

NephroTube Synopsis of Conventional Hemodialysis

First Edition



Mohammed Abdel Gawad

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First Edition

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NephroTube Synopsis of Conventional Hemodialysis, First Edition

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To my wife, daughter, and son—the three most important people in my life.

To my mother and the soul of my father, who I miss.

To the soul of my MD/PhD mentor, Prof Hussein Sheashaa.

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Preface

This first edition of *NephroTube Synopsis of Conventional Hemodialysis* aims to simplify hemodialysis practice. The book is divided into chapters, and each chapter is divided into subtitles that keep the topic flowing stepwise. This edition is updated to the time of its release. *NephroTube Synopsis of Conventional Hemodialysis* covers all what is related to hemodialysis, from the basics to the complications commonly seen in hemodialysis units. One of the main aims of this book is to present the available evidence in a practical clinical manner. Enjoy the book, and feel free to send the author any suggestions for the next editions.

Mohammed Abdel Gawad

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10/April/2024

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Chapter 1

Physiological Principles of Hemodialysis

Hemodialysis is one of the kidney replacement therapies (KRT) which includes also peritoneal dialysis and kidney transplantation. It is a process in which blood is exposed to another solution, called dialysate, through a semipermeable membrane within the dialyzer. A semipermeable membrane is a sheet perforated by pores (Figure 1.1). Solutes and water molecules can pass through semipermeable membranes from one side to the other. The dialyzer can remove solutes of low and medium molecular weight according to the type of the dialyzer flux (dialyzer flux will be discussed in Chapter 5).

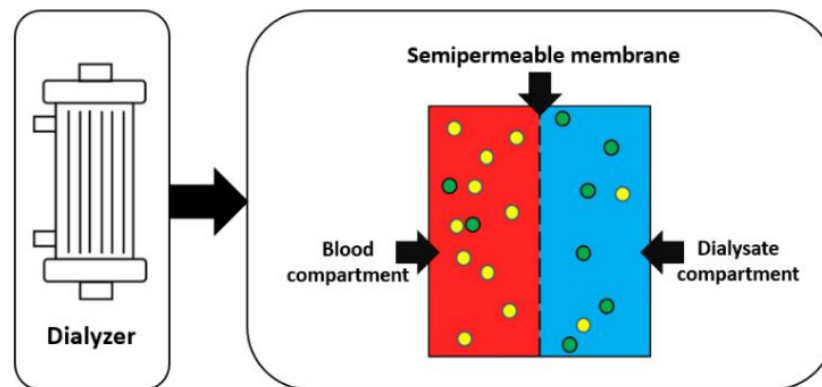


Figure 1.1. Dialyzer: Semipermeable membrane, blood, and dialysate compartments

Physiological principles (mechanisms) of solutes and water transport

Solutes and water can be transported (i.e., pass) through the semipermeable membrane pores by different mechanisms: diffusion, ultrafiltration, and convection.

I. Diffusion

Definition: Diffusion is the movement of solutes through a semipermeable membrane from a region of high concentration to an area of low concentration (i.e., down the concentration gradient) (Figure 1.2).

Diffusion and back diffusion in hemodialysis (Figure 1.3):

- In hemodialysis, solutes move by diffusion from the blood to the dialysate compartment.
- The movement of solutes from the dialysate to the blood compartment according to the concentration gradient is called back-diffusion.

Factors affecting diffusion: The rate of diffusion of a molecule through a semipermeable membrane is inversely proportional to its size.

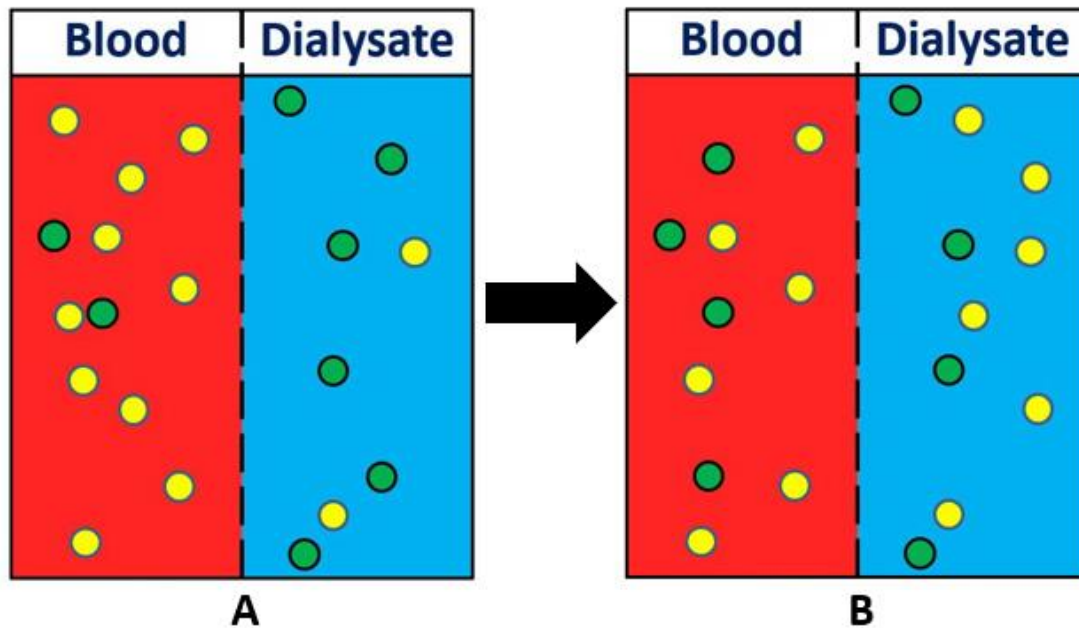


Figure 1.2. Diffusion: In Figure A, yellow particles have a higher concentration in the blood compartment than in the dialysate compartment, whereas green particles have the opposite. Yellow particles move from blood to dialysate, and green particles move in the other direction, as in Figure B.

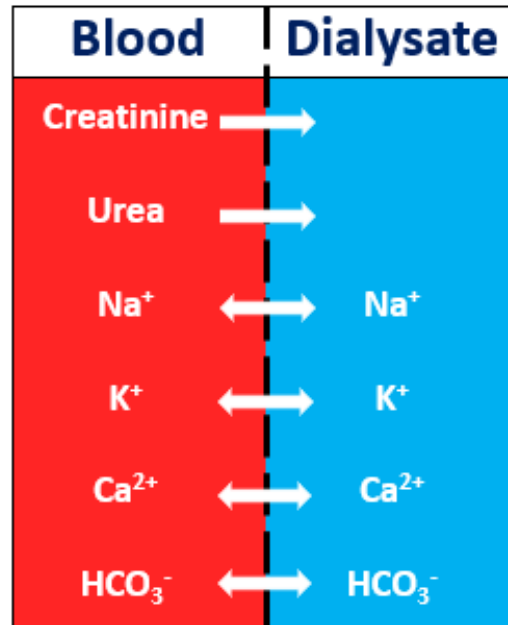


Figure 1.3. Diffusion and back diffusion in hemodialysis: Creatinine and urea concentrations are always higher in the blood than in the dialysate compartment, as the dialysate contains no creatinine or urea, so they will always move from the blood to the dialysate. Na⁺, K⁺, Ca²⁺, and HCO₃⁻ move from the blood to the dialysate or the opposite, according to the concentration difference between the blood and dialysate.

II. Ultrafiltration

Definition: Ultrafiltration (UF) is the procedure by which water moves from the blood compartment to the dialysate compartment through the dialyzer membrane under hydrostatic pressure.

Transmembrane pressure (TMP) (Figure 1.4):

- **Definition:** Transmembrane pressure (TMP) is the difference in pressure between the blood and dialysate compartments within the dialyzer. It is calculated as the pressure in the blood compartment minus the pressure in the dialysate compartment).
- **Blood and dialysate compartment pressure:**
 - **Pressure in the blood compartment:** Hydrostatic pressure in the blood compartment is usually positive.
 - **Pressure in the dialysate compartment:**
 - This is usually negative.
 - This negative pressure is generated by reducing the dialysate inflow rate with a clamp (i.e., inflow resistance) while there is a dialysate effluent pump on the outflow line.
- **Ultrafiltration:** The pressure difference between the blood and dialysate compartments (i.e., TMP) causes water movement (ultrafiltration) from the positive-pressure blood compartment to the negative-pressure dialysate compartment.
- **Transmembrane pressure monitor and related alarm** will be discussed in Chapter 5.

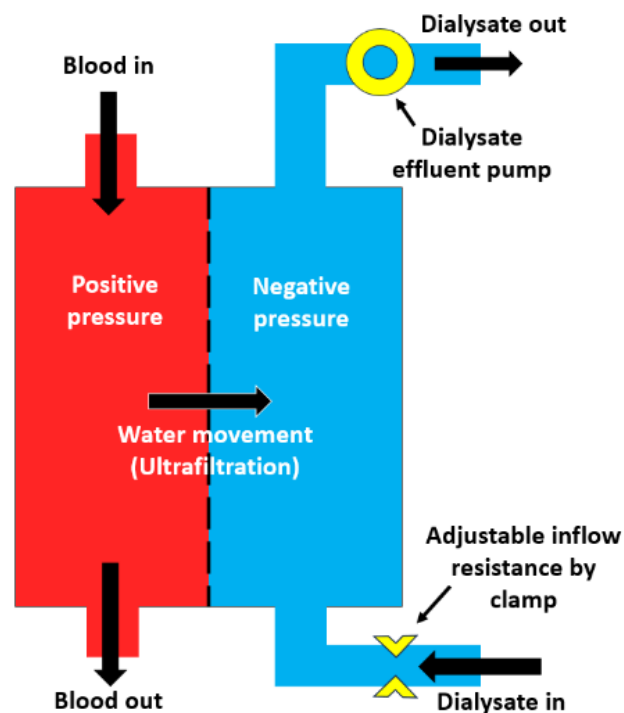


Figure 1.4. Transmembrane pressure (TMP) and ultrafiltration (UF)

III. Convection (solvent drag)

Definition: Convection is a mechanism for solute movement through the semipermeable membrane from the blood to the dialysate compartment. When water (solvent) passes through the semipermeable membrane (by ultrafiltration), it carries (drags) solute molecules to pass through the membrane pores of the dialyzer (Figure 1.5).

Solute concentration in ultrafiltered water: The concentration of the solutes (moved by convection) in ultrafiltered water is close to their concentrations in the blood compartment.

Convection versus diffusion: Compared to diffusion, convection is the most important method for removing medium-sized solutes such as β 2-microglobulin (11,818 Dalton).

Factors affecting convective transport:

1. The convective transport of the dialyzer membrane is dependent on and can be assessed by the “**sieving coefficient of the membrane (SC)**”:
 - **Definition:** SC is the ratio between the solute concentration in the ultrafiltrate (removed only by a convective mechanism) and the average solute concentration in the blood (i.e., the average solute concentration at the blood inlet and outlet sides) (Figure 1.6).
 - **Normal range:** SC values range between 0 and 1. A SC of 1 indicates that the solute is 100% filterable, whereas a SC of 0 indicates that the solute is 0% filterable. An increase in the SC value of a dialyzer near 1 indicates better convection and a higher dialyzer permeability to the solute and vice versa.
 - **Factor affecting the sieving coefficient:** SC is determined by the size of the pores in the membrane. Dialyzers with large pores have high solute permeability and SC.
2. **Solute size:** Convection of solutes is inversely proportional to their size.
3. **Transmembrane pressure (TMP) and ultrafiltration (UF) volume:** With a greater increase in TMP, there will be more UF with more water movement, which will cause more solute movement (i.e., more convection).

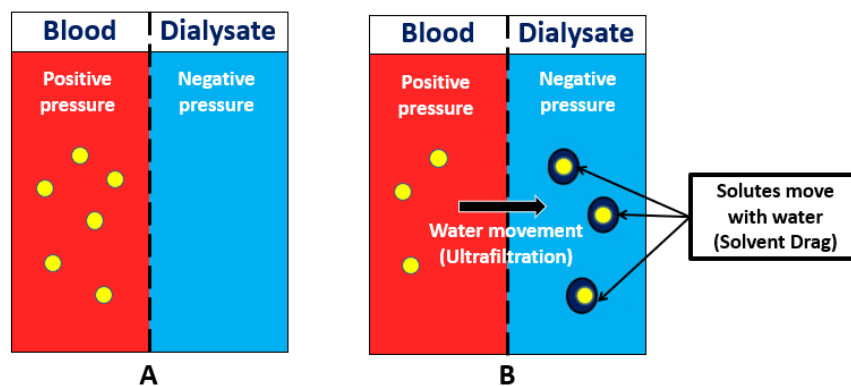


Figure 1.5. Convection (solvent drag): In Figure A, solutes are present in the blood compartment. Figure B shows that these solutes are dragged by water from the blood to the dialysate compartment. The water is moved by ultrafiltration.

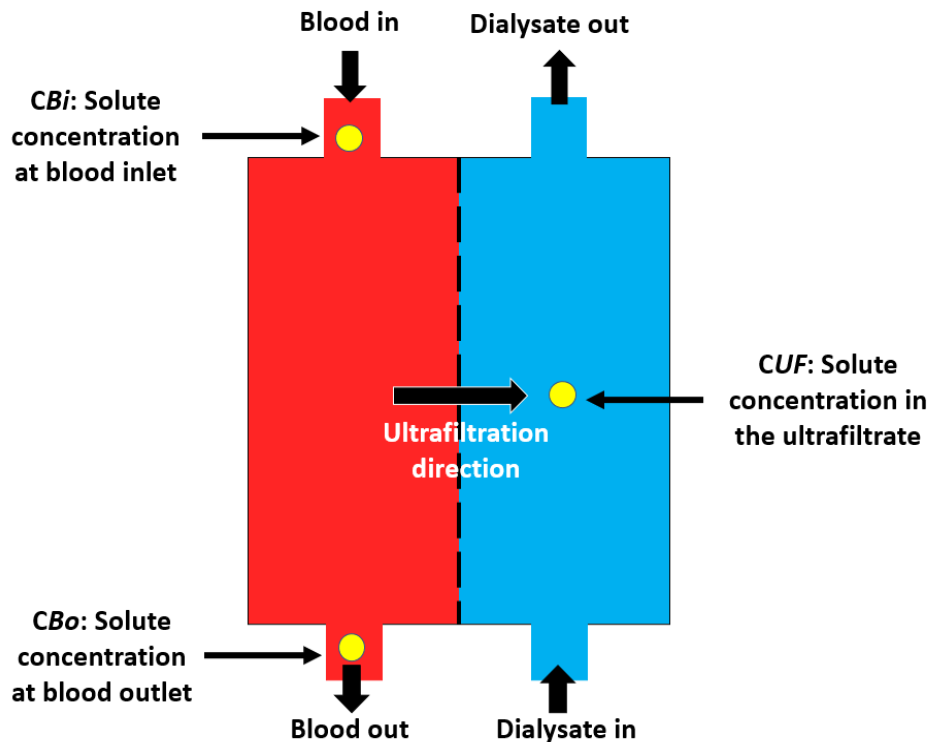


Figure 1.6. Sieving coefficient = $\frac{C_{UF}}{(C_{Bi} + C_{Bo}) / 2}$

Diffusion versus ultrafiltration and convection in hemodialysis

- In hemodialysis, diffusion is the predominant method of solute clearance.
- In hemodialysis, there is a very small volume of ultrafiltration required to remove the excess fluid volume gained between dialysis sessions. This means that the solute clearance by convection is small.

