

# High-Efficiency and High-Flux Hemodialysis

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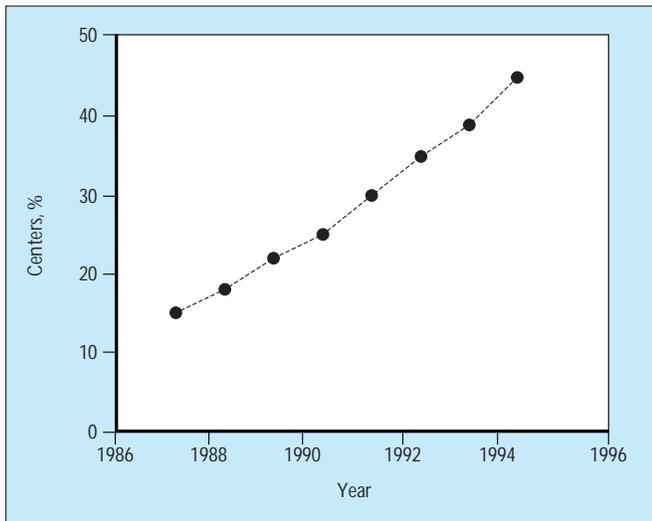
**H**emodialysis remains the major modality of renal replacement therapy in the United States. Since the 1970s the drive for shorter dialysis time with high urea clearance rates has led to the development of high-efficiency hemodialysis. In the 1990s, certain biocompatible features and the desire to remove amyloidogenic  $\beta_2$ -microglobulin has led to the popularity of high-flux dialysis. During the 1990s, the use of high-efficiency and high-flux membranes has steadily increased and use of conventional membrane has declined [1]. In 1994, a survey by the Centers for Disease Control showed that high-flux dialysis was used in 45% and high-efficiency dialysis in 51% of dialysis centers (Fig. 3-1) [1].

Despite the increasing use of these new hemodialysis modalities the clinical risks and benefits of high-performance therapies are not well-defined. In the literature published over the past 10 years the definitions of high-efficiency and high-flux dialysis have been confusing. Currently, treatment quantity is not only defined by time but also by dialyzer characteristics, *ie*, blood and dialysate flow rates. In the past, when the efficiency of dialysis and blood flow rates tended to be low, treatment quantity was satisfactorily defined by time. Today, however, treatment time is not a useful expression of treatment quantity because efficiency per unit time is highly variable.

CHAPTER

3

## Dialyzers



**FIGURE 3-1**

Centers using high-flux dialyzers have increased threefold from 1986 to 1996 because of their ability to remove middle molecules. (From Tokars and coworkers [1]; with permission.)

### DEFINITIONS OF FLUX, PERMEABILITY, AND EFFICIENCY

#### Flux

Measure of ultrafiltration capacity

Low and high flux are based on the ultrafiltration coefficient ( $K_{uf}$ )

Low flux:  $K_{uf} < 10$  mL/h/mm Hg

High flux:  $K_{uf} > 20$  mL/h/mm Hg

#### Permeability

Measure of the clearance of the middle molecular weight molecule (eg,  $\beta_2$ -microglobulin)

General correlation between flux and permeability

Low permeability:  $\beta_2$ -microglobulin clearance  $< 10$  mL/min

High permeability:  $\beta_2$ -microglobulin clearance  $> 20$  mL/min

#### Efficiency

Measure of urea clearance

Low and high efficiency are based on the urea  $K_oA$  value

Low efficiency:  $K_oA < 500$  mL/min

High efficiency:  $K_oA > 600$  mL/min

$K_o$ —mass transfer coefficient; A—surface area.

### HIGH-PERFORMANCE EXTRA-CORPOREAL THERAPIES FOR END-STAGE RENAL DISEASE

High-efficiency hemodialysis  
High-flux hemodialysis  
Hemofiltration, intermittent  
Hemodiafiltration, intermittent

**FIGURE 3-2**

The four high-performance extra-corporeal therapies for end-stage renal disease are listed [2].

