrombocytopenia and disseminated intravascular coagulation, and hypoglycemia. MARS also eliminates both water- and protein-bound drugs and may alter their levels in the blood, thereby compromising their clinical efficacy.

24.5.2.3 Fractionated Plasma Separation and Adsorption (Prometheus System)

The Prometheus system differs from the aforementioned MARS in applying albumin-permeable membrane to separate albumin-bound toxins and thereby obviating the need for exogenous albumin (Figure 24.5b). Blood exits the patient via a central vein vascular access and flows through a filter with a high-molecular-weight cut-off polysulfone membrane (AlbuFlow; 250 kDa cut-off; albumin sieving coefficient 0.6). This allows albumin and all albumin-bound substances to be separated from the blood across the membrane and into the dialysate compartment. This separated plasma is subsequently purified by the removal of albumin-bound toxins by flowing it through two adsorbent columns connected in series. The first column, Prometh01, is a neutral resin column and the second column, Prometh02, is an anion exchange resin column. Following this, the "endogenous" albumin is returned to the patient along with

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the blood. The blood exiting the AlbuFlow flows through a regular high-flux polysulfone dialyzer where the water-soluble toxins are removed by dialysis against bicarbonate buffered dialysate. The Prometheus circuit is integrated on a modified hemodialysis unit (4008H). The blood flow is set at around 200 mL/min, the dialysate flow is at 300–500 mL/min and the flow of separated plasma in the secondary circuit at 300 mL/min). The circuit is anticoagulated with heparin or citrate.

In comparison to MARS, studies have demonstrated that the Prometheus system has better clearance rates and reduction ratios for both water-soluble and albumin-bound substances, except for bile acids [38]. In another study comparing the two procedures, mean arterial pressure and peripheral resistance was improved only in patients treated with MARS [39]. Other than a transient and reversible decrease in mean arterial pressure and white blood cell count [40], treatment with Prometheus was safe.

24.5.2.4 Other Artificial Liver Devices

Besides the two commonly used systems discussed earlier, other techniques are also being evaluated. Single-pass albumin dialysis (SPAD) is performed on a regular dialysis setup using a high-flux albumin-impermeable membrane. The removal of protein-bound substances is facilitated by the addition of albumin to the dialysate side [41,42]. Selective plasma filtration (SEPET) involves the selective removal of albumin-bound and water-soluble substances using a medium pore (cut-off 100 kDa) filter. The "spent" plasma is discarded and replaced by an electrolyte solution, 5% albumin, and fresh frozen plasma [43]. Slow plasma exchange plus high flow dialysate continuous HDF using a filter with PMMA membrane is used in Japan for the management of ALF and has shown promising results [44].

24.5.3 Blood Filtering in Respiratory Diseases

Mechanical ventilation in patients with respiratory failure may be associated with ventilator-induced lung injury. Lung protective ventilator strategies are met with a worrisome consequence of hypercapnia and hypercapnic acidosis. Technological development over the years, in particular, the introduction of microfiber nonmicroporous poly-4-methyl-1-pentelene membrane, has allowed low blood flow extracorporeal carbon dioxide removal (ECCO2R). Unlike extracorporeal membrane oxygenation (ECMO), which depending on how it is implemented has the capability to totally replace cardiac and respiratory function, ECCO2R is used as an adjunct with mechanical ventilation to allow for ultralung protective ventilation in severe respiratory failure. In select cases of hypercapnic respiratory failure, ECCO2R may even successfully obviate the need for mechanical ventilation.

Low blood flow ECCO2R may be established via an arteriovenous or a venovenous route. Arteriovenous CO_2 removal is represented by Novalung (GmbH, Hechingen, Germany), a single-use, high-molecular-weight heparin-coated, ultracompact gas exchange system, consisting of a very low resistance but highly efficient PMP membrane lung (pressure drop of 10 mmHg at blood flow of 2 L/min) [45]. The surface area available for gas exchange is 1.3 m^2 and O_2 flows can be regulated at 1–15 L/min, based on the patient's $PaCO_2$. Blood is accessed via the femoral artery and returned via the femoral vein (15–21 Fr catheters). Extracorporeal blood flow generated by the arteriovenous pressure gradient of the patient causes a significant amount of AV shunting, between 1 and 2.5 L/min (up to one-quarter of cardiac output). This is continuously monitored by an ultrasound sensor. Therefore, for optimal functioning, a MAP of >70 mmHg (with or without vasopressor support) and a cardiac index >3 L/min/m^2 is required [46]. The CO_2 removal capacity is 80–200 mL/min (50% of body's CO_2 production) and is proportional to the $PaCO_2$, sweep gas flow, and blood flow [45]. The contraindications for AVCO2R are cardiac failure, shock, heparin-induced thrombocytopenia, and severe peripheral vascular disease.