Other different techniques of blood-based dialysis therapies rather than hemodialysis

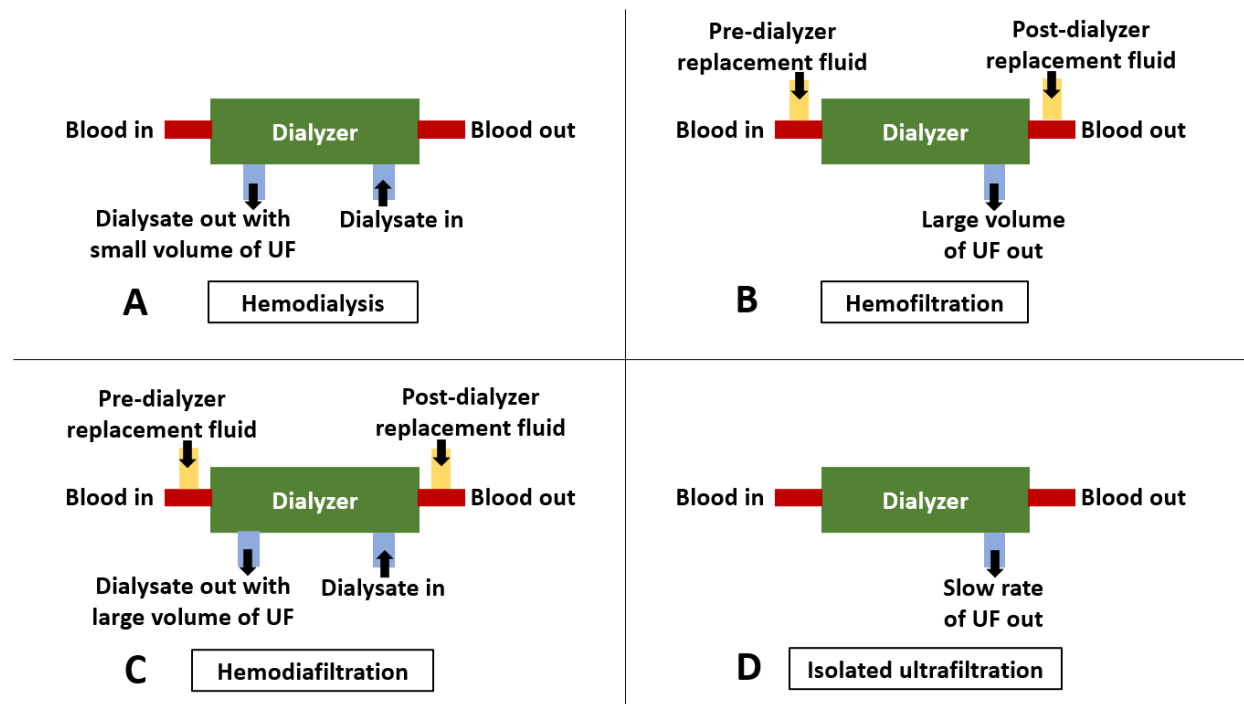
- Based on diffusion, ultrafiltration, and convection, there are different blood-based dialysis techniques, which are:
 - Hemodialysis (HD)
 - Hemofiltration (HF)
 - Hemodiafiltration (HDF)
 - Isolated ultrafiltration
- These techniques are discussed in detail in Table 1.1, summarized in Table 1.2, and explained in Figure 1.7.

Table 1.1. Details of different techniques of blood-based dialysis therapies

Technique	Description
Hemodialysis (HD) (Figure 1.7-A)	<ul style="list-style-type: none"> As mentioned before, diffusion is the predominant method of solute clearance in HD. There is a very small amount of ultrafiltration to remove the excess fluid volume gained between dialysis sessions. This means that the solute clearance by convection is small.
Hemofiltration (HF) (Figure 1.7-B)	<ul style="list-style-type: none"> No dialysate flow is used in HF, so there is no solute removal by diffusion. Ultrafiltration is the predominant method of solute clearance in HF. HF makes a large quantity of ultrafiltration. This large ultrafiltrate is replaced with a plasma-like electrolyte solution (pre-prepared in bags by the manufacturer) to avoid significant hemodynamic, fluid, and electrolyte changes. Replacement fluid can be supplied through a pre-dialyzer or post-dialyzer inlet. In HF, solute removal is achieved only by convection (solvent drag).
Hemodiafiltration (HDF) (Figure 1.7-C)	<ul style="list-style-type: none"> It is a mix between HD and HF. In HDF, a large volume of ultrafiltration (as in HF) is combined with diffusive transport using dialysate (as in HD). HDF makes a large quantity of UF. This large ultrafiltrate is replaced with a plasma-like electrolyte solution to avoid significant hemodynamic, fluid, and electrolyte changes. Replacement fluid can be supplied through a pre-dialyzer or post-dialyzer inlet. Replacement solution in HDF is of one of two types: <ul style="list-style-type: none"> Pre-prepared by the manufacturer in bags. Prepared by the dialysis machine during the session (online HDF “ol-HDF”). In HDF, solute removal is achieved by convection (solvent drag) and diffusion.
Isolated ultrafiltration (Figure 1.7-D)	<ul style="list-style-type: none"> No dialysate flow is used in isolated ultrafiltration, so there is no solute removal by diffusion. Excess volume is removed at a very slow rate by ultrafiltration (without administration of replacement solution). Slow blood and dialysate flow rates are used in this technique to induce a slow UF rate. Convective clearance of solutes is negligible.

Table 1.2. Summary of different techniques of blood-based dialysis therapies

	Hemodialysis (HD)	Hemofiltration (HF)	Hemodiafiltration (HDF)	Isolated ultrafiltration
Diffusion (dialysate flow)	Yes, the main method	No, there is no dialysate flow in this technique	Yes	No, there is no dialysate flow in this technique
Ultrafiltration	Yes, but small volume	Yes, very large volume	Yes, very large volume	Yes, but at a slow rate
Replacement fluid	No	Yes	Yes	No
Convection	Yes, but a small amount	Yes, a very large amount	Yes, a very large amount	Yes, but at a slow rate

**Figure 1.7. Different techniques of blood-based dialysis therapies***UF: ultrafiltration*

Different modalities of blood-based kidney replacement therapy

- Three well-known modalities of blood-based kidney replacement therapy (KRT) are discussed in detail in Table 1.3. This book discusses intermittent (conventional) hemodialysis in detail. Other dialysis modalities are beyond the scope of this study.
- HD, HF, HDF, and isolated ultrafiltration can be performed in the form of IKRT, PIKRT, or CKRT.
- Online-HDF (ol-HDF) is a form of IKRT.

Table 1.3. Blood-based kidney replacement therapy modalities

	Intermittent kidney replacement therapy (IKRT)	Prolonged intermittent Kidney replacement therapy (PIKRT)	Continuous kidney replacement therapy (CKRT)
Rate of solute clearance/ultrafiltration	Rapid solute clearance and ultrafiltration	Slower rates of solute clearance and ultrafiltration than IKRT but more rapid than CKRT	More gradual fluid removal and solute clearance
Duration of one session	3–5 hours	6–12 hours	Optimally 24 hours per day
Frequency	3–4 days/week	4–7 days/week	Continuous
<i>N.B. More differences are present between the three modalities, but this is beyond the scope of this book.</i>			

This book discusses intermittent (conventional) hemodialysis, which is usually performed three times per week for approximately four hours for each treatment.

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Chapter 2

Extracorporeal Blood Circuit

This chapter discusses hemodialysis extracorporeal blood circuit components, sterilization, monitoring, and related alarms.

Extracorporeal blood circuit components

- The extracorporeal blood circuit consists of a blood pump, blood tubing set, and dialyzer (Figure 2.1).
- Blood is obtained from the patient via vascular access to the blood tubing set and then to the dialyzer. After undergoing treatment in the dialyzer, the blood is transported back to the patient through the blood tubing set.
- Different components of the extracorporeal blood circuit are discussed below.

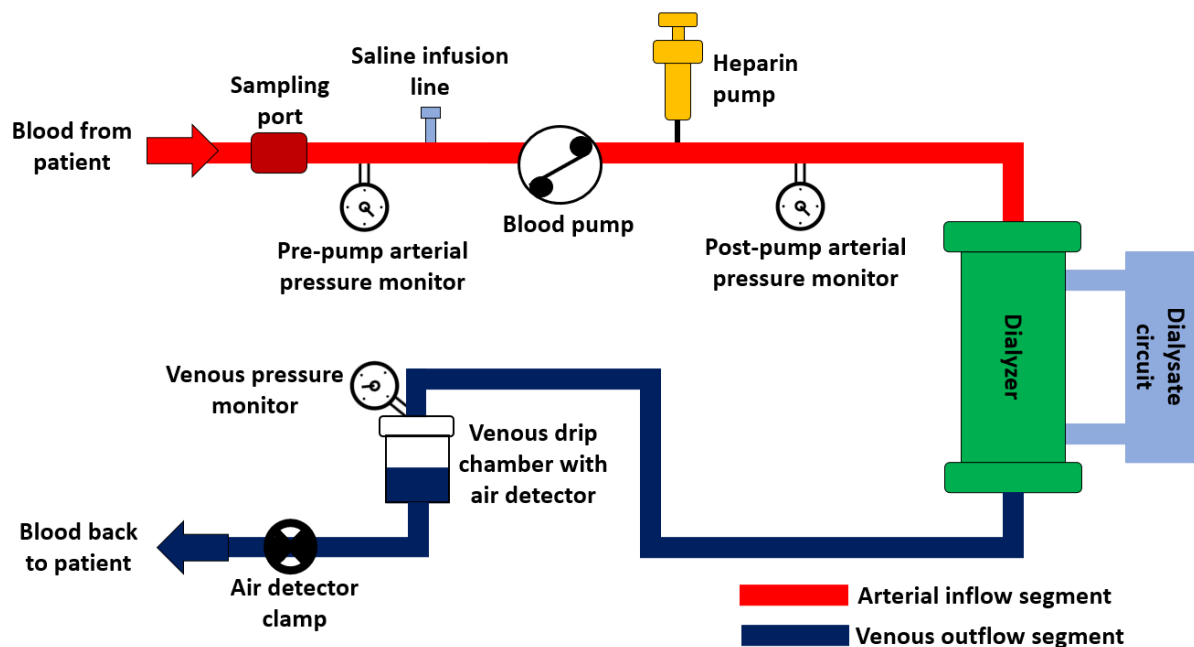


Figure 2.1. Extracorporeal Blood Circuit of Hemodialysis

I. Blood tubing set

The blood tubing set is divided into two segments (Figure 2.1):

1. Arterial segment (*inflow segment*):

- It brings blood from the patient into the dialyzer.
- It is also called the “inflow segment” as it allows blood to flow into the dialyzer.
- It consists of three segments, which are listed in Table 2.1.

Table 2.1. Different segments of blood tubing arterial segment

Segment	Site	Formed of
Pre-pump segment	Between the vascular access of the patient and the blood pump	Polyvinyl chloride
Pump segment	The tubing segment inside the blood pump itself	Silicone rubber (thicker and more rigid material)
Post-pump segment	Between the blood pump and the dialyzer	Polyvinyl chloride

2. Venous segment (outflow segment):

- It returns blood to the patient from the dialyzer.
- It is also called the “outflow segment” as it moves blood out from the dialyzer.
- This segment has a venous drip chamber that receives blood flow. The air ascends to the top of the blood inside this chamber.

II. Blood pump

- **Mechanism of action:** The blood pump is designed as a roller pump. The roller works by completely occluding a small portion of the pump segment of the blood tubing set, then drawing the obstructed segment forward in a milking motion and propelling the blood forward. The stroke volume of the pump is the volume of blood pumped per one roller sweep.
- **Blood pump and tubing set relation:** Over time, the pump segment of the blood tubing set may become flattened due to repeated compression and relaxation caused by the roller. As a result, the "stroke volume" is reduced, which can ultimately lead to a decrease in the effective blood flow rate. A pump segment of a rigid material must be used to minimize this problem.
- **The blood flow rate per minute** is determined by the speed of the blood pump rotation, which typically ranges from 200 to 500 ml/min for adults, with a median rate of 350 ml/min.

III. Dialyzer

Dialyzer is one component of the extracorporeal hemodialysis blood circuit. Dialyzers will be discussed separately in Chapter 5.

Extracorporeal blood circuit priming volume

- **Definition of priming volume:** The volume of blood filling a compartment is called the priming volume.
- **Extracorporeal blood circuit priming volume:**
 - The priming volume of the blood tubing set ranges from 100 to 150 mL, whereas the priming volume of the dialyzer ranges from 60 to 120 mL.
 - The total priming volume of all components of the extracorporeal blood circuit (i.e., blood tubing set and dialyzer) ranges from 160 to 270 mL.

Blood tubing set sterilization

- **Blood tubing set is commonly sterilized using ethylene oxide (EtO)**, which requires a thorough rinse before connecting the tubing set to the patient.
- **EtO may hide during the rinsing in the heparin line:**
 - During rinsing, EtO may migrate back to the heparin line. Suppose the heparin line is not flushed during rinsing before connecting it to the patient. In that case, there is a risk that the heparin pump will administer EtO to the extracorporeal circuit, which could lead to an allergic reaction.
 - It is essential to thoroughly flush the heparin line and other side branches during the rinse cycle.

Extracorporeal blood circuit-related alarms

Two main monitors and alarms are related to the extracorporeal blood circuit, which are the pressure monitors and the air detector.

I. Pressure monitors

- Figure 2.1 and Table 2.2 illustrate and discuss the different pressure monitors in the blood circuit. If the pressure in any monitor falls outside the set range, an alarm will sound, and the blood pump stops.
- The causes of the changes in the different circuit pressure monitors are discussed in Tables 2.3, 2.4, and 2.5.

Table 2.2. Pressure monitors in the extracorporeal blood circuit

Pressure monitor	Site	Accepted pressure
Pre-pump arterial pressure monitor	Present in the pre-pump segment (Figure 2.1).	Negative pressure ranges from -60 to -200mmHg.
Post-pump arterial pressure monitor (inflow pressure monitor)	Present between the blood pump and the dialyzer in the segment following the pump (Figure 2.1).	The pressure in this area is consistently positive (greater than the pressure monitored in the venous pressure monitor), indicating the dialyzer's resistance.
Venous pressure monitor	Present in the venous drip chamber (Figure 2.1).	Positive pressure ranges from +60 to +200mmHg. N.B. The decrease in pressure from the post-pump pressure monitor to the venous pressure monitor reflects the influence of ultrafiltration.

Table 2.3. Causes of changes in pre-pump arterial pressure

Causes of less negative pre-pump arterial pressure	Causes of more negative pre-pump arterial pressure
A. Air leak before the pre-pump pressure monitor: <ol style="list-style-type: none"> 1. Separation between the patient's vascular access and the arterial blood line. 2. Air leaking between the patient's vascular access and the arterial blood line. 3. Air leaking at any point along the arterial blood line before the pre-pump pressure monitor. B. Decreased blood pump speed.	A. Difficulty in delivering blood to the blood pump due to vascular access-related problem: <ol style="list-style-type: none"> 1. Kink, clamp, or occlusion in the arterial blood line before the pre-pump pressure monitor. 2. The arterial fistula needle may suffer from poor positioning, clotting, or infiltration. 3. Stenosis of the arterial anastomosis or clotting of the arterial limb of the vascular access. 4. Venous catheter improper positioning or clotting. B. Blood flow rate-related problem: <ol style="list-style-type: none"> 1. High blood flow rate through a small needle gauge. 2. Blood pump speed greater than the arterial blood supply from the patient's vascular access. 3. Hypotension or poor cardiac status. C. Increased blood viscosity: <ol style="list-style-type: none"> 1. Increased blood viscosity due to ultrafiltration. 2. High hematocrit level.

Table 2.4. Causes of changes in post-pump arterial pressure

Causes of less positive post-pump arterial pressure	Causes of more positive post-pump arterial pressure
A. Difficulty to deliver blood to the post-pump pressure monitor: Kink, clamp, or occlusion in the bloodline between the blood pump and the pressure monitoring device. B. Air leak after the post-pump pressure monitor: Separation in the arterial line between the pressure monitoring device and the dialyzer.	A. Difficulty to deliver blood to the patient because of: <ol style="list-style-type: none"> 1. Arterial line-related problem: <ul style="list-style-type: none"> ▪ Kink, clamp, or occlusion in the arterial line between the pressure monitor and the dialyzer. ▪ Clotting in the arterial line between the pressure monitoring device and the dialyzer 2. Dialyzer-related problem: Clotting of the dialyzer. 3. Venous access-related problem: <ul style="list-style-type: none"> ▪ Venous catheter improper positioning or clotting. ▪ Poor positioning or infiltration of venous fistula needle. ▪ Spasms, vasoconstriction, or stenosis of the venous limb of the vascular access. B. Blood flow-related problem: High blood flow rate through small needle gauge. C. Increased blood viscosity: <ol style="list-style-type: none"> 1. Increased blood viscosity due to ultrafiltration. 2. High hematocrit level.