**FIGURE 3-3**

Definitions of flux, permeability, and efficiency. The urea value  $K_oA$ , as conventionally defined in hemodialysis, is an estimate of the clearance of urea (a surrogate marker of low molecular weight uremic toxins) under conditions of infinite blood and dialysate flow rates. The following equation is used to calculate this value:

$$K_oA = \frac{Q_b Q_d}{Q_b - Q_d} \ln \left[ \frac{1 - K_d/Q_b}{1 - K_d/Q_d} \right]$$

where  $K_o$  = mass transfer coefficient

A = surface area

$Q_b$  = blood flow rate

$Q_d$  = dialysate flow rate

ln = natural log

$K_d$  = mean of blood and dialysate side urea clearance

As conventionally defined in hemodialysis, flux is the rate of water transfer across the hemodialysis membrane. Dissolved solutes are removed by convection (solvent drag effect).

Permeability is a measure of the clearance rate of molecules of middle molecular weight, sometimes defined using  $\beta_2$ -microglobulin (molecular weight, 11,800 D) as the surrogate [3,4]. Dialyzers that permit  $\beta_2$ -microglobulin clearance of over 20 mL/min under usual clinical flow and ultrafiltration conditions have been defined as high-permeability membrane dialyzers. Because of the general correlation between water flux and the clearance rate of molecules of middle molecular weight, the term *high-flux membrane* has been used commonly to denote *high-permeability membrane*.

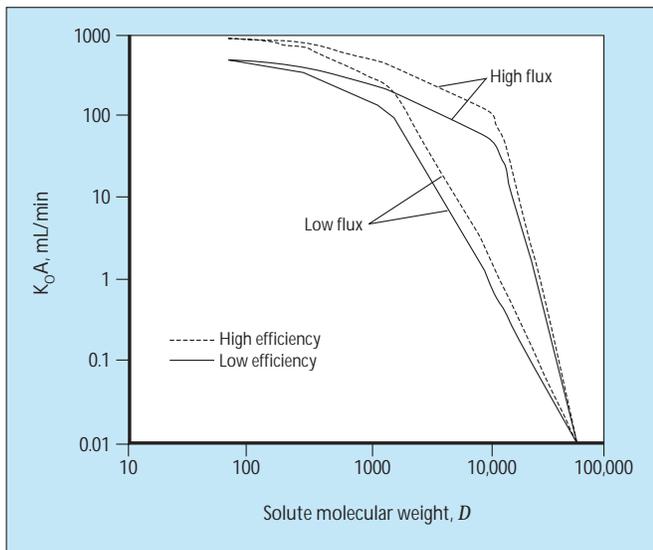


FIGURE 3-4

Theoretic  $K_oA$  profile of high- and low-flux dialyzers and high- and low-efficiency dialyzers. Note that here the definition of  $K_oA$  applies to the product of the mass transfer coefficient and surface area for solutes having a wide range of molecular weights, and is not limited to urea. Note also the logarithmic scales on both axes [3].  $K_o$ —mass transfer coefficient;  $A$ —surface area. (From Cheung and Leypoldt [3]; with permission.)

### CLASSIFICATION OF HIGH-PERFORMANCE DIALYSIS

High-efficiency low-flux hemodialysis  
High-efficiency high-flux hemodialysis  
Low-efficiency high-flux hemodialysis

FIGURE 3-5

Classification of high-performance dialysis. Some authors have defined high-efficiency hemodialysis as treatment in which the urea clearance rate exceeds 210 mL/min. High-flux dialysis, arbitrarily defined as a  $\beta_2$ -microglobulin clearance of over 20 mL/min, is achieved using high-flux membranes [3,4].