The Decap/Decapsmart ECCO2R device, operating in venovenous mode, is a modified renal replacement circuit incorporating a neonatal polypropylene membrane lung (0.3 m^2), coupled in series with a polysulfone hemofilter (1.35 m^2). The blood flow into the membrane is aided by a nonocclusive roller pump (maximum 450 mL/min), whereby CO_2 is eliminated by diffusion against a concentration gradient, created by sweep gas flow of 6–8 L/min of O_2. After exiting the membrane, blood is ultrafiltered by

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a hemofilter, connected in series, before returning to the body. The ultrafiltrate is recirculated back into the membrane prior to membrane inflow, by another roller pump (0–150 mL/min). The process of recirculation not only enhances the removal of dissolved CO_2 in the plasma water but also dilutes the blood premembrane, which helps one to reduce the anticoagulation need. The hemofilter also contributes to increased resistance within the membrane, thereby reducing chances of bubble formation [47]. Prolung (Estor, Italy) membrane lung is similar to DECAP, but does not have the hemofilter connected in series.

As the majority of CO_2 is transported in blood as bicarbonate, dialytic clearance of CO_2 in the form of bicarbonate is an appropriate option. Earlier experiments have shown that this strategy was capable of removing 26–38 mL of CO_2/100 mL blood flow [48] and the newer hydrophilic polysulfone membranes also remove CO_2 at rates of up to 15% of the CO_2 metabolic production rate [49]. However, respiratory dialysis is limited by the options available to correct the ensuing metabolic acidosis secondary to bicarbonate removal. Sodium hydroxide, trishydroxy-methylaminomethane (THAM), and other organic anions have been tried as bicarbonate replacement, but their use has been hindered by metabolic acidosis, hyperchloremia, hemolysis, and fluid gain [50].

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24.5.4 Blood Filtering in Sepsis

The pathophysiology of sepsis is generally accepted as involving proinflammatory and anti-inflammatory mediators. Most of these immune mediators of sepsis are water soluble and belong to the medium-molecular-weight category of substances (5–50 kDa) and thus are amenable to extracorporeal removal by techniques of diffusion, convection, or adsorption. However, given the high generation rates of these mediators, conventional RRT doses may not be able to influence adequate removal. Consequently, various modalities have been attempted to increase the removal of these inflammatory mediators.

1. *Continuous high-flux hemodialysis (CHFD)*: This method uses a highly permeable dialyzer, with blood and dialysate flowing in countercurrent direction. The ultrafiltrate volume is controlled by a pump and thus filtration in the proximal part of the dialyzer is balanced by an equal volume of backfiltration of the ultrafiltrate in the distal part of the dialyzer. This obviates the need for replacement fluid while providing increased convective clearance of middle molecules without compromising urea clearance (Ref. 1, p. 884).
2. *High-volume hemofiltration (HVHF)*: HVHF attempts blood purification by the convective removal of mediators using high ultrafiltration volumes of 50–100 mL/kg/h [51–53]. The application of HVHF is usually done at centers with extensive experience in CRRT. It requires a good vascular access to accommodate high blood flows, bicarbonate buffered replacement fluid to be administered as pre- and postdilution (33–67%) to achieve a best compromise between loss of treatment efficacy and optimization of blood flow, and the use of synthetic large surface area biocompatible high-flux (Kuf 30–40 mL/mm Hg/h) membrane dialyzer. Also, appropriate heating of the replacement fluid to maintain body temperature control is important. To circumvent some of the operational logistics and effects of HVHF, pulse HVHF was proposed as an alternative, wherein pulses of HVHF at an ultrafiltration rate of 85 mL/kg/h is applied for intervals of 6–8 h. This pulse of HVHF is preceded and followed by the implementation of conventional CRRT at doses of 35 mL/kg/h [54,55].
3. *High cut-off hemodialysis or hemofiltration*: This modality involves the performance of hemodialysis or hemofiltration using conventional equipment and doses, but using high cut-off (HCO) membranes. These membranes are highly porous and allow for the removal of substances of molecular weights between 15 and 60 kDa with greater efficiency. This modality has demonstrated better cytokine removal characteristics [56], but expectedly has been associated with increased albumin losses [57].
4. *Hemoadsorption*: This technique utilizes the capability of sorbents to attract substances of varying molecular weights, including substances exceeding molecular weight cut-off of high-flux membranes, and binding with them through hydrophobic interactions, electrostatic attractions,

hydrogen bonds, or van der Waals forces. Modification of pore structure and size can impart selectivity to the adsorbent resins, while an outer biocompatible layer reduces bioincompatibility.