Table 2.5. Causes of changes in venous pressure

Causes of less positive venous pressure	Causes of more positive venous pressure
<p>A. Difficulty to deliver blood to the venous pressure monitor:</p> <ol style="list-style-type: none"> 1. Kink, clamp, or occlusion in the bloodline between the blood pump and the venous pressure monitoring device. 2. Clotting of the dialyzer <p>B. Air leak after the venous pressure monitor: Separation in the venous line between the pressure monitoring device and the patient.</p> <p>C. Decrease in blood pump speed.</p>	<p>A. Difficulty to deliver blood to the patient because of:</p> <ol style="list-style-type: none"> 1. Venous chamber-related problem: Clotting at the venous drip chamber. 2. Vascular access-related problem: <ul style="list-style-type: none"> ▪ Kink, clamp, or occlusion in the venous bloodline. ▪ Venous catheter improper positioning or clotting. ▪ Poor positioning or infiltration of venous fistula needle. ▪ Spasms, vasoconstriction, or stenosis of the venous limb of the vascular access. ▪ Clotting at the venous needle or the venous limb of the vascular access. <p>B. Blood flow rate-related problem:</p> <ol style="list-style-type: none"> 1. High blood flow rate through a small needle gauge. 2. Increase in blood pump speed. <p>C. Increased blood viscosity:</p> <ol style="list-style-type: none"> 1. Increased blood viscosity due to ultrafiltration. 2. Higher hematocrit.

II. Air Detector

The venous drip chamber has a blood level and air detector (Figure 2.1). If the blood level falls below the detector level due to an excessive amount of air:

- The system will trigger an alarm and automatically stop the blood pump.
- Additionally, the blood tubing segment below the drip chamber contains an air detector clamp (Figure 2.1) that will be clamped to prevent air from entering the patient.

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Chapter 3

Dialysis Water Unit

Dialysis treatments involve the use of dialysate (dialysis solution). During each treatment, patients with end-stage kidney disease (ESKD) are exposed to 120-200 L of dialysate. It is crucial to ensure the purity of the dialysate, as any contaminants in it can enter the patient's bloodstream and cause harm. The dialysate is prepared using purified water and concentrates. In this chapter, we discuss how purified water is formed, and in Chapter 4, we will discuss what is related to concentrates.

Water source for dialysis

- City tap water is used as the water source for dialysis.
- Tap water contains contaminants (chemical, microbiological, etc.) and large quantities of electrolytes that must be cleared before the water reaches the dialysis machine.
- If tap water contaminants or electrolytes reach the patient's blood, they can cause many toxic effects (Table 3.1 and 3.2).

Table 3.1. Toxic effects caused by exposure of hemodialysis patients to water contaminants

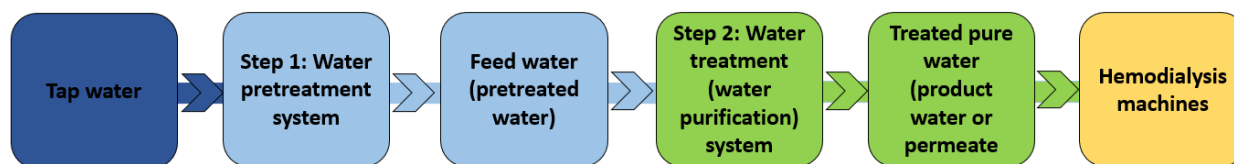
Contaminant	Associated toxic effect
Aluminum	Neurologic deterioration, encephalopathy, bone disease, anemia
Chlorine	Hemolysis, hyperkalemia, shortness of breath, cardiac arrest
Chloramine	Hemolysis, anemia, methemoglobinemia, EPO resistance
Copper	Nausea, hemolysis, chills, death
Zinc	Anemia, cardiovascular events
Fluoride	Bone disease, pruritus, chest pain, nausea, cardiac arrest
Nitrate	Nausea and vomiting, hypotension, methemoglobinemia
Sulfate	Nausea and vomiting, metabolic acidosis
Calcium	Nausea, vomiting, weakness, and hypertension
Magnesium	Nausea, vomiting, muscle weakness
Potassium	Cardiovascular events
Sodium	Hypertension, pulmonary edema, headache, confusion, seizures, coma
Bacteria and endotoxins	Chills, fever, septicemia, shock
Blue-green algae (cyanobacteria)	Microcystins produced by cyanobacteria could be fatal. It could cause acute neurotoxic illness or subacute liver failure.

Table 3.2. Presentation and possible related water contaminant

Presentation	Possible water contaminant
Anemia	Aluminum, chloramines, copper, zinc, nitrates
Bone disease	Aluminum, fluoride
Hemolysis	Chloramines, chlorine, copper, nitrates
Hypertension	Calcium, sodium
Hypotension	Bacteria, endotoxins, nitrates
Muscle weakness	Calcium, magnesium
Nausea and vomiting	Bacteria, calcium, copper, magnesium, nitrates, zinc, endotoxins
Neurological deterioration & encephalopathy	Aluminum
Death	Aluminum, fluoride, chloramine, bacteria, endotoxins

Tap water purification by dialysis water unit

- Major disasters affecting large groups of patients have been attributed to improperly treated water that contains impurities that enter the bloodstream (Table 3.1). Therefore, using a reliable water treatment system and regular water quality assessment are essential.
- Tap water purification occurs in two steps (Figure 3.1):
 - Step 1:** Tap water goes through several steps called the “**water pretreatment system**” to form what is called pretreated water (also called feed water).
 - Step 2:** The formed pretreated water (feed water) from step 1 goes through a “**water treatment (water purification) system**” to prepare what is called treated pure water (also called product water or permeate) that is used by hemodialysis machines to form the final dialysis solution.

**Figure 3.1. Tap water purification occurs in two steps**

Step 1:

Water pretreatment system: Formation of pretreated (feed) water

- The pretreatment system forms what is called pretreated water (also called feed water) that is directed to the water treatment system (step 2) for more purification.
- The pretreatment system consists of several components and steps, shown in Figure 3.2 and explained in Table 3.3.

Table 3.3. Components/steps of water pretreatment system (step 1) and their functions

Component/Step	Function
Optional steps may be present at the beginning	<ul style="list-style-type: none"> • A valve that blends hot and cold water to maintain a consistent temperature in extremely cold environments. • Acid feed pump: pH correction may be necessary in regions with excessively alkaline water by injecting hydrochloric acid. The presence of alkalinity can hinder the ability of carbon beds to eliminate chlorine and chloramine, and it may result in the fouling of reverse osmosis membranes by calcium and magnesium salts (see below).
Sediment filter (multimedia/depth filter)	<ul style="list-style-type: none"> • It eliminates large particles and sediments (5–500 μm) from the water, such as sand, rocks, plant debris, silt, rust, silica, and clay.
Activated carbon filter	<ul style="list-style-type: none"> • Chlorine and chloramine in tap water are adsorbed on the carbon surface and removed from the water. • The carbon filter protects the RO membrane from being damaged by chloramine and chlorine. • Testing for total chlorine should be performed at the beginning of each treatment session before patients initiate treatment to ensure proper functioning of the carbon columns.
Water softener	<ul style="list-style-type: none"> • Tap water is considered hard water as it contains Ca^{++} and Mg^{++}. This hard water needs to be softened by removing Ca^{++} and Mg^{++}. • The water softener contains resin that has been charged with Na^+ ions. As water moves through the resin beads, it undergoes an ion exchange process in which Ca^{++} and Mg^{++} present in the water are exchanged for Na^+. As a result, the water that emerges from the softener contains a reduced amount of Ca^{++} and Mg^{++}. • The routine softener maintenance involves periodically recharging it with brine (i.e., concentrated sodium chloride). • The water softener protects the downstream RO membrane from the harmful effects of calcium and magnesium in the source water, which can be deposited on the RO membrane and result in its rapid fouling. • Carbon filter and water softener are exchanged in some centers.
Pre-reverse osmosis (pre-RO) microfilters (cartridge filters)	<ul style="list-style-type: none"> • One or more gradually decreasing sizes of filters are replaced before RO (1 to 5 μm). They remove smaller particles. • They scavenge particles released from softeners or carbon filters.
Other microfilters (cartridge filters)	<ul style="list-style-type: none"> • These filters can be placed at various points in the water unit. • Their size and distribution depend on the local center's policy. The distribution and sizes shown in Figure 3.2 is an example.

- **Monitoring of water pretreatment system filter pressure:**
 - Installing pre- and post-filter pressure gauges on all filters is essential, and monitoring the pressure difference between the two gauges is crucial.
 - Recording the pressure differences between pre-and postfilter gauges can help to detect any problem within the filter, for example:
 - With use, all filters become progressively obstructed with debris, resulting in increased pressure difference and/or decreased filtrate flow rate.
 - A decrease in pressure difference without a corresponding decrease in flow rate can indicate a breach of filter integrity.
- **Filters should be backwashed daily** when no patients are connected to the hemodialysis machines.

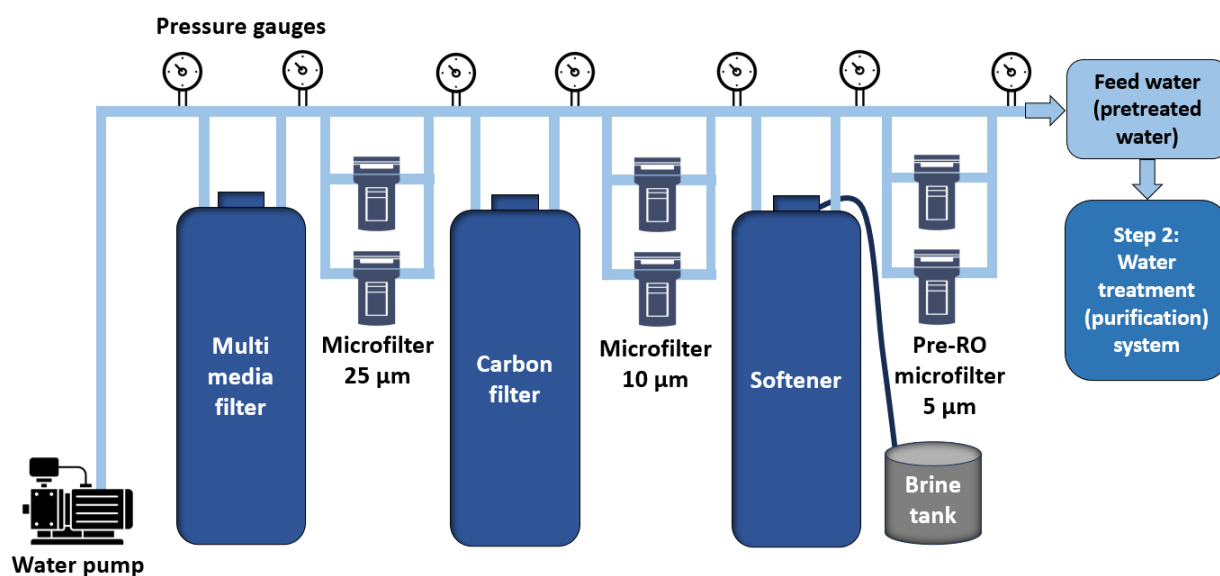


Figure 3.2. Water pretreatment system (step 1)

Step 2:**Water treatment (purification) system: Formation of treated pure water (product water or permeate)**

- The pretreated water (feed water) passes through the final water treatment (purification) system to form treated pure water (product water or permeate) that hemodialysis machines will use to create the final dialysis solution.
- Components of the water treatment system are reverse osmosis (RO) and deionization (DI).
 - The RO system is the one that is mainly used.
 - DI is seldom used as an alternative to RO, but it is occasionally used in conjunction with RO to purify water further after it has been processed through RO.
- Next, we are discussing RO and DI in detail.

I. Reverse osmosis (RO)

Preparation of pure water by RO (product water or permeate):

- RO is formed of semipermeable membranes with very small holes. Water molecules can pass through the small holes, while larger molecules are prevented.
- Hydrostatic pressure forces and squeezes the pretreated water (feed water) across the RO holes, which exclude 90-99% of ionic compounds and >95% of the contaminants (e.g., ions, bacteria, and endotoxin) behind the holes' membrane (as shown in Figure 3.3). That's why it is called reverse osmosis, as it squeezes water molecules in other direction against high osmolar pressure created by excluded retained ions by the membrane.
- The water that passes through the RO membrane holes is called "product water or permeate," while the excluded water with contaminants is called "rejected water."
- After RO separates "product water" from "rejected water":
 - The rejected water is drained out.
 - The product water is allowed to pass to the hemodialysis machine.
- One reverse osmosis (RO) system typically fulfills the microbiological and chemical requirements for hemodialysis. Nevertheless, if the quality of the feed water is inconsistent and does not satisfy the necessary criteria, then a double- or two-stage RO system may be more suitable, especially in the absence of a deionization system following the RO process.

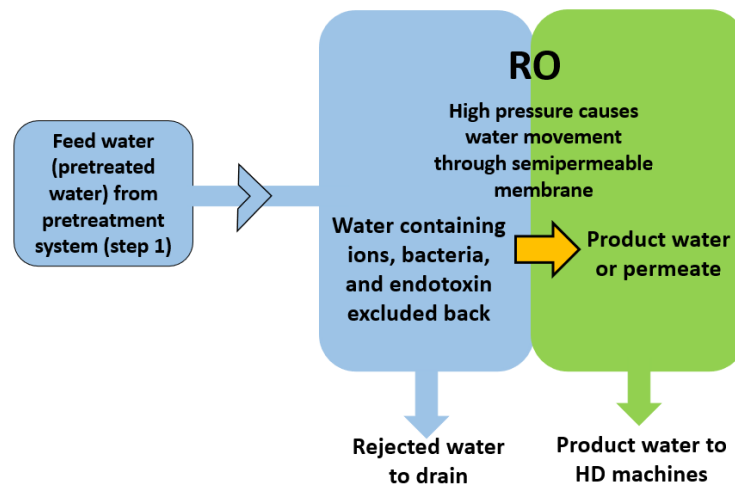


Figure 3.3. Water treatment system (step 2) by reverse osmosis

Monitoring RO membrane efficacy can be done by one of two methods:

1. Percent rejection:

- **It measures** the ability of the membrane to remove ionic contaminants. This is done by measuring conductivity through measuring total dissolved solutes (TDS). TDS unit is expressed as part per million (ppm) or as mg/mL (1 ppm = 1 mg/L).
- **Percent rejection** = $[(\text{feed water TDS} - \text{product water TDS}) \div \text{feed water TDS}] \times 100$.
- **Value:** Percent rejection value below 90% indicates the need to clean the membranes or change the membrane module.

2. Percent recovery:

- **It measures** the membrane fouling, i.e., measures resistivity.
- **Percent recovery** = $[\text{product water flow rate} \div (\text{product water flow rate} + \text{rejected water flow rate})] \times 100$.
- **Value:** Percent recovery value below 90% indicates the need to clean the membranes or change the membrane module.

RO connection with hemodialysis machine has two designs:

1- RO indirect feed system (product/permeate storage tank) (Figure 3.4):

- In this system, product water from RO is stored in a stainless steel or polyethylene storage tank to be used later by hemodialysis machines:
 - The tank must be of the minimum required size.
 - This tank is at risk for bacterial contamination and bacterial biofilm formation. It is important to be frequently disinfected.
- In indirect feed with a product/permeate storage tank, additional steps must be added after the tank to maintain water purity. One of the following can be used:
 - Ultrafilter (bacteria- and endotoxin-retentive ultrafilter) of 0.001 to 0.05 μm . It removes both bacteria and endotoxin.
 - Ultraviolet (UV) disinfection:
 - It destroys bacterial cell walls.
 - A negative side effect of UV irradiation is that it can increase the degree of microbial contamination by causing the release of fragments from the bacteria cell walls (e.g., endotoxins). For this reason, a further purification step must be added after the UV irradiator:
 - a. Following UV disinfection, a bacteria- and endotoxin-retentive ultrafilter (0.001 to 0.05 μm) must be installed to remove both bacteria and endotoxin.
 - b. Some centers use submicron filter instead of the ultrafilter. The submicron filter is usually of 0.22 μm pore size membranes. Some bacterial species of minute size can cross 0.22 μm pores and will be removed only with 0.1 μm pore size membranes. It is important to mention that the submicron filter reduces only the level of bacteria in the water but does not reduce the endotoxin level.
- The product water from the storage tank is permitted to flow through the piping system of the dialysis unit:
 - The hemodialysis machines use part of pure water to form the final dialysate.
 - The part of water not used by the machines:
 - This part returns to the storage tank through the loop-designed piping system and recirculates.
 - Some units add submicron filters on the pipes returning the non-used pure water to the storage tank.