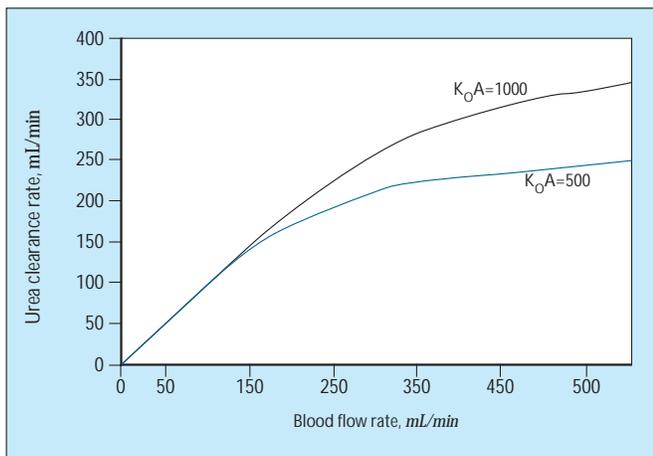


FIGURE 3-6

Comparison of urea clearance rates between low- and high-efficiency hemodialyzers (urea  $K_oA = 500$  and  $1000$  mL/min, respectively). The urea clearance rate increases with the blood flow rate and gradually reaches a plateau for both types of dialyzers. The plateau value of  $K_oA$  is higher for the high-efficiency dialyzer. At low blood flow rates (<200 mL/min), however, the capacity of the high-efficiency dialyzer cannot be exploited and the clearance rate is similar to that of the low-flux dialyzer [3,6].  $K_o$ —mass transfer coefficient;  $A$ —surface area. (From Collins [6]; with permission.)

### CHARACTERISTICS OF HIGH-EFFICIENCY DIALYSIS

Urea clearance rate is usually >210 mL/min  
Urea  $K_oA$  of the dialyzer is usually >600 mL/min  
Ultrafiltration coefficient of the dialyzer ( $K_{uf}$ ) may be high or low  
Clearance of middle molecular weight molecules may be high or low  
Dialysis can be performed using either cellulosic or synthetic membrane dialyzers

$K_o$ —mass transfer coefficient;  $A$ —surface area.

FIGURE 3-7

Characteristics of high-efficiency dialysis. High-efficiency dialysis is arbitrarily defined by a high clearance rate of urea (>210 mL/min). High-efficiency membranes can be made from either cellulosic or synthetic materials. Depending on the membrane material and surface area, the removal of water (as measured by the ultrafiltration coefficient or  $K_{uf}$ ) and molecules of middle molecular weight (as measured by  $\beta_2$ -microglobulin clearance) may be high or low [3,4,6,7].

### DIFFERENCES BETWEEN HIGH- AND LOW-EFFICIENCY HEMODIALYSIS

	High efficiency, mL/min	Low efficiency, mL/min
Dialyzer $K_oA$	$\geq 600$	$< 500$
Blood flow	$\geq 350$	$< 350$
Dialysate flow	$\geq 500$	$< 500$
Bicarbonate dialysate	Necessary	Optimal

$K_o$ —mass transfer coefficient; A—surface area.

**FIGURE 3-8**

Differences between high- and low-efficiency hemodialysis. Conventional hemodialysis refers to low-efficiency low-flux hemodialysis that was the popular modality before the 1980s [3,6].

### TECHNICAL REQUIREMENTS FOR HIGH-EFFICIENCY DIALYSIS

High-efficiency dialyzer  
 Large surface area (A)  
 High mass transfer coefficient ( $K_o$ )  
 Both (high  $K_oA$ )  
 High blood flow ( $\geq 350$  mL/min)  
 High dialysate flow ( $\geq 500$  mL/min)  
 Bicarbonate dialysate

### CONCENTRATION OF DIALYSATE IN HIGH-EFFICIENCY DIALYSIS

Dialysate	Concentration
Sodium	139–145 mEq/L
Potassium	0–4 mEq/L
Acetate	2.5–4.5 mEq/L
Bicarbonate	35–40 mEq/L
Magnesium	1 mEq/L
Calcium	2.5–3.5 mEq/L
Glucose	0–200 mg/dL

### FACTORS INFLUENCING BLOOD FLOW IN HIGH-EFFICIENCY HEMODIALYSIS

Type of access  
 Native arteriovenous fistulae, polytetrafluoroethylene grafts, twin catheter systems:  
 high blood flow rate,  $> 350$  mL/min  
 Permanent catheters, temporary intravenous catheters: low blood flow rate,  $< 350$  mL/min  
 Needle design: size, thickness, and length  
 Blood tubing  
 Pump design

**FIGURE 3-9**

Technical requirements for high-efficiency dialysis. The  $K_oA$  is the theoretic value of the urea clearance rate under conditions of infinite blood and dialysate flow. High blood and dialysate flow rates are necessary to achieve optimal performance of high-efficiency dialyzers. Bicarbonate-containing dialysate is necessary to prevent symptoms associated with acetate intolerance (*ie*, nausea, vomiting, headache, and hypotension), worsening of metabolic acidosis, and cardiac arrhythmia [6,8,9].  $K_o$ —mass transfer coefficient; A—surface area.