Endotoxemia has been associated with the severity of sepsis secondary to Gram-negative bacteria. Polymyxin B is an antibiotic that is able to compromise the bacterial outer membrane of Gram-negative bacteria and bind lipopolysaccharide, thereby neutralizing its toxic effects. Perfusion of blood through a cartridge in which polymyxin B is immobilized to polystyrene fibers has been used in the management of patients with Gram-negative sepsis. This technique has demonstrated improvement in the hemodynamic parameters and a reduction in vasopressor support; however, no survival advantage could be convincingly demonstrated [58].

5. *Plasma therapy and coupled plasma filtration and adsorption (CPFA)*: Plasma therapy involves plasmapheresis and plasma exchange. In plasmapheresis, the plasma is separated by a centrifugal pump or filtered by a plasma filter, following which it is reprocessed, to facilitate the removal of components of interest, by passing it through adsorbent columns. The reprocessed plasma is then returned to the patient, thus eliminating the need for the replacement of plasma. In contrast, in plasma exchange, the separated or filtered plasma is discarded and is substituted in the body with the replacement fluid (e.g., 5% albumin) or fresh frozen plasma. The process of CPFA, whereby the filtered plasma is passed through a nonspecific adsorbent column placed in series downstream of the plasma filter, helps enhance the nonselective removal of circulating soluble mediators potentially involved in the pathogenesis of sepsis and could improve hemodynamic stability over CRRT [59,60]. Using a monoclonal or polyclonal antibody-coated resin column, coupled plasma filtration immunoadsorption could improve the removal of specific mediators.

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24.6 Emerging Technologies for Blood Purification

24.6.1 Hemodialysis Technologies

Researchers have tried to develop a wearable artificial kidney (WAK) with the dream of improving dialysis patients' quality of life. Recently, Gura et al. developed a belt-type wearable kidney, the WAK [61]. Patients were connected to the WAK via their usual vascular access. The WAK regenerates dialysate using REDY® sorbent cartridge with only 375-mL dialysate volume. Here, 0.6-m^2 high-flux hemodialyzer was used and the total system weight was 2.3 kg. This device was powered by two standard 9 V batteries and applied for 4–8 h to eight patients with mean blood and dialysate flow rates of 58.6 and 47.1 mL/min, respectively. However, this device showed some limitations such as clotting of vascular access and needle dislodgment associated with the device's mobility. Inaccurate electrolytes, acid–base control, and ammonium ion accumulation in the sorbent cartridge are also typical problems of REDY cartridge. Further modification has been made by adopting a double-channel pulsatile pump to enhance convective transport. The ammonium accumulation problem was resolved by increasing the pH of the dialysate [62]. Further modifications of the WAK are ongoing with the integration of electrical control and safety system.

24.6.2 Peritoneal Dialysis

In contrast to hemodialysis, because vascular access is not required in peritoneal dialysis (PD), it might be appropriate for a wearable device. Ronco et al. proposed a concept of wearable PD device (ViWAK: Vicenza Wearable Artificial Kidney) as a possible alternative to automated peritoneal dialysis (APD) or continuous ambulatory peritoneal dialysis (CAPD). Based on sorbent cartridge technology, double-lumen PD catheter, and handheld computer for remote control, it performs a continuous-flow PD [63]. However, the system requires the addition of an injection system for glucose and bicarbonate and sorbent for small-molecule removal. Lee and Roberts proposed an automated wearable artificial kidney (AWAK) using modified SORB® cartridge for dialysate regeneration. This device regenerates a PD solution of

4 L/h, which is 8–12 times the current rate. The cycler weighs 0.55 lb and there are two types of sorbent cartridges according to the usage (1.65 lb for 7-h treatment with a flow rate of 2 L/h and 3.75 lb for 12-h treatment with a flow rate of 4 L/h). However, proteinaceous components and the accumulation of fibrin in the spent peritoneal dialysate requires a minifilter in series with sorbent and the packing density of the sorbent should be optimized considering adsorption capacity and flow resistance of the recycling circuit [64]. Currently, the manufacturer is preparing for clinical trials of AWAK on pediatric patients.

24.6.3 Hemofiltration

Gura et al. modified the WAK as a lightweight wearable continuous ambulatory ultrafiltration device consisting of hemofilter, pulsatile pump, and two micropumps to control anticoagulant and ultrafiltration volume [65]. It was applied to six patients with fluid overload for 6 h using a central venous dual-lumen catheter. Blood flow averaged at 116 mL/min, the ultrafiltration rate ranged from 120 to 288 mL/h with about 150 mmol of sodium removed. Recently, Ronco suggested a vest-type wearable device for ultrafiltration, WAKMAN: an easy-to-wear system compatible with daily activities and life allowing a fully ambulatory treatment [66]. It is equipped with an integrated pump-hemofilter unit, which is extremely compact and lightweight, a unit for the control/monitoring system utilizing wireless communication technology, and a rechargeable battery placed in the back. The maximum flow rate of blood pump and UF pump is 50 mL/min and 300 mL/h, respectively, and disposable blood pressure sensor (−50–300 mmHg) and blood leak detector were integrated in the pump-hemofilter unit. This unit can be easily connected to the control unit by means of a single connector. The jacket also includes two waste bags ($0.75 \times 2 = 1.5$ L) that can be easily replaced in case of long-lasting treatments. The wireless remote control system with 2.4" color touch screen and loudspeaker allows the user to monitor the treatment parameters, start or stop pumps, and manage alarm conditions. However, at this moment, this system is a prototype and requires more modification and evaluation in clinical trials in the future. These devices could have a major impact on the quality of life of fluid-overloaded patients with heart failure.