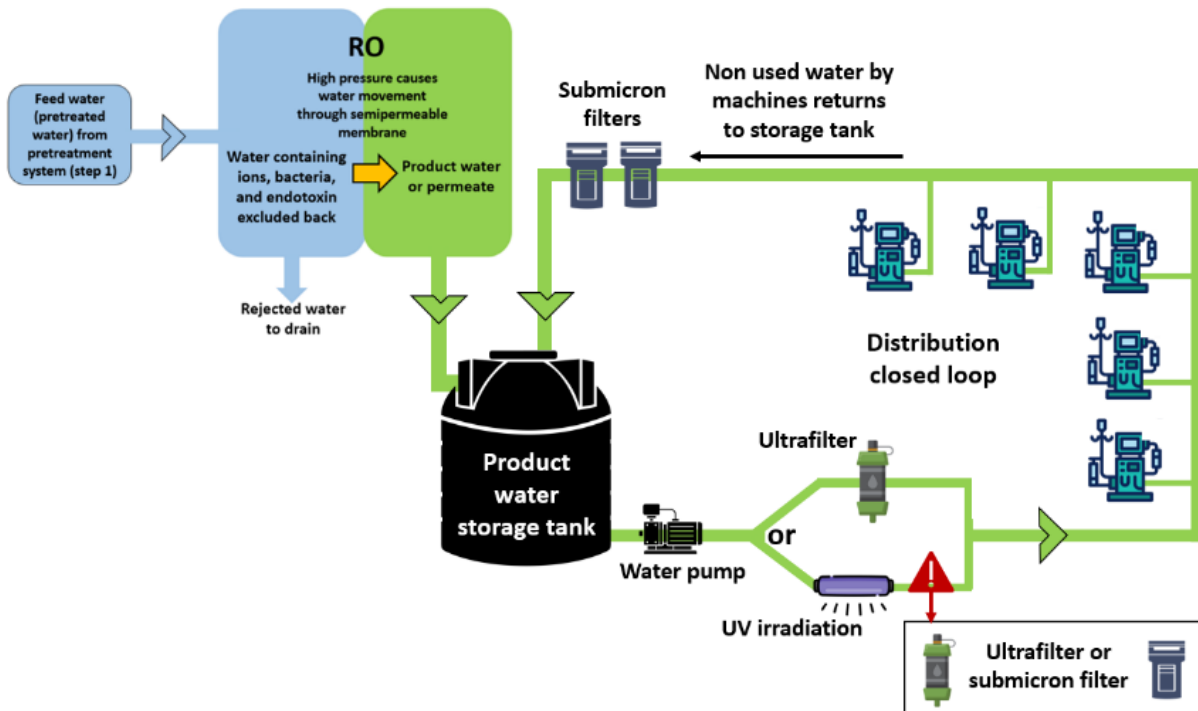


Figure 3.4. Water treatment system (step 2) by reverse osmosis: Indirect feed system

2- RO direct feed system:

- In this system, RO is directly connected to the dialysis unit piping system and feeds product water to the hemodialysis machines without using a product/permeate storage tank.
- RO usually provides pure water of sufficient quality that doesn't need any further purification and can be used by hemodialysis machines to prepare dialysate (Figure 3.5). However, some centers add optional purification steps downstream to RO for more purification of product water before it reaches the hemodialysis machine (Figure 3.6):
 - Ultrafilter (bacteria- and endotoxin-retentive ultrafilter): 0.001 to 0.05 μm . It removes both bacteria and endotoxin.
 - Ultraviolet (UV) disinfection (check the abovementioned precautions for UV disinfection).
- The product water from the storage tank is permitted to flow through the piping system of the dialysis unit:
 - The hemodialysis machines use part of pure water to form the final dialysate.
 - The part of water not used by the machines:
 - This part returns to the storage tank through the loop-designed piping system and recirculates.
 - Some units add submicron filters on the pipes returning the non-used pure water to the storage tank.

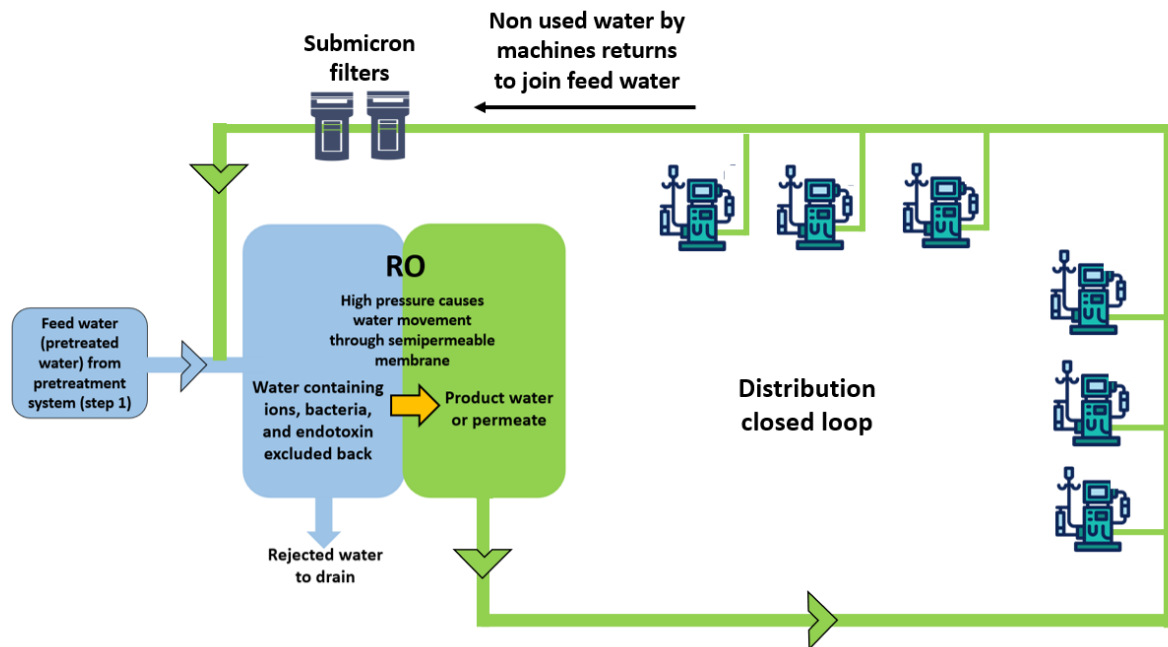


Figure 3.5. Water treatment system (step 2) by reverse osmosis: Direct feed system

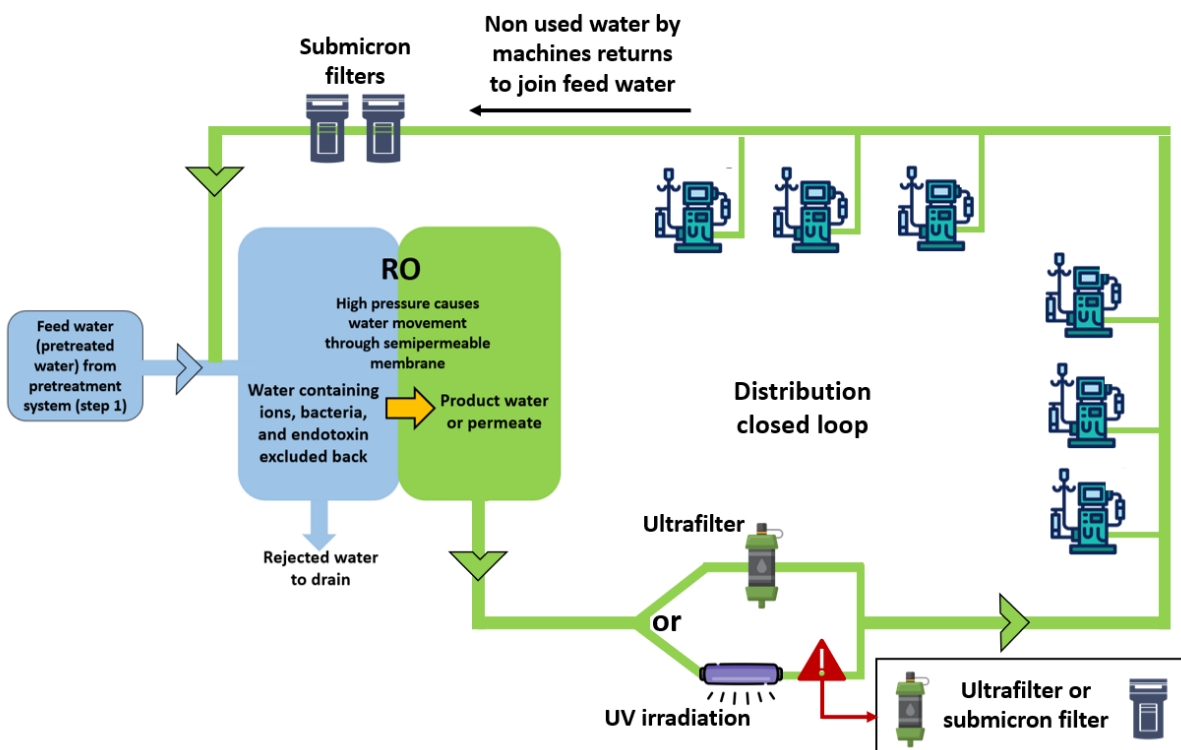


Figure 3.6. Water treatment system (step 2) by reverse osmosis: Direct feed system (with extra optional purification steps)

II. Deionization (DI)

Relation to RO: As mentioned before, DI is seldom used as an alternative to RO, but it is more frequently used in combination with RO to purify water further after it has been processed through RO.

Preparation of pure water by DI (Figure 3.7):

- The process of deionization (DI) involves replacing inorganic ions in the feed water with H^+ and OH^- ions, resulting in the removal of inorganic ions.
- DI system is formed of a mixed bed that consists of resins coated with H^+ (cation) and other resins coated with OH^- (anion):
 - Water passes first through the cation exchange resin, where the dissolved cations (Na^+ , Ca^{++} , Mg^{++} , etc.) are exchanged for H^+ .
 - Water then passes through the anion exchange resins where anions (Cl^- , Fl^- , NO_3^- , etc.) are exchanged with OH^- .

Post DI obligatory purification step (Figure 3.7):

- Mixed-bed deionizers effectively remove ionic contaminants but cannot remove uncharged contaminants, bacteria, or endotoxins. Furthermore, the resins in these systems can promote bacterial growth, which can negatively impact the microbiological quality of the water and increase the need for bacterial control measures.
- Therefore, the installation of DI should be accompanied by an ultrafilter (bacteria- and endotoxin-retentive ultrafilter of 0.001 to 0.05 μm) to safeguard the water distribution system from contamination.

Monitoring DI efficacy: The resistivity of the water coming out of DI is monitored. The acceptable level of pure water resistivity from the DI system is $\geq 1 M\Omega/cm$.

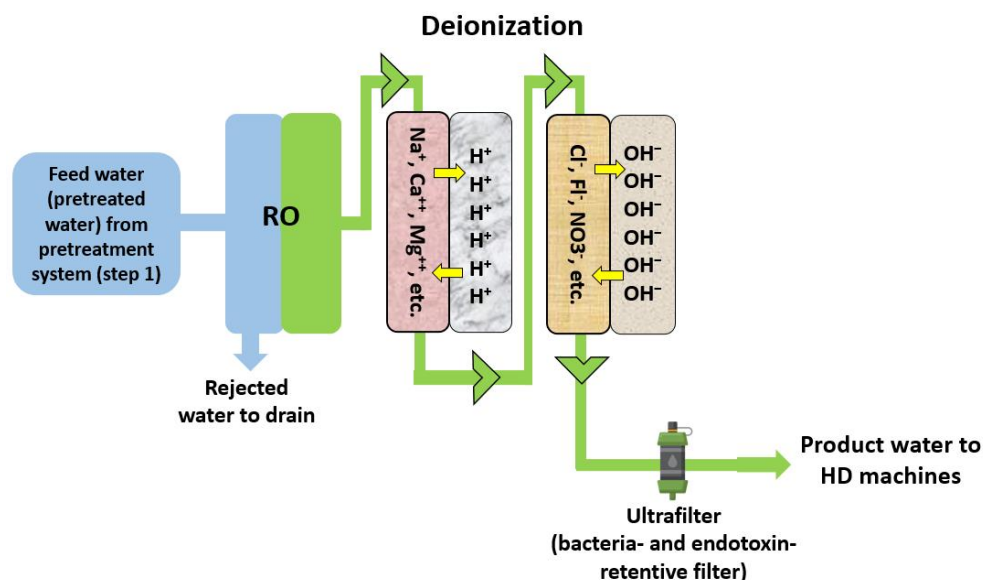


Figure 3.7. Water treatment system (step 2) by deionization

DI connection with hemodialysis machines:

- **Direct feed system (Figure 3.8):** The pure water (product water or permeate) produced after the ultrafilter is permitted to flow through the piping system of the dialysis unit:
 - The hemodialysis machines use part of pure water to form the final dialysis solution.
 - The part of the pure water not used by the machines returns to join the feed water again through the loop-designed piping system and then recirculates. Some units add submicron filters on the pipes that return the non-used pure water to join the feed water.
- **Indirect feed system (Figure 3.9):** If the storage tank is placed after DI, precautions must be taken, as mentioned above, with the RO indirect feed system.

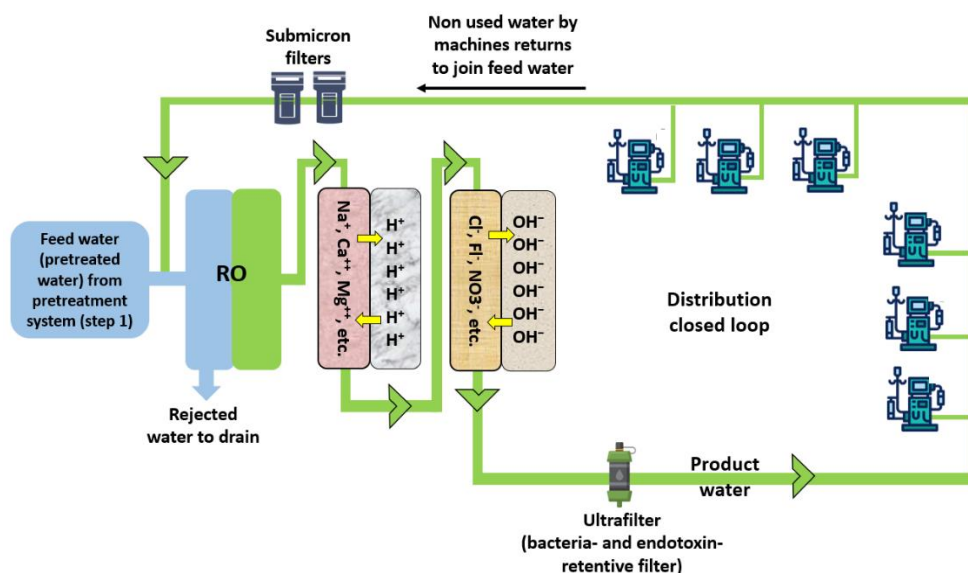


Figure 3.8. Water treatment system (step 2) by deionization: Direct feed system

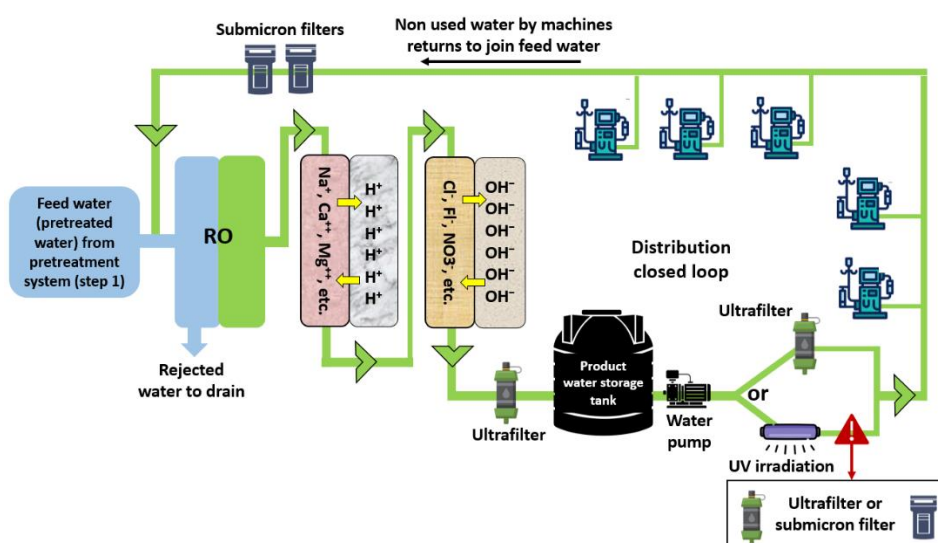


Figure 3.9. Water treatment system (step 2) by deionization: Indirect feed system

Water piping (distribution) system

- **Importance of an ideal water piping system design:** The water distribution system must be carefully designed and constructed to:
 - Avoid chemical contaminants.
 - Prevent stagnation and microbial contamination.
- **Configuration:**
 - The water piping system should be designed as a loop circuit without any branches, dead ends, or areas of stagnation.
 - If valves are required in the water distribution system, they should be placed on lateral arms whose length does not exceed the diameter of the principal circuit.
 - Continuous water circulation is necessary to prevent water stagnation, bacterial growth, and biofilm formation.
- **Pipes:**
 - Pipes should have a smooth and polished inner surface.
 - Inert materials for water piping (e.g., inox or synthetic polymers) are used to avoid chemical contaminants.
 - Stainless steel that can be welded without crack formation is ideal, but its high cost has precluded its routine use.
 - High-grade synthetic polymer materials, such as PVC, PEX, PVDF, and PTFE, are commonly used because of their lower cost and ease of handling.