**FIGURE 3-10**

Concentration of dialysate in high-efficiency dialysis. Although the concentration of other ions is variable, high bicarbonate concentration, relative to that of acetate, is essential for high-efficiency dialysis in order to minimize the transfer of acetate into the patient.

**FIGURE 3-11**

Factors influencing blood flow in high-efficiency hemodialysis. Arteriovenous fistulae often have blood flow rates of over 1000 mL/min, as measured by current noninvasive devices. Polytetrafluoroethylene grafts and the newly introduced twin catheter systems also are capable of providing the blood flow rates necessary for high-efficiency hemodialysis. In contrast, most other temporary or semipermanent catheters cannot provide sufficient blood flow reliably enough for adequate dialysis delivery in a short time period. Needles, blood tubing diameter, and blood pumps may also contribute to this problem [8,9].

**CAUSES OF HIGH-EFFICIENCY DIALYSIS FAILURE**

Access-related  
 Low blood flow rate  
 High recirculation rate  
 Time-related  
 Patient not adherent to prescribed time  
 Staff not adherent to prescribed time  
 Failure to adjust time for conditions such as alarm, dialysate bypass, and hypotension

**FIGURE 3-12**

Causes of high-efficiency dialysis failure. The maintenance of a high blood flow rate (>350 mL/min) is essential for high-efficiency hemodialysis. Fistula recirculation, regardless of the blood flow rate, compromises achievement of the urea  $Kt/V$  goal. Interruptions during the prescribed short treatment time further compromise the overall delivery of the prescribed  $Kt/V$  [6,7]. K—urea clearance; t—time of therapy; V—volume of distribution.

**BENEFITS OF HIGH-EFFICIENCY DIALYSIS**

Higher clearance of small solutes, such as urea, compared with conventional dialysis without increase in treatment time  
 Better control of chemistry  
 Potentially reduced morbidity  
 Potentially higher patient survival rates

**FIGURE 3-13**

Benefits of high-efficiency dialysis. With improved control of biochemical parameters (such as potassium, hydrogen ions, phosphate, urea, and other nitrogenous compounds) the potential exists for reduced morbidity and mortality without increasing dialysis treatment time [5,7].

**LIMITATIONS OF HIGH-EFFICIENCY DIALYSIS**

Hemodynamic instability  
 Low margin of safety if short treatment time is prescribed  
 Potential vascular access damage  
 Dialysis disequilibrium syndrome

**FIGURE 3-14**

Limitations of high-efficiency dialysis. Removal of a large volume of fluid over a short time period (2–2.5 h) increases the likelihood of hypotension, especially in patients with poor cardiac function or autonomic neuropathy. The loss of a fixed amount of treatment time has a proportionally greater impact during a short treatment time than during a long treatment time. Thus, the margin of safety is narrower if a short treatment time is used in conjunction with high-efficiency dialysis compared with conventional hemodialysis with a longer treatment time. Although unproved, high blood flow rates may predispose patients to vascular access damage. Rapid solute shifts potentially precipitate the dialysis disequilibrium syndrome in those patients with a very high blood urea nitrogen concentration, especially during the first treatment [3,7,9].

**CHARACTERISTICS OF HIGH-FLUX DIALYSIS**

Dialyzer membranes are characterized by a high ultrafiltration coefficient ( $K_{uf} > 20$  mL/h/mm Hg)  
 High clearance of middle molecular weight molecules occurs (eg,  $\beta_2$ -microglobulin)  
 Urea clearance can be high or low, depending on the urea  $K_oA$  of the dialyzer  
 Dialyzers are made of either synthetic or cellulosic membranes  
 High-flux dialysis requires an automated ultrafiltration control system

**FIGURE 3-15**

Characteristics of high-flux dialysis. Because of the high ultrafiltration coefficients of high-flux membranes, high-flux dialysis requires an automated ultrafiltration control system to avoid accidental profound intravascular volume depletion. Because high-flux membranes tend to have larger pores, clearance of middle molecular weight molecules is usually high. Urea clearance rates for high-flux dialyzers are still dependent on urea  $K_oA$  values, which can be either high (ie, high-flux high-efficiency) or low (ie, high-flux low-efficiency) [3,4,10].  $K_o$ —mass transfer coefficient; A—surface area.