In current clinical practice, the application of dialysis equipment to pediatric patients weighing below 10 kg is of great concern about side effects of extracorporeal therapy. The cardio-renal, pediatric dialysis emergency machine (CARPEDIEM) project was designed to create the basis for the conception of an RRT equipment specifically dedicated to newborns and small infants with a weight range of 2.5–9.9 kg and with a body surface area from 0.15 to 0.5 m^2 [67]. The miniaturization effort has currently resulted in the development of three extracorporeal circuits with new polysulfone hemofilters with surface areas of 0.075, 0.147, and 0.245 m^2 and priming volumes of 27.2, 33.5, and 41.5 mL. The blood pump flow rate ranges from 5 to 50 mL/min. The maximum total achievable UF and dialysis/hemofiltration rates range from 5 mL/min with the largest hemofilter, down to 2.5 mL/min for the smallest one. This technical setup is considered to be able to meet the target of small solute clearance of 2 L/h/1.73 m^2 and/or 25–35 mL/kg/h in patients weighing <10 kg [68]. The CARPEDIEM project is aimed to achieve five short- and medium-term goals: (i) identify optimal prescriptions and technical requirements for neonatal CRRT; (ii) design a dedicated equipment; (iii) manufacture such a machine and make possible the large-scale production of its disposable material; (iv) validate its use in clinical practice; and (v) develop a multicenter trial to define ideal prescription and application of neonatal CRRT. Currently, CARPEDIEM is CE-marked and ready for clinical trial.

24.6.4 Fractionated Plasma Separation and Adsorption

As a project of the Framework Programme (FP7) for research and technological development, a Dutch company is developing ICT-enabled wearable artificial kidney (iNephron) and personal renal care system with a target dimension of $10 \times 6 \times 4$ cm^3 and weight less than 2 kg. Based on fractionated plasma separation and adsorption (FPSA), a high-flux filter separates blood from plasma, which is purified by nanostructured sorbents and then returned to the blood; so no dialysate fluid is needed.

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24.6.5 Intracorporeal Approaches

As an intracorporeal approach, slow and continuous intracorporeal plasmapheresis (SCIP) was developed for direct intravenous hemofilter filtration, with a special hollow-fiber morphology composed of four layers providing several performance advantages over conventional hollow fibers and showed clinical feasibility for 72 h with an ultrafiltration volume of 3 L in animal experiments [69]. However, it needs to combine with an extracorporeal hemofilter to support congestive heart failure patients.

The concept of implantable artificial kidney (IAK) introduced by Fissel et al. is another paradigm toward a continuously functioning artificial kidney [70]. It supposes the application of MEMS (microelectromechanical system) technology, silicon nanoporous membranes with a highly monodisperse pore size distribution to overcome the limitations of conventional polymer membranes. Humes suggested the concept of renal assist device (RAD) to replace not only filtrative but also metabolic and endocrinologic functions of the kidney [71,72]. It is composed of hemofilter and hollow-fiber cartridges containing human tubular cells derived from donor organs unsuitable for human transplantation and shows promising results in clinical trials in acute kidney failure patients. By integrating with RAD technology to incorporate cellular function, with connection to the iliac vessel and the bladder, IAK is under development.

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24.7 Summary

Blood-filtering technologies have supported functions of vital organs by various combinations of hollow-fiber technology and sorbent technology. Diffusion, convection, and adsorption are the main mechanisms of toxin removal. Vascular access is the most complicated issue in clinical practice, which should be resolved in the near future to improve the patient's quality of life with wearable medical devices. Although the development of new polymer membranes and sorbents improves treatment adequacy and biocompatibility, mimicking metabolic and endocrinologic functions of the kidney remains to be resolved. Dialysate quality monitoring and control is another important issue for extracorporeal RRT. Biofeedback control system takes account of physiological signals from the patient to adjust treatment parameters. However, these extracorporeal blood-purification techniques support rather than replace internal organ functions since they cannot serve such a wide range of physiologic needs. In conclusion, for sustainable development of blood-purification technology, efforts of biomedical engineers to integrate new technologies are essential.

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