Water storage tank and piping system disinfection

- The water storage tank and piping distribution system must be regularly disinfected to prevent bacterial colony growth and minimize biofilm formation. The presence of biofilm, once established, can be challenging to remove and may require the replacement of the piping system.
- **Methods of disinfection:**
 - Chemical germicides: Generally performed at least monthly.
 - Hot water or ozone: These systems can provide more frequent disinfection.

Standards of treated pure water (product water or permeate)

- The Association for the Advancement of Medical Instrumentation (AAMI) has recommended standards (ANSI/AAMI RD62:2006) to establish the maximum acceptable levels of chemicals known to be toxic to hemodialysis patients, as well as bacteria and their endotoxins.
- Table 3.4 shows the standards related to bacteria levels and their toxins.
- Refer to ANSI/AAMI RD62:2006 for the maximum allowed levels of chemicals
- Ensuring the water used in dialysis meets the required purity levels is crucial.

Table 3.4. AAMI standards for purity of the treated pure water

Contaminants	Treated Pure Water Standard	Treated Pure Water Action Level
Colony-forming units of bacteria	< 100 CFU/mL	≥ 50 CFU/mL
Endotoxin units	< 0.25 EU/mL	≥0.125 EU/mL

Frequency of water unit quality monitoring

- The frequency of testing may vary according to the requirements of local or regional healthcare authorities.
- When there is a suspicion of contamination, increasing the frequency of monitoring is essential.
- Suggested monitoring frequencies and accepted levels for some tests are shown in Table 3.5.

Table 3.5. Monitoring frequencies and accepted levels for some tests to assess water unit quality

Test	What does it assess?	Frequency of testing	Accepted level
Chlorine	Carbon filter function	Testing should be performed at the beginning of each treatment session before patients initiate treatment	<0.5mg/L
Other chemical contaminants rather than chloramine	Water pretreatment and treatment systems	Every 1 to 3 months	Refer to ANSI/AAMI RD62:2006 for the maximum allowed levels of chemicals
Total dissolved solutes (TDS)	Reverse osmosis rejected percentage	Daily	The rejected percentage must be ≥ 90 %
Microbiological testing to assess total viable bacteria (colony forming units) and endotoxin content	Water contamination	Every 1 to 3 months	Check Table 3.4

Green Dialysis (Green nephrology)

- The deterioration of the global natural environment is a widely acknowledged phenomenon.
- Dialysis appears to have a detrimental environmental impact, indicating the critical role the nephrology community must assume in promoting eco-friendly healthcare practices.
- Kidney care facilities must adopt sustainable practices and reduce resource consumption and waste generation. Examples of opportunities to reduce dialysis environmental impact:
 - Repurposing of rejected water of RO: this water can be reused for:
 - Recycling back to RO to be reused by the hemodialysis unit (this may shorten the RO membrane life).
 - Toilet cleaning.
 - Gardening purposes.
 - Decrease water consumption: Dialysate regeneration and decrease of dialysate flow.
 - Utilize renewable energy.
 - Less than one-third of the non-infectious garbage was possibly recyclable.
 - Use recycled paper and monitor paper usage.

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Chapter 4

Dialysate Circuit

This chapter discusses dialysate (dialysis solution) formation, dialysate monitoring, and related alarms.

Dialysate circuit components

The two main components of the dialysate circuit are the concentrates (concentrated dialysate) and the dialysate delivery system. Both are discussed in detail below.

Concentrates (concentrated dialysate)

- It is the first component of the dialysate circuit.
- In order to decrease bulk and transportation expenses, dialysate is produced in two highly concentrated forms.
- The two concentrated dialysates are discussed in Table 4.1.

Table 4.1. Concentrated dialysates

Concentrated solution name	Formed of	Available forms
Acid concentrate (also called A-concentrate)	<ul style="list-style-type: none"> • Acidifying agent (see Table 4.2). • Also contains sodium, chloride, calcium, magnesium, potassium, \pm dextrose 	<ul style="list-style-type: none"> • It is available in both liquid and dry form. • The dry concentrate should be dissolved in an appropriate volume of treated water before connecting it to the machine.
Bicarbonate concentrate (also called B-concentrate)	Sodium bicarbonate (NaHCO_3) as a buffer is the main buffer used in hemodialysis (see below about other buffers).	Bicarbonate is available in powder form (see below to know how this powder is used).
<ul style="list-style-type: none"> • Why is concentrated NaHCO_3 (B-concentrate) separated from A-concentrate? This is because if concentrated NaHCO_3 is mixed in the same canister with concentrated Ca or Mg in A-concentrate before being used by the machine, this will lead to the precipitation of CaCO_3 and MgCO_3. • These two concentrated forms are mixed later by the dialysate delivery system (see below) with treated pure water (coming from the water unit) to form the final diluted dialysate (that will pass through the dialyzer). 		

- **Bicarbonate powder methods of use:**
 - The powder is usually pre-filled by the manufacturer in a cartridge and then attached to the machine.
 - At some centers, the powder is manually mixed with an appropriate quantity of pure water before it is connected to the machine.
 - In some other centers, bicarbonate concentrate is centrally prepared by mixing the powder with water in central containers, then distributed to individual dialysis machines. Frequent disinfection of these containers is crucial as bicarbonate concentrates are highly susceptible to bacterial contamination.
 - N.B. To avoid bacterial contamination, any bicarbonate solution that has been prepared mustn't be left unused for a prolonged time (more than 4 hours), as bacteria thrive in this type of environment.
- **Buffers rather than bicarbonate:**
 - **Lactate-containing dialysate:** The NxStage machine, used by some home dialysis patients, uses lactate-rich dialysate instead of the conventional bicarbonate solution.
 - **Acetate-containing dialysate:**
 - It was previously used instead of bicarbonate.
 - The liver and skeletal muscles metabolize acetate to form bicarbonate.
 - It is not recommended to use acetate solution because of its side effects, as it is a vasodilator that leads to headache and hypotension.
- **Why is acid added to the A-concentrate (Table 4.2)?**
 - The dialysis machine will mix A-concentrate and B-concentrate through the dialysis delivery system (see below), so if concentrated NaHCO_3 is mixed with concentrated Ca or Mg (present in A-concentrate), this will lead to the precipitation of CaCO_3 and MgCO_3 .
 - This precipitation is prevented by the acid already present in the A-concentrate.
 - When the machine mixes A-concentrate with B-concentrate, the hydrogen ion from the acid in A-concentrate reacts with bicarbonate (B-concentrate) to form carbonic acid ($\text{HCO}_3^- + \text{H}^+ \rightarrow \text{H}_2\text{CO}_3$).
 - Carbonic acid maintains the pH of the final, diluted pure dialysate at a level of approximately 7.0–7.4, and this prevents precipitation formation.

Table 4.2. Types of acidifying agents in A-concentrate

Type	Acidifying agent	Advantages	Disadvantages
Acid concentrate (A-concentrate) containing acetate	Acetic acid	-----	<ul style="list-style-type: none"> • Vasodilatation and hypotension • Activation of inflammatory proteins
Acid concentrate (A-concentrate) containing citrate	Citric acid	Reduce clotting	<ul style="list-style-type: none"> • Hypocalcemia • Hypomagnesemia

Dialysate delivery system

The dialysate delivery system mixes (proportionate) A- and B-concentrated dialysate with treated pure water (coming from the water unit) to form the final diluted dialysate that will pass through the dialyzer.

Types of dialysate delivery system

There are two main types of dialysate delivery systems (Figure 4.1):

- I. Single-patient dialysate delivery system (SPDDS).
- II. Central dialysate delivery system (CDDS).

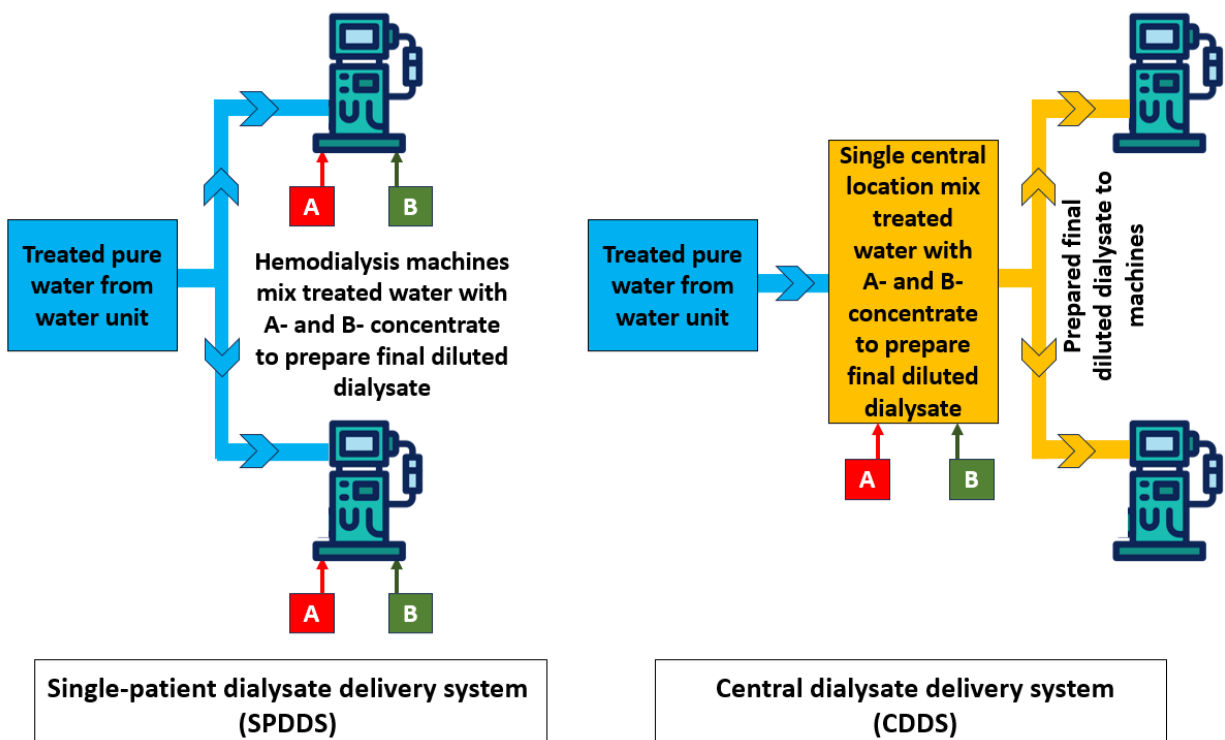


Figure 4.1. Dialysate Delivery Systems

I. Single-patient dialysate delivery system (SPDDS) (Figure 4.1):

- In this system, the treated pure water (coming from the water unit) is sent to each dialysis machine.
- Each dialysis machine mixes pure water with A- and B-concentrated dialysate to prepare the final diluted dialysate.
- So, in SPDDS, the final diluted dialysate is formed by the dialysate delivery system of the dialysis machine itself.
- SPDDS is used worldwide rather than in Japan.
- We will discuss SPDDS components later in detail.

II. Central dialysate delivery system (CDDS) (Figure 4.1):

- In this system, the treated pure water (from the water unit) is sent to a single central location, which mixes water with A- and B-concentrated dialysate to prepare the final diluted dialysate. Then, the prepared final diluted dialysate is sent to each dialysis machine.
- So, in CDDS, the final diluted dialysate is not formed by the dialysis machine but is prepared in the central area and then sent to the dialysis machine.
- CDDS was developed as a unique system of dialysis in Japan. It is used in very few other areas of the world.
- The main advantage of CDDS is cost saving.
- Disadvantages of CDDS include:
 - No availability for individualization of dialysate composition for certain patients.
 - Any central machine dysfunction will affect all patients.

Single-patient dialysate delivery system (SPDDS) components

SPDDS (Figure 4.1) can prepare final diluted “pure” dialysate or final diluted “ultrapure” dialysate.

I. Preparation of “pure” dialysate by SPDDS (Figure 4.2):

“Pure” dialysate is formed by mixing the pure water from the water unit with a proportionate volume of A- and B-concentrates. SPDDS, which forms “pure” dialysate, is made up of three main components: the water preparation system, the proportioning system, and the volumetric control system. These components are discussed below.

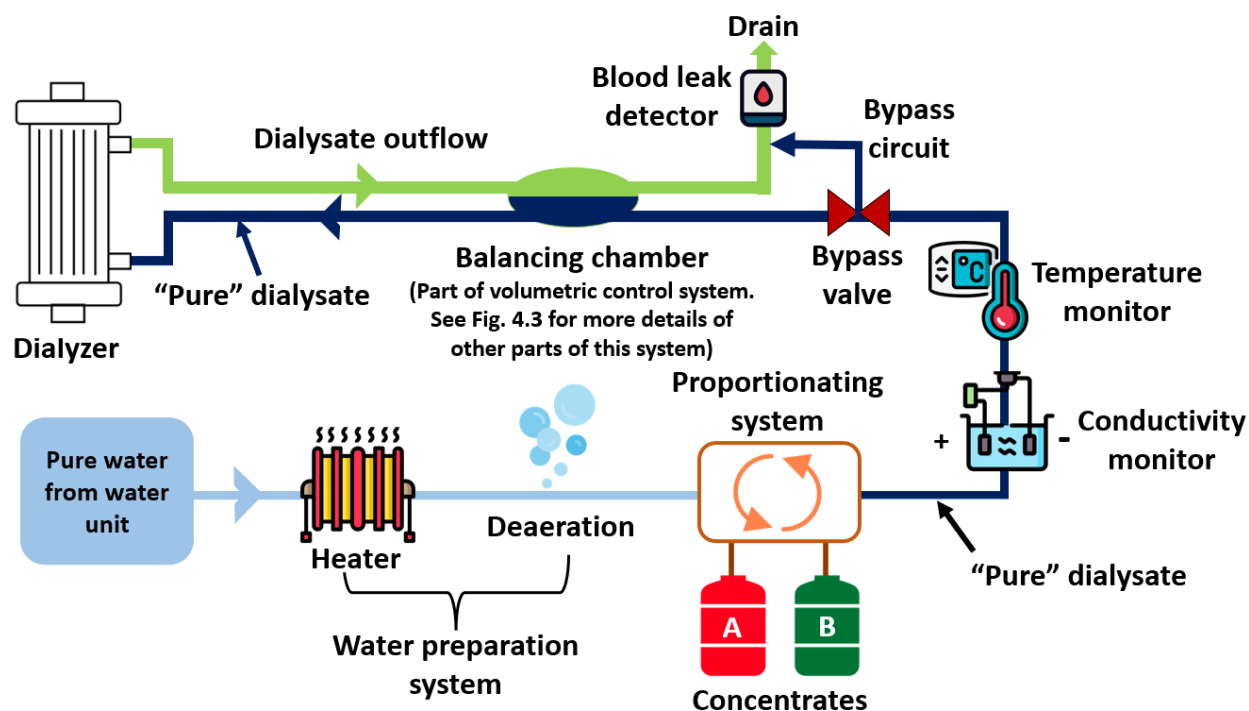


Figure 4.2. Preparation of final diluted “pure” dialysate by single-patient dialysate delivery system (SPDDS)

1. Water preparation system (Figure 4.2):

- Pure water is delivered to the machine's water preparation system.
- In the water preparation system of the machine, the following changes occur to the treated water:
 - The water is heated to a suitable temperature (35–38°C) by a heater.
 - As the water is heated, the gases that were dissolved in it expand and rise to the surface as bubbles. These gas bubbles should be removed from the water. To remove these gases, the treated water is deaerated, i.e., degassed, by applying negative pressure to heated water with a pump.
- Following the heating and deaeration of treated water, it is transported to the proportioning system.