### TECHNICAL REQUIREMENTS FOR HIGH-FLUX DIALYSIS

High-flux dialyzer  
Automated ultrafiltration control system

**FIGURE 3-16**

Technical requirements for high-flux dialysis. Because of the potential for reverse filtration (movement of fluid from dialysate to the blood compartment) to occur, use of a pyrogen-free dialysate is preferred but not mandatory. Bicarbonate concentrate used to prepare dialysate is particularly prone to bacterial overgrowth when stored for more than 2 days [5,8].

### POTENTIAL BENEFITS OF HIGH-FLUX DIALYSIS

Delayed onset and risk of dialysis-related amyloidosis because of enhanced  $\beta_2$ -microglobulin clearance [11,12]  
Increased patient survival resulting from higher clearance of middle molecular weight molecules [12,13,15,16]  
Reduced morbidity and hospital admissions [14,16]  
Improved lipid profile [16,17]  
Higher clearance of aluminum [18]  
Improved nutritional status [19,20]  
Reduced risk of infection [16,21]  
Preserved residual renal function [22]

**FIGURE 3-17**

Potential benefits of high-flux dialysis. Data are accumulating that support many potential benefits of high-flux dialysis. Large-scale randomized prospective trials, however, are unavailable.

### LIMITATIONS OF HIGH-FLUX DIALYSIS

Enhanced drug clearance, requiring supplemental dose after dialysis  
High cost of dialyzers

**FIGURE 3-18**

Limitations of high-flux dialysis. The enhanced clearance of drugs depends on the physicochemical characteristics of the specific drug and dialysis membrane. Because of their relative high costs, high-flux dialyzers are usually reused.

### EXAMPLES OF COMMONLY USED DIALYZERS

Dialyzer type	Material	Surface area, m <sup>2</sup>	K <sub>o</sub> A (in vitro), mL/min
Low-flux low-efficiency			
CA90	Cellulose acetate	0.9	410
CF12	Cuprammonium	0.7	418
Low-flux high-efficiency			
CA150	Cellulose acetate	1.5	660
T150	Cuprammonium	1.5	730
High-flux low-efficiency			
F50	Polysulfone	0.9	520
PAN 150P	Polyacrylonitrile	1.0	420
High-flux high-efficiency			
CT190	Cellulose triacetate	1.9	920
F80	Polysulfone	1.8	945

K<sub>o</sub>—mass transfer coefficient; A—surface area.

Adapted from Leypoldt and coworkers [4] and Van Stone [22].

**FIGURE 3-19**

Examples of commonly used dialyzers. “Efficiency” refers to the capacity to remove urea; “flux” refers to the capacity to remove water, and indirectly, the capacity to remove molecules of middle molecular weight. Cellulosic membranes can be either low flux or high flux. Similarly, synthetic membranes can be either low flux or high flux. High-efficiency membranes usually have large surface areas.

## Solute

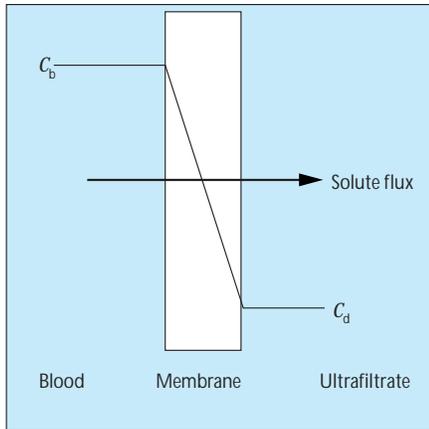


FIGURE 3-20

Solute transport in hemodialysis. The primary mechanism of solute transport in hemodialysis is diffusion, although convective transport is also contributory. Solutes small enough to pass through the dialysis membrane diffuse down a concentration gradient from a higher plasma concentration ( $C_b$ ) to a lower dialysate concentration ( $C_d$ ). The arrow represents the direction of solute transport.