2. Proportioning system (Figure 4.2):

- The proportionating system of the machine is responsible for producing the final mixed pure diluted dialysate.
- The machine's proportioning system ensures that the suitable quantities of A-concentrate and B-concentrate are combined with the correct volume of treated pure water in the appropriate ratio, resulting in the production of a final pure diluted dialysate that will be supplied to the dialyzer. Examples of proportionate ratios (A-concentrate: B-concentrate: water): 1:1.72:42.28 (45x) and 1:1.83:34 (36.83x).
- The composition of the final diluted pure dialysate is shown in Table 4.3.
- After proportionating, the final diluted “pure” dialysate conductivity and temperature are checked through monitors (see conductivity and temperature monitors below), and if the conductivity or the temperature is out of the target range, an alarm will sound, and the dialysate will be redirected to the bypass circuit and drained rather than sent to the dialyzer.

Table 4.3. Composition of final diluted dialysate

Component	Concentration / Value
Sodium*	135–145 mmol/L
Potassium	2–3 mmol/L
Calcium	1.25–1.75 mmol/L (2.5–3.5 mEq/L)
Magnesium	0.25–0.375 mmol/L (0.5–0.75 mEq/L)
Chloride	98–124 mmol/L
Acetate	3–8 mmol/L
Citrate	0.8–1.0 mmol/L (2.4–3.0 mEq/L)
Bicarbonate*	25–35 mmol/L
Glucose	0–11 mmol/L (0–200 mg/dl)
pCO ₂	40–110 mm Hg
pH	7.0–7.4

* Sodium and bicarbonate concentrations can be modified through machine controls.

3. Volumetric control system (Figure 4.3):

Hemodialysis machines have volumetric control consisting of two essential parts (balancing chamber and ultrafiltration controller) to ensure accurate ultrafiltration.

- **First part: balancing chamber:**
 - There are two balancing chambers in the hemodialysis machine acting in alternate cycles.
 - Each chamber is divided into two halves by a flexible membrane. Each chamber half has an inlet and outlet.
 - The balancing chamber guarantees that the dialysate flow into and out of the dialyzer is equal. When a certain amount of dialysate is introduced into the chamber, the fixed deflection of the flexible membrane in the center causes an equal amount of dialysate to be expelled out from the chamber.
 - Four sets of one-way valves are installed at the inflow and outflow of the chamber to guarantee that an equal amount of dialysate is entering and exiting the dialyzer.
 - N.B. The dialysate flow into the dialyzer is pulsatile in nature.
- **Second part: ultrafiltration (UF) controller:**
 - A separate line diverges from the dialysate outflow line, and a UF pump regulates the flow in this line.
 - A central computer unit controls the UF pump:
 - This computer unit receives data from the inlet and outlet pressures for blood and dialysate, as well as the required rate and net volume of UF before the treatment begins.
 - The computer unit then controls the UF rate by controlling the UF pump that withdraws from the dialysate outflow line a fluid volume equals to the UF volume.

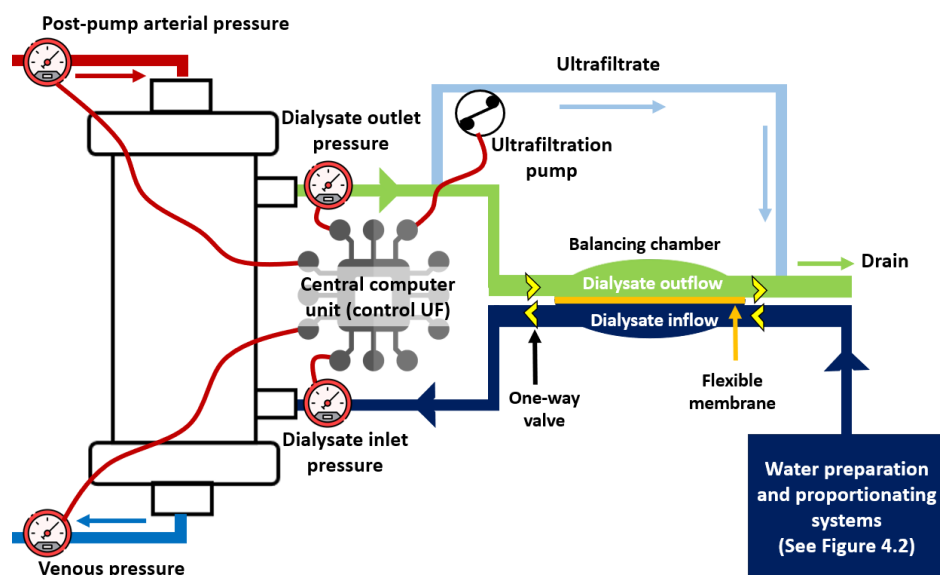


Figure 4.3. Volumetric control system

II. Preparation of “ultrapure” dialysate by SPDDS

- To prepare an “ultrapure” dialysate, an extra step is performed after the three steps mentioned above.
- This extra step is done by using bacterial- and endotoxin-retentive ultrafilter (Figure 4.4):
 - Dialysis devices now available include a bacteria- and endotoxin-retentive ultrafilter (0.001 to 0.05 μm) located in the dialysis machine itself.
 - The “pure” dialysate passes first through this bacteria- and endotoxin retentive ultrafilter before passing to the dialyzer.
 - The bacteria- and endotoxin-retentive ultrafilter filters the “pure” dialysate more and forms the “ultrapure” dialysate that will pass through the dialyzer.
- “Ultrapure” dialysate benefits over “pure” dialysate:
 - Although the low bacterial count and endotoxin level in “pure” dialysate (Table 4.4) are not causing pyrogenic reactions, they may contribute to a chronic inflammatory response (which may increase the risk of developing long-term complications).
 - It is proven that “ultrapure” dialysate is linked to the following benefits because of its lower bacterial and endotoxin levels than “pure” dialysate (Table 4.4):
 - Decreased C-reactive protein and interleukin-6 plasma levels.
 - Improved response of anemia to erythropoietin therapy.
 - Better nutritional status.
 - Reduced plasma levels of $\beta 2$ -microglobulin.
 - Residual renal function loss is slower.
 - Cardiovascular morbidity is lower.
- “Ultrapure” dialysate formation is now highly desirable for hemodialysis, especially when using high permeable high-flux dialyzers, as with the use of these high-flux dialyzers, there is an increased likelihood of contaminants being drawn from the dialysate into the bloodstream.

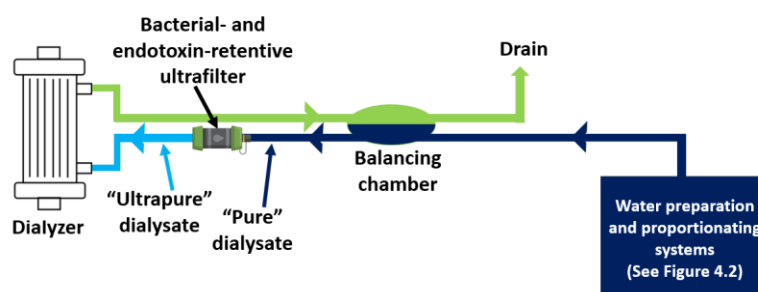


Figure 4.4. Preparation of “ultrapure” dialysate.

Table 4.4. AAMI standards for purity: Differences between “pure” and “ultrapure” dialysate

	Pure Dialysate	Ultrapure dialysate
Colony-forming units of bacteria	< 100 CFU/mL (action level when ≥ 50 CFU/mL)	< 0.1 CFU/mL
Endotoxin units	< 0.50 EU/mL (action level when ≥ 0.25 EU/mL)	< 0.03 EU/mL.

CO₂ production during hemodialysis and Dialysate-related acidosis

- **CO₂ production by dialysate (Figure 4.5):**
 - As mentioned before, when the machine mixes A-concentrate with B-concentrate, the hydrogen ion from the acid in A-concentrate reacts with bicarbonate (B-concentrate), and the following reaction happens in dialysate and forms CO₂ (this CO₂ diffuses from dialysate to the patient's blood): $\text{HCO}_3^- + \text{H}^+ \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 + \text{H}_2\text{O}$
 - Also, when bicarbonate (HCO_3^-) diffuses into the patient's blood from the dialysate, it binds to H^+ in the patient's blood, and the following reaction happens to form CO₂: $\text{HCO}_3^- + \text{H}^+ \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 + \text{H}_2\text{O}$.
- **Patient response to increased CO₂ production during hemodialysis:**
 - Typically, in patients with no respiratory problem (Figure 4.5-A), the elevation of CO₂ is transient because CO₂ stimulates both the peripheral and central chemoreceptors and increases respiratory rate, which results in CO₂ exhalation.
 - Dialysis patients with respiratory problems, e.g., chronic obstructive pulmonary disease (COPD) and congestive heart failure (Figure 4.5-B):
 - These patients have impaired pulmonary CO₂ exhalation causing CO₂ retention.
 - Elevated pCO₂ will reform H^+ , which causes acidosis, and it can compromise O₂ exchange, causing hypoxia with multiple adverse consequences, including increased mortality.
 - It is advised in these patients to avoid using high dialysate HCO_3^- and to avoid rapid correction of acidosis to decrease the load of CO₂ production.

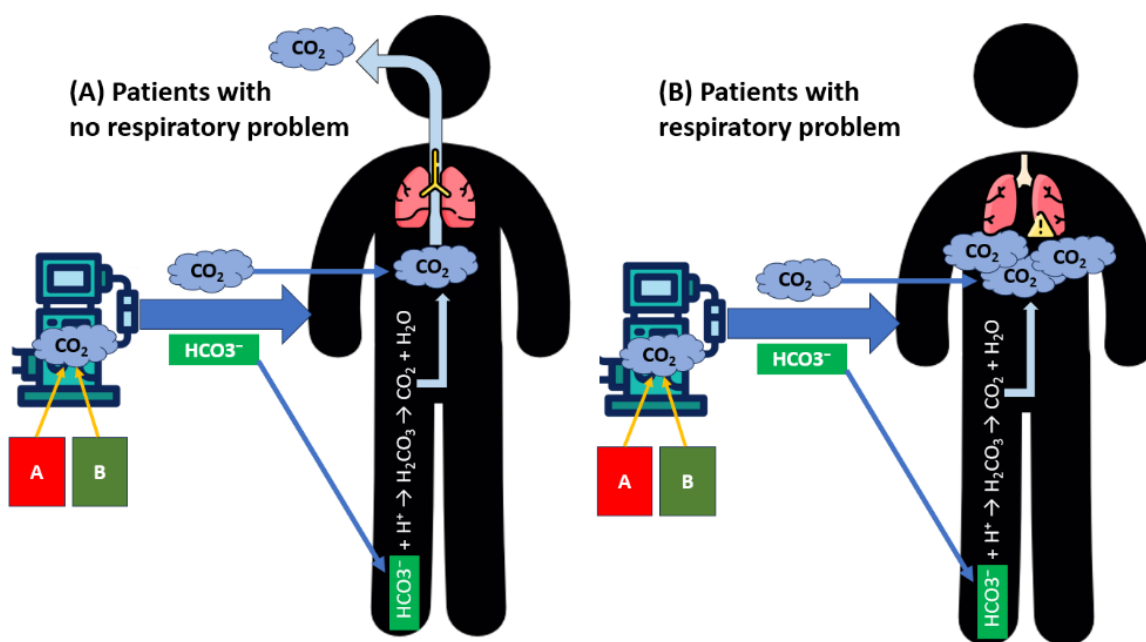


Figure 4.5. Carbon dioxide production during hemodialysis and dialysate-related acidosis

Dialysate circuit-related alarms

Monitoring dialysate is mandatory to detect any abnormalities from recommended targets.

I. Conductivity monitor

A measure of dialysate electric conductance is taken to verify the proper mixing of the diluted "pure" dialysate before its inflow into the dialyzer. Check Figure 4.2 to see the location of the conductivity monitor in the dialysate circuit.

General concept: The flow rate of an electric current through a solution is directly proportional to the concentration of electrolytes in the solution. The salt concentration in diluted "pure" dialysate can be determined by measuring its electrical conductance rate.

Accepted conductivity range:

- The conductance of a diluted "pure" dialysate is roughly equivalent to one-tenth of the sodium concentration, so a dialysate with a sodium concentration of 135mEq/L would have a conductivity value of approximately 13.5 milli siemens per centimeter (mS/cm).
- If the conductivity of the dialysate falls within the acceptable range of 12 to 16 mS/cm, then the dialysate is permitted to flow into the dialyzer.
- If the conductivity deviates from the specified range, an alarm will sound, and the dialysate will be redirected to the bypass circuit (Figure 4.2) and drained rather than sent to the dialyzer.

Relation to sodium level: The conductivity of diluted "pure" dialysate directly corresponds to the level of sodium in it. Thus, any change in sodium level due to inappropriate proportioning (mixing) will cause a change in conductivity. The causes of inappropriate dialysate conductivity and their adverse effects are discussed in Table 4.5.

Table 4.5. Causes of abnormalities in dialysate conductivity and their adverse effects

Conductivity level	Causes	Adverse effects
Low conductivity: This is due to low Na concentration in the dialysate, i.e., hypotonic dialysate.	<ul style="list-style-type: none"> • Incorrect concentrate being used. • The concentrate canister is empty. • The concentrate line is not dropped into the canister properly. • Concentrate line kink. • Air in acid or bicarbonate line. • Proportioning pump running too slow. 	Hypotonic (hypo-osmolar) dialysate causes: Low blood pressure, cramps, and other hyponatremia consequences.
High conductivity: This is due to high Na concentration in the dialysate, i.e., hypertonic dialysate.	<ul style="list-style-type: none"> • Untreated incoming water • Interruption in water supply. • Proportioning pump running too fast. • Acid or bicarbonate are not mixed well. 	Hypertonic (hyper-osmolar) dialysate causes: Increased thirst and other consequences of hypernatremia.

II. Temperature monitor

The temperature of the diluted dialysate is monitored before it is sent through the dialyzer. Check Figure 4.2 to see the location of the temperature monitor in the dialysate circuit.

Acceptable safe temperature range:

- If the temperature of the dialysate is in the acceptable safe range (usually 35–38°C), the dialysate is allowed to inflow into the dialyzer.
- If the dialysate temperature deviates from the specified range, an alarm will sound, and the dialysate will be redirected to the bypass circuit (Figure 4.2) and drained rather than sent to the dialyzer.

Changes in dialysate temperature may cause the following adverse effects:

- Dialysate temperature of <35°C is associated with the patient's feeling of:
 - Coldness.
 - Shivering.
 - Discomfort.
- Dialysate temperature of >42°C is correlated with:
 - Severe hemolysis.
 - Protein denaturation.
 - Risk of cardiopulmonary arrest.

III. Blood leak detector

Cause of blood leak: Blood leaking from the dialyzer blood compartment to the dialyzer dialysate compartment occurs due to ruptured dialyzer fibers.

Location of blood leak detector: It is positioned on the dialysate outflow line (Figure 4.2). Any detected blood leak in the dialysate outflow leads to an alarm sound, and dialysis is stopped.

False blood leak alarm:

- It occurs if there are air bubbles in the dialysate, deposits of grease or scale on the blood detector sensor lens, or in patients who received hydroxocobalamin infusion.
- To diagnose false alarms, Hemastix® strips can be dipped in the outflow dialysate:
 - If it detects blood, the dialyzer should be changed.
 - If it doesn't detect blood, clear the blood sensor lens or search for other causes.

IV. pH sensors

- The pH of the final diluted pure dialysate is approximately 7.0–7.4.
- Certain machines are equipped with a pH electrode as a component of proportioning system.
- The primary purpose of this pH electrode is to ensure that the correct concentrates are connected to the machine by identifying any abnormalities in the dialysate pH. For example, this sensor will alarm if the B-concentrate is not connected to the machine.

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Chapter 5

Dialyzers Overview

Dialyzer has a semipermeable membrane separating two sides, one for blood flow and the other for dialysate flow. The dialyzer transports molecules and water between the blood and dialysate compartments.

Types of dialyzers

- **Parallel plate dialyzer:** Historically, this dialyzer was commonly utilized and comprised of parallel plate sheets.
- **Hollow fiber (capillary) dialyzer:** It is the dialyzer used nowadays. It consists of thousands of capillary fibers. The hollow fiber dialyzer is discussed in this chapter, and the word “dialyzer” later on always refers to the hollow fiber dialyzer.

Dialyzer structure

Dialyzer components include blood ports, dialysate ports, header space, potting material, and capillary fibers. All these components are discussed in Table 5.1 and illustrated in Figures 5.1 and 5.2.

Table 5.1. Components of the dialyzer

Component	Characteristics
Blood ports	<ul style="list-style-type: none"> • Arterial port (blood inlet): It carries blood into the dialyzer. • Venous port (blood outlet): It carries blood out of the dialyzer.
Dialysate ports	<ul style="list-style-type: none"> • On the side of the dialyzer case are two dialysate ports, one for the inflow of dialysate and the other for the outflow.
Header space	<ul style="list-style-type: none"> • Blood from the arterial blood port flows into the arterial header space. • The venous header space receives dialyzed blood before it enters the venous blood port. • Clotting of the space between the header and fibers is common.
Potting material	<ul style="list-style-type: none"> • The dialyzer case is connected to the hollow capillary fibers using a potting material, which separates the blood and dialysate compartments.
Capillary hollow fibers	<ul style="list-style-type: none"> • Approximately 10,000 capillary fibers made of permeable material are found inside the dialyzer case. • The blood passes through the hollow fibers while the dialysate surrounds the outside of them.

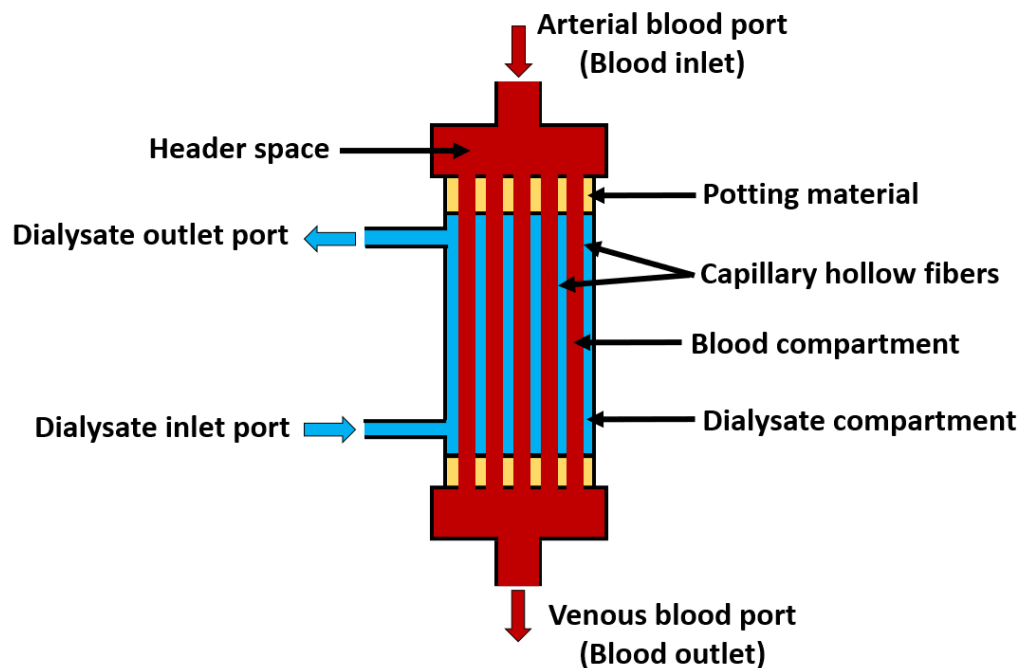


Figure 5.1. Hollow fiber (capillary) dialyzer structure

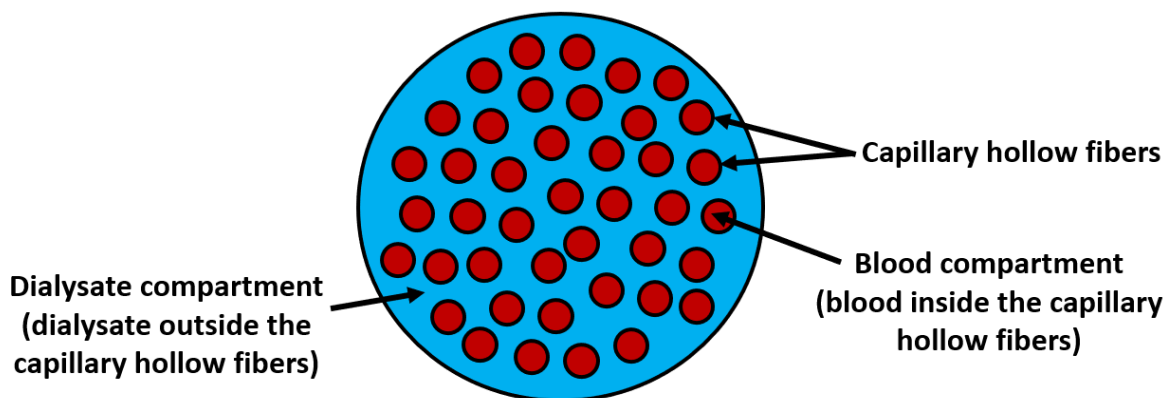


Figure 5.2. Cross section of hollow fiber (capillary) dialyzer

The flow direction of blood and dialysate in the dialyzer: Counter-current flow

- In dialyzers, blood and dialysate flow parallel to each other in opposite directions, i.e., counter-current flow (Figure 5.1).
- The counter-current flow of blood and dialysate within the dialyzer creates an optimal concentration gradient for solutes, allowing for the continuous diffusion of waste products from the blood to the dialysate.

Materials of the dialyzer membranes

The different materials of the dialyzer membrane are discussed in Table 5.2. Each material type has various characteristics.

Table 5.2. Dialyzer membranes different materials, and their characteristics

Membrane	Material	Characteristics
Cellulose membrane	<ul style="list-style-type: none"> • Cuprammonium rayon • Cuprammonium cellulose • Regenerated cellulose 	<p>All cellulose materials have the following characteristics:</p> <ul style="list-style-type: none"> • Less expensive. • The least biocompatibility: Cellulose membrane contains free hydroxyl groups that trigger immune activation by stimulating blood cells and initiating the complement cascade, leading to increased immune response. The activation of these cells and complement causes them to produce cytokines, which can result in a range of adverse reactions and complications during dialysis.
Modified or substituted cellulose	<ul style="list-style-type: none"> • Cellulosynthetic, e.g., Hemophan® • Cellulose acetate • Cellulose diacetate • Cellulose triacetate • Cellulose hydrate • Cellulosynthetic 	<p>It differs from cellulose membrane in the following:</p> <ul style="list-style-type: none"> • Substituted cellulose membranes have been produced by bonding free hydroxyl groups to materials like acetate. • Intermediate biocompatibility: Adding a tertiary amine compound to the modified cellulose membrane enhances biocompatibility.
Synthetic	<ul style="list-style-type: none"> • Polysulfone, polyethersulfone, • Polyacrylonitrile (PAN) • Polymethylmethacrylate (PMMA) • Polyamide • Polycarbonate 	<p>It differs from cellulose and modified cellulose membranes in the following:</p> <ul style="list-style-type: none"> • The best biocompatibility. • Higher permeability. • More expensive. • Certain dialyzers are manufactured with a coating of antioxidant materials on their membranes, such as vitamin E. • Some membranes also adsorb middle-molecular weight molecules (e.g., β2-microglobulin), plasma proteins, immunoglobulins, and complements.

Physical properties of the dialyzer

- **Dialyzer surface area:**
 - The typical surface area for most dialyzer membranes ranges from 0.8 to 2.5m².
 - As a general guide, to choose a suitable dialyzer for the patient, the surface area of the dialyzer membrane could be roughly equivalent to the patient's body surface area.
- **Dialyzer priming volume:** As mentioned in Chapter 1, dialyzer priming volume is the blood compartment volume in a dialyzer. It typically ranges from 60 to 120 mL.

Dialyzer sterilization

1. **Ethylene oxide (Eto):**
 - It is the sterilization method most frequently used.
 - It is crucial to eliminate Eto completely before using the dialyzer by conducting a thorough rinsing, as some individuals have been known to experience severe allergic reactions to even minimal amounts of Eto (type A dialyzer reaction, this will be discussed in chapter 8).
 - An alternative dialyzer sterilization method should be used in Eto-sensitive patients.
2. **Other sterilization methods are gamma radiation, steam autoclaving, and electron beam.**

Dialyzer reuse

- **Reuse versus no reuse:** The rising cost of dialysis supplies without reuse is a significant concern, particularly when considering the environmental impact of increased contaminated waste. However, there has now been a shift in focus from reuse to no reuse.
- **The reuse technique:**
 - Clean the dialyzer by using clean water rinse and/or cleaning agents such as sodium hypochlorite (bleach), hydrogen peroxide, or peracetic acid.
 - After a thorough cleaning, the dialyzer is typically sterilized using:
 - Formaldehyde, which is the most commonly utilized agent.
 - Glutaraldehyde.
 - Heat sterilization.
- **Before the dialyzer is used again, several safety checks are mandatory:**
 - Dialyzers are subjected to chemical testing to ensure no sterilizing agent remains.
 - Membrane patency is checked by the use of a pressure test.
 - The effectiveness of a dialyzer is evaluated to ensure that there is enough membrane surface area available for dialysis by determining the fiber bundle volume (FBV). The dialyzer is considered to have a sufficient number of functional fibers if the FBV is between 80-85% of its initial value. The dialyzer should be replaced if the FBV is lower than this range.

Dialyzer efficiency and flux

Dialyzer efficiency is related to the ability of the dialyzer to remove small molecules, while dialyzer flux is related to the ability to remove water and middle molecules (Table 5.3). Before discussing dialyzer efficiency and flux, we must first discuss what extraction ratio means.

Table 5.3. Classification of solutes according to molecular weight

Classification of solutes	Examples
Small molecules (<500 Dalton)	Urea (60 Da), creatinine (133 Da), phosphate (134 Da), electrolytes.
Middle molecules (500-15,000 Dalton)	β 2-microglobulin (11,818 Da), vitamin B ₁₂ (1,355 Da), parathormone (9,425 Da).
Large molecules (>15,000 Dalton)	Albumin, lambda light chain, Kappa light chain, myoglobin.

Extraction ratio (ER)

Definition: Extraction ratio is the percentage reduction of urea (or any other solute) across the dialyzer.

Calculation:

- **Equation:** The extraction ratio is calculated by subtracting the outlet concentration of a substance from the inlet concentration and then dividing the result by the inlet concentration:

$$(\text{inlet concentration} - \text{outlet concentration}) / \text{inlet concentration}$$
- **Example of extraction ratio calculation (Figure 5.3):** If the blood urea concentration across a hemodialyzer drops from 100 mg/dl at the inlet to 40 mg/dl at the outlet, the urea ER is 60%. This 60% decline represents urea diffusion from blood into the dialysate.

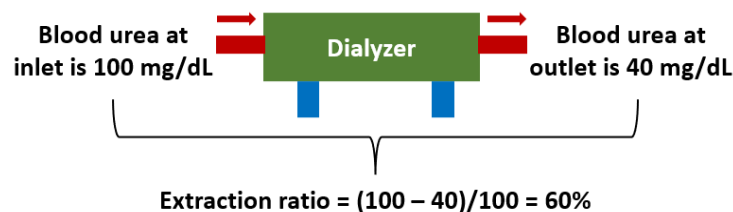


Figure 5.3. Extraction ratio calculation

Dialyzer efficiency

- Dialyzer efficiency denotes the ability of the dialyzer to remove small molecules (<500 Dalton, e.g., urea, creatinine, phosphate, and electrolytes – Table 5.3) by diffusion.
- Dialyzer efficiency can be measured by calculating dialyzer clearance (KD); however, it is more accurately detected by measuring the dialyzer's mass transfer-area coefficient (KoA). Both KD and KoA are discussed below.

Dialyzer clearance (KD or K):

- **Definition:** It is the volume of blood from which a solute is removed (cleared) in a given unit of time.
- **Unit:** KD is measured in mL/min.
- **Calculation of KD:**
 - KD is calculated as blood flow rate (QB) multiplied by the extraction ratio (ER) of urea or other solutes, i.e., $KD = QB \times ER$.
 - Example: If the ER of urea is 70% at QB of 200 mL/min, then KD of urea = $0.7 \times 200 = 140$ mL/min.
 - The in vitro KD values given by the manufacturer (see Table 5.4 as an example) are typically greater than the actual in vivo blood clearance levels observed in the patient body.

Table 5.4. An example of a manufacturer pamphlet for a dialyzer in vitro KD for different molecules

Molecule	Dialyzer clearance (KD) mL/min = $QB \times ER$
Urea	180
Creatinine	165
Phosphate	141
Vitamin B ₁₂	88
The above clearances are measured at a blood flow rate (QB) of 200 ml/min, a dialysate flow rate (QD) of 500 ml/min, and an ultrafiltration flow rate (QF) of 0 mL/min.	

- **Factors affecting KD:**
 - **Thickness of the membrane:** Thicker membranes have lower permeability and clearance (KD) than thinner membranes. However, thicker membranes generally have a higher ability to withstand transmembrane pressure (TMP) compared to thinner membranes.
 - **Density and size of the pores.**
 - **Surface area of the membrane.**
 - **Blood flow rate (QB):**
 - As $KD = QB \times ER$, an increase in QB will increase KD.
 - However, the relation between QB and KD is not linear, as at very high QB, the clearance will plateau (see Chapter 6, Figure 6.3)

Mass transfer-area coefficient (KoA)

- **Definition:**
 - It is the solute's theoretical maximum dialyzer clearance, assuming that both QB and QD are limitless.
 - "Ko" is the permeability coefficient of the dialyzer membrane for a given solute.
 - "A" is the total effective surface area of the dialyzer membrane.
- **Unit:** KoA is measured in mL/min.

- **Dialyzer efficiency classification according to KoA:**
 - **Low-efficiency dialyzer membranes** have a KoA urea of <500 mL/min.
 - **High-efficiency dialyzer membranes** have a KoA urea of >600 mL/min. Most dialyzers commonly used today have in vitro KoA values ranging from 1,200 to 1,600 mL/min.
- **Factors affecting KoA:**
 - “Ko” is affected mainly by:
 - Thickness of the membrane
 - Density and size of the pores.
 - “A” is the effect of surface area.
- **The relation between KoA and solute clearance (Figure 5.4):**
 - The greater the value of KoA, the more permeable the membrane becomes for solutes, resulting in a higher clearance of the solutes.
 - However, the relationship between KoA and clearance is not linear, as the clearance will plateau at a very large surface area.

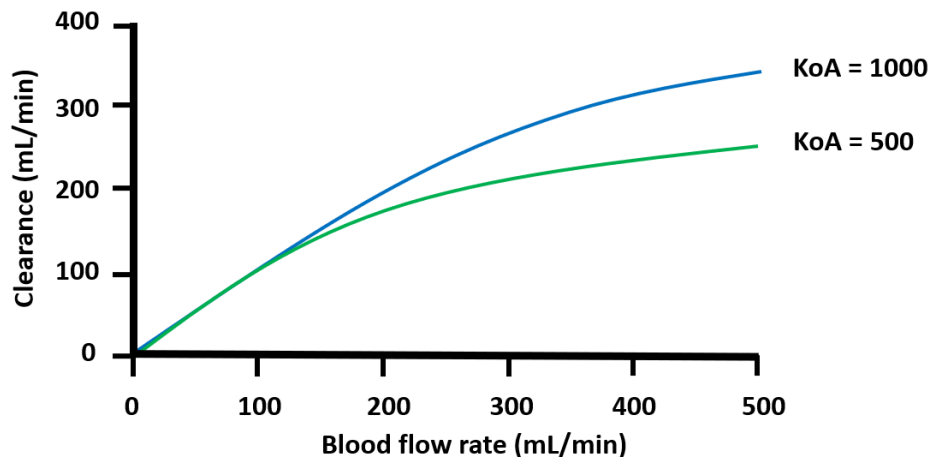


Figure 5.4. Estimated dialyzer clearance (K) based on blood flow rate (QB) and dialyzer mass-transfer area coefficient (KoA). Note that when QB is low, 200 mL/min, dialyzers with 500 and 1000 mL/min KoA have nearly similar clearances, while at QB 400, dialyzers with 1000 mL/min KoA have higher clearance than dialyzers with 500 mL/min KoA. Thus, while using dialyzers of high KoA, it is advised to deliver a high QB to get a higher clearance.

Dialyzer flux

- Dialyzer flux is related to the ability of the dialyzer to remove water and middle molecules (500-15,000 Dalton, e.g., β_2 -microglobulin, vitamin B₁₂ – Table 5.3).
- Dialyzer flux can be detected by:
 - Ultrafiltration coefficient (KUF).
 - β_2 -microglobulin clearance, β_2 -microglobulin sieving coefficient, or membrane pore size.
- All these factors are discussed below.