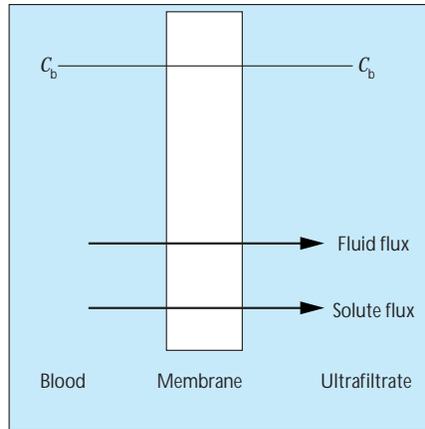


FIGURE 3-21

Solute clearance in hemofiltration. Hemofiltration achieves solute clearance by convection (or the solvent drag effect) through the membrane. In contrast to diffusive hemodialysis, fluid flux is a prerequisite for the removal of solutes during hemofiltration, whereas the concentration gradient is not. For small solutes (eg, urea) that traverse the membrane unimpeded, concentrations in the blood compartment ( $C_b$ ) and ultrafiltrate compartment ( $C_{uf}$ ) are equivalent. For some molecules of middle molecular weight whose movement across the membrane is partially restricted,  $C_{uf}$  is lower than is  $C_b$  (ie, the sieving coefficient, defined as  $C_{uf}/C_b$ , is less than 1.0).

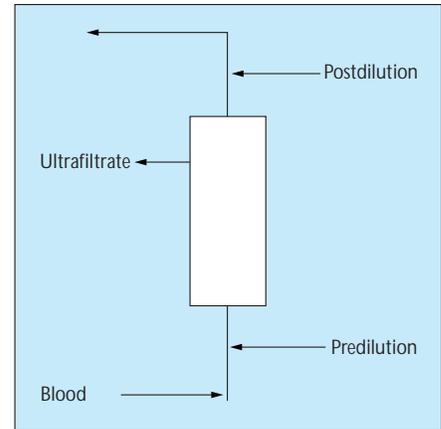


FIGURE 3-22

Fluid replacement in hemofiltration. Because hemofiltration achieves substantial solute clearance by removing large volumes of plasma water (which contains the dissolved solutes), the removed fluid must be replaced. The replacement fluid can be infused into the extracorporeal circuit before the blood enters the filter (predilution, or replacement before expenditure) or after the blood leaves the filter (postdilution). More replacement fluid is required when it is given before filtration rather than after to provide equivalent solute clearance because the plasma in the filter (and therefore the ultrafiltrate) is diluted in the predilution mode.

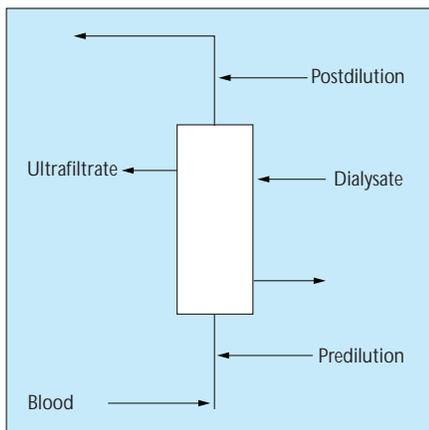
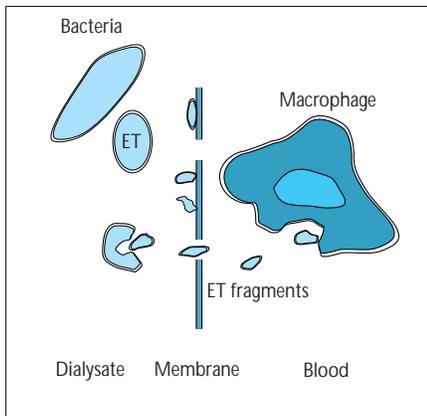


FIGURE 3-23

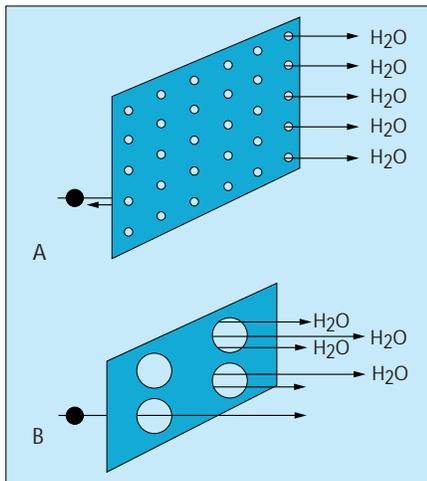
Addition of diffusive transport in hemodiafiltration. In hemodiafiltration, diffusive transport is added to hemofiltration to augment the clearance of solutes (usually small solutes such as urea and potassium). Solute clearance is accomplished by circulating dialysate in the dialysate-ultrafiltrate compartment. Hemodiafiltration is particularly useful in patients who have hypercatabolism with large urea generation.

## Membranes



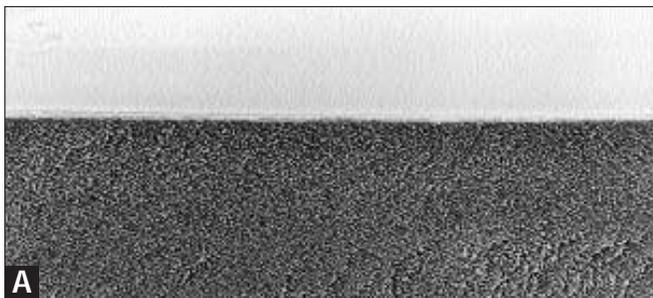
**FIGURE 3-24**

Backfiltration, or reverse filtration, of endotoxins (ET) from dialysate to blood. Reverse filtration of ET is particularly prone to occur when high-flux membranes are used and the dialysate is heavily contaminated with bacteria (>2000 CFU/mL) and may result in pyrogenic reactions. The dialysis membranes are impermeable to intact ET; however, their fragments (some of which still are pyrogenic) may be small enough to traverse the membrane. Although the membrane is impermeable to bacteria and blood cells, a mechanical break in the membrane could result in bacteremia.



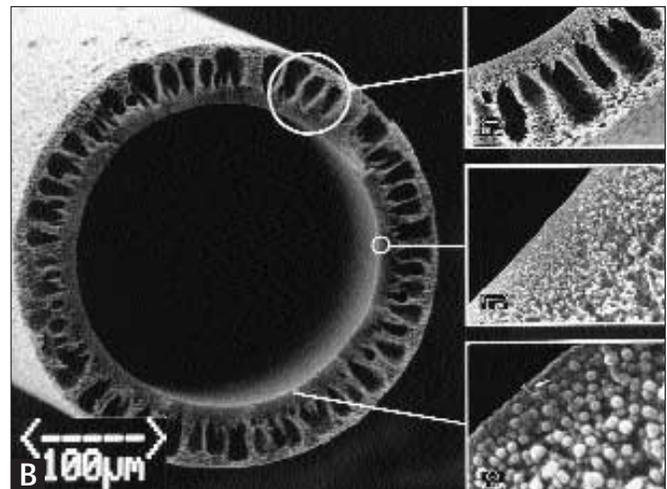
**FIGURE 3-25**

Dialysis membranes with small and large pores. Although a general correlation exists between the (water) flux and the (middle molecular weight molecule) permeability of dialysis membranes, they are not synonymous. **A**, Membrane with numerous small pores that allow high water flux but no  $\beta_2$ -microglobulin transport. **B**, Membrane with a smaller surface area and fewer pores, with the pore size sufficiently large to allow  $\beta_2$ -microglobulin transport. The ultrafiltration coefficient and hence the water flux of the two membranes are equivalent.

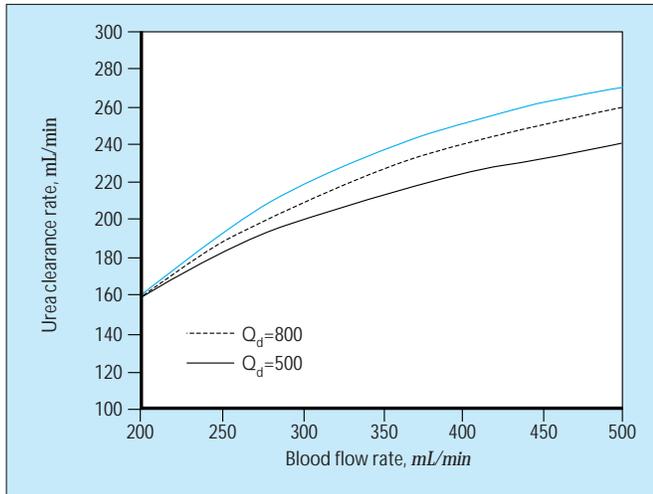


**FIGURE 3-26**

Scanning electron microscopy of a conventional low-flux-membrane hollow fiber (*panel A*) and a synthetic high-flux-membrane hollow fiber (*panel B*). The low-flux membrane consists of a single layer of relatively homogenous material. The high-flux membrane has a three-layer structure, *ie*, finger, sponge, and skin. The skin is a thin semipermeable layer that functions as the selective barrier; it is mechanically supported by the sponge and finger layers. (Magnification: finger,  $\times 14,000$ ; sponge  $\times 17,000$ ; skin  $\times 85,000$ .) (Courtesy of Goehl H, Gambrogroup).



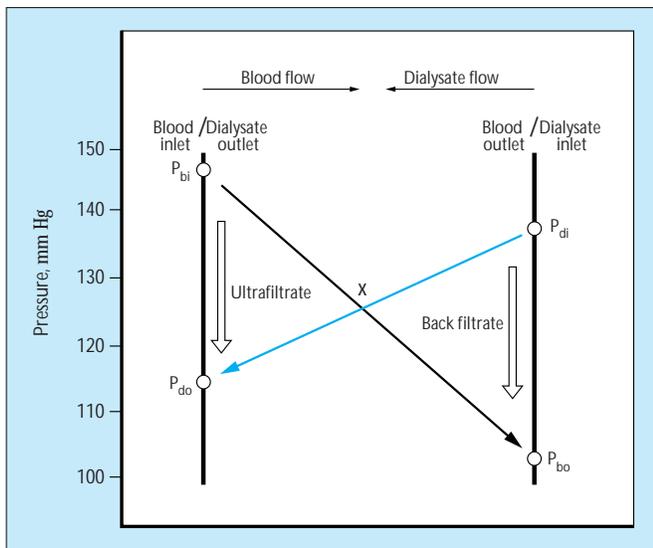
## Dialysate flow rate



**FIGURE 3-27**

Effect of the dialysate flow rate ( $Q_d$ ) on the urea clearance rate by a high-efficiency dialyzer with a urea  $K_oA$  value of 800 mL/min. At low blood flow rates (<200 mL/min), no difference exists in urea clearance rates between the two different  $Q_d$  conditions, because equilibrium in urea concentrations between blood and dialysate is readily achieved. When the blood flow rate is high (>300 mL/min), the higher  $Q_d$  maintains a higher concentration gradient for diffusion of urea, and therefore, the urea clearance rate is higher. Recent studies have shown that the  $K_oA$  value of dialyzers also increases with higher dialysate flow rates [4], presumably because of more uniform distribution of dialysate flow. Therefore, the actual urea clearance rate may increase further (red line).  $K_o$ —mass transfer coefficient;  $A$ —surface area.

## Backfiltration



**FIGURE 3-28**

Pressure inside the blood compartment (*dark colored arrow*) and the dialysate compartment (*light colored arrow*) with a fixed net zero ultrafiltration rate. The pressure gradually decreases in the blood compartment as blood travels from the inlet toward the outlet. Beyond a certain point along the dialyzer length ( $x$ , where the two pressure lines intersect), the pressure in the dialysate compartment exceeds that in the blood compartment, forcing fluid to move from the dialysate to the blood compartment. This movement of fluid in the direction opposite to that of the designed ultrafiltration is called *backfiltration*. Backfiltration may carry with it contaminants (eg, endotoxins) from the dialysate. Increasing the net ultrafiltration rate shifts the pressure intersection point to the right and diminishes backfiltration.

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