Ultrafiltration Coefficient (*KUF*) to detect dialyzer flux:

- **Definition:**
 - The Ultrafiltration coefficient (*KUF*) is a measure of the volume of water (mL) that is transferred across a membrane per 1 hour per 1 mmHg difference of transmembrane pressure gradient (TMP) (Figure 5.5).
 - Thus, *KUF* is equivalent to water permeability (i.e., ultrafiltration) by the dialyzer.
- **Unit:** *KUF* is measured in mL/h/mmHg.

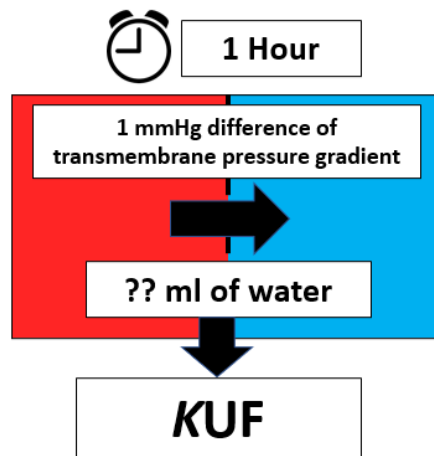


Figure 5.5. Ultrafiltration Coefficient (*KUF*)

- **Factors affecting *KUF*:**
 - Membrane thickness.
 - Pore size (Table 5.5, 5.6).
- ***KUF* is used to specify dialyzer flux (Table 5.5, 5.6):**
 - Low-flux membrane dialyzer membranes have *KUF* (water permeability or ultrafiltration) of <10mL/h/mmHg.
 - High-flux membrane dialyzer membranes have *KUF* (water permeability or ultrafiltration) of >20mL/h/mmHg.
- **Issues related to high-flux membrane dialyzers:**
 - **Over ultrafiltration with the use of high-flux membrane dialyzers:** Dialyzers that possess a high *KUF* can lead to excessive ultrafiltration, making it crucial to have machines that can precisely regulate the UF rate at all times during the treatment process.
 - **Back-filtration (back-leak) with the use of high-flux membrane dialyzers (Figure 5.6):** Dialyzers with high *KUF* result in a significant drop in pressure along the entire length of the dialyzer blood compartment. Conversely, the pressure in the dialysate compartment increases. This can lead to back-filtration of dialysate, which may result in the infusion of dialysate from the venous end of the fibers back into the blood. As a result, highly porous dialyzers may only be safe to use with ultrapure dialysate.

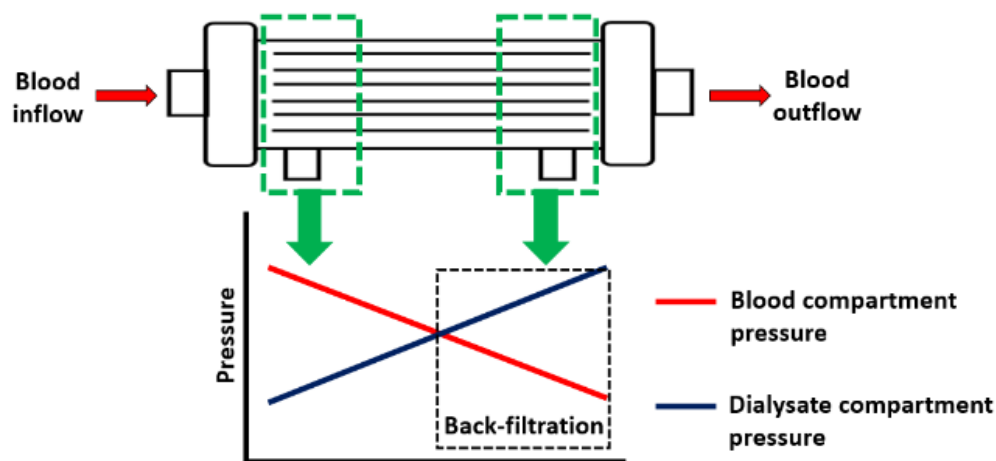


Figure 5.6. Back-filtration in high-flux dialyzer

- **Membrane fouling with the use of high-flux membrane dialyzers:** As mentioned before in Table 5.2, some of the membranes adsorb proteins when they come in contact with blood. Protein adsorption to the membrane can result in clogging and fouling of the membrane, which in turn can reduce its solute removal performance.

β 2-microglobulin clearance, pore size, and sieving coefficient to detect dialyzer flux:

Dialyzer flux can be detected by measuring β 2-microglobulin clearance, β 2-microglobulin sieving coefficient, and membrane pore size (Tables 5.5 and 5.6).

Table 5.5. Characteristics of low- and high-flux membrane dialyzers

Flux	Ultrafiltration Coefficient (KUF)	β 2-microglobulin clearance	β 2-microglobulin sieving coefficient*	Membrane pore size	Molecular weight cut-off (MWCO)
Low-flux	<10 mL/h/mmHg	<10 mL/min	---	<1.8 nanometer	<5,000 Dalton
High-flux	10-50 mL/h/mmHg	>20 mL/min	≥ 0.6	≥ 3.3 nanometer	<25,000 Dalton

* Sieving coefficient was discussed in Chapter 1.

Table 5.6. Japanese classification of dialyzers

Flux	Dialyzer	β 2-microglobulin clearance
Low-flux	I	< 10 mL/min
High-flux	II	≥ 10 to < 30 mL/min
	III	$30 \geq$ to < 50 mL/min
Super-high flux	IV	≥ 50 to < 70 mL/min
	V	≥ 70 mL/min

Available evidence comparing the use of low- versus high-flux membranes:

1. HEMO study (Effect of Dialysis Dose and Membrane Flux in Maintenance Hemodialysis):

- In this study, 1846 patients undergoing thrice-weekly dialysis were assigned to a standard or high dialysis dose and a low- or high-flux dialyzer.
- The primary outcome (death from any cause) and also secondary outcomes were not significantly different between the high- and low-flux groups or between the standard and the high-dose dialysis groups.
- However, In the high-flux group, in comparison to the low-flux group, there were significant reductions in the risk of death from cardiac causes and the combined outcome of first hospitalizations or death from a cardiac cause.

2. MPO study (The Membrane Permeability Outcome study):

- A prospective randomized study investigated the impact of high- or low-flux dialysis membranes on survival in incident hemodialysis patients who had low albumin (≤ 4 g/dl) and normal albumin (> 4 g/dl).
- No difference in survival was found between the use of high- or low-flux dialysis membranes in patients with normal albumin levels.
- Patients with serum albumin ≤ 4 g/dl had significantly better survival rates in the high-flux group compared with the low-flux group.
- Moreover, a post hoc secondary analysis showed that high-flux membranes may significantly improve survival in diabetic patients.

Interrelation between dialyzer efficiency and dialyzer flux:

- Typically, the high-flux dialyzers usually have high efficiency and vice versa.
- But this is not always the situation as there is a small, low-efficiency dialyzer (e.g., for use in children) that is of high-flux. Also, there may be a high-efficiency dialyzer that is of low-flux.

Expanded hemodialysis (HDx): Medium cut-off (MCO) membrane

- **What is Expanded hemodialysis (HDx)?**
 - It is a novel development that aims to improve the efficacy of hemodialysis treatments.
 - The process of HDx is typically performed using a medium cut-off (MCO) membrane, also known as the high retention onset membrane.
- **Molecular weight cut-off (MWCO) of MCO:** MCO enhances large middle-molecule clearance up to 45,000 Dalton:
 - MCO MWCO is higher than low- and high-flux dialyzer membranes (Figure 5.7) which promotes more removal of uremic toxins.
 - MCO MWCO is lower than that of high cut-off dialyzers (Figure 5.7) which promotes the removal of uremic toxins without causing a significant decrease in albumin levels as in high cut-off dialyzers, and this makes MCO dialyzers more physiological.

- **Benefits of HDx and MCO dialyzers:** Numerous studies have demonstrated that using the MCO membrane in HDx has the following benefits:
 - It reduces inflammatory mediators.
 - It improves erythropoiesis stimulating resistance.
 - Improves the physical components of QOL.
 - It improves uremic pruritus.
 - It provides clinical benefits and better outcomes.

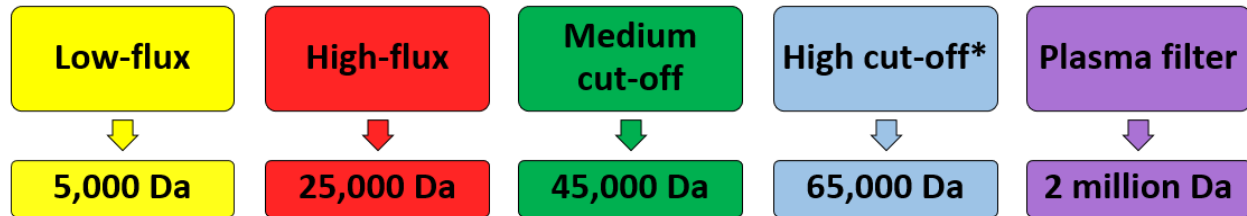


Figure 5.7. Molecular weight cut-off (MWCO) for different dialyzer membranes

* The MWCO of high cut-off dialyzers is close to that of the native kidney (65kDa). They are characterized by high protein loss. They are usually used for kidney replacement therapy in patients with multiple myeloma to remove serum monoclonal free light chains. With the use of high cut-off membranes there is a high albumin loss which precludes its use in chronic hemodialysis prescription.

Albumin and amino acids loss during hemodialysis

Albumin loss during hemodialysis:

- **Hypoalbuminemia with hemodialysis:**
 - Hypoalbuminemia is a major risk factor for morbidity and mortality in dialysis patients.
 - With increasing interest in highly permeable membranes to improve middle-molecule removal, transmembrane albumin loss increases accordingly. However, hypoalbuminemia-associated mortality may be a consequence of inflammation and malnutrition rather than low albumin levels per se.
- **Albumin loss with different dialyzer membranes:**
 - With conventional low-flux hemodialysis albumin leakage is usually absent.
 - With conventional high-flux hemodialysis albumin loss is usually absent or low (<2.4 g/4 h treatment).
 - Albumin loss with high cut-off dialyzers varied from less than 1 g to nearly 8 g per 4 h hemodialysis session.
 - With the use of MCO dialyzer, albumin losses of 2.0–4.0 g per session were reported.

Amino acids loss during hemodialysis:

- Given the small size of amino acids, a considerable mass of them is lost into the dialysate with each hemodialysis session.
- Data suggest that patients lose approximately 6–8 g of total amino acids per session. Nevertheless, a loss of up to 12 g of amino acids per session has been reported. Increased membrane surface area and blood flow have been associated with increased amino acid loss.

Dialyzer monitoring and related alarms**I. Transmembrane pressure (TMP) monitoring**

- **Definition:** As discussed in Chapter 1, transmembrane pressure (TMP) refers to the difference in pressure between the blood and dialysate compartments within the dialyzer. The pressure in the blood compartment is positive, whereas the pressure in the dialysate compartment is negative.
- **Accepted TMP limit:** Manufacturers typically provide information about the maximum TMP for dialyzers in their brochure. The European Renal Best Practice (ERBP) guidelines suggest a TMP limit of +300 mmHg as a safe upper limit.
- **Transmembrane pressure alarm:**
 - If there is any abnormal change in TMP, the dialysis machine produces an alarm sound.
 - Following are the causes of changes in TMP:
 - TMP may be increased if:
 - The surface area of the dialyzer decreased due to clotting.
 - Using a small surface area dialyzer with a targeted high ultrafiltration volume.
 - TMP will decrease in case of opening the dialysate compartment of the dialyzer to the atmosphere.

II. Blood leak detector

- The rupture of dialyzer fibers can leak blood from the blood compartment to the dialysate compartment.
- Blood leak sensors are placed on the dialysate outflow line to detect any blood leak. The blood leak detector was discussed in detail in Chapter 4.

III. Pressure monitors

A clotted dialyzer causes more positive post-pump pressure and less positive venous pressure. Pressure monitors were discussed in detail in Chapter 2.

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Chapter 6

Hemodialysis Adequacy and Dose

Adequate optimum hemodialysis can enhance well-being and enable patients to maintain social autonomy. **Target all of the following to achieve adequate OPTIMUM hemodialysis:**

1. Good patient well-being (physically, mentally, and socially).
2. Dialysis should not interrupt the patient's social life or interfere with his job.
3. Achieve adequate ultrafiltration.
4. Maintain residual kidney function as long as possible.
5. Control of blood pressure.
6. Control of anemia.
7. Control of bone disease and calcium-phosphate product.
8. Control of acidosis.
9. Absence of intradialytic symptoms.
10. Absence of interdialytic symptoms.
11. Shorter dialysis recovery time.
12. No dialysis-related hospitalization.
13. Good vascular access flow with no complications and no related hospitalizations.
14. Control inflammatory state.
15. **Lack of malnutrition and achievement of accepted value of normalized protein catabolic rate (nPCR):**

- **What is nPCR?**

- nPCR is a marker of dietary protein intake and nutritional status in stable (neither catabolic nor anabolic) dialysis patients.
- nPCR is usually established from the urea generation rate.

- **Pitfall:** nPCR is widely recognized as a reliable marker for stable dialysis patients. However, patients with increased muscle breakdown may have a high nPCR, even though protein intake may be lower in such patients. So, it is important to note that nPCR is not always an accurate indicator of protein consumption, as other factors may affect urea generation.

- **Accepted value:**

- nPCR >1.0g/kg/day is generally needed to maintain a positive nitrogen balance.
- A decrease in the incidence of morbidity was noticed in individuals with a high nPCR, likely due to their increased dietary protein consumption.

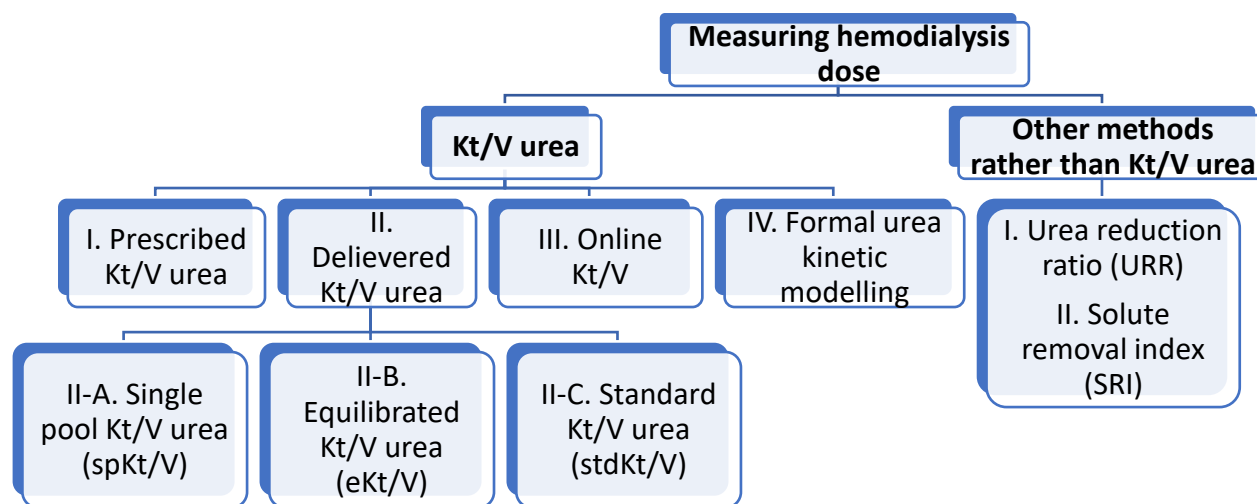
- **How to calculate nPCR:**

- An online calculator is available at <http://ureaкинetics.org> (Daugirdas, 2009) to calculate nPCR and other data that will be mentioned later.
- On the website, click "Solute-Solver LITE single patient calculator (Urea)." To log in to this website, use the username "solute" and the password "solver," then enter the required data to get the patient's nPCR and other data.



16. Achieve a hemodialysis dose within the recommended target:

- **Uremic toxins removal effect:**
 - Dialysis helps to eliminate uremic toxins, thereby enabling survival in individuals with end-stage kidney disease (ESKD).
 - The influence of dialysis is determined by the amount of dialysis treatment received and the extent of toxin removal.
- **Uremic toxins are classified into three categories:**
 - Low-molecular-weight solutes that are water-soluble (e.g., urea).
 - Middle-molecular-weight solutes (e.g., beta2-microglobulin).
 - Protein-bound solutes (e.g., indoles and phenols).
- **Which uremic toxin is used to measure hemodialysis dose?**
 - The measurement of hemodialysis dose has traditionally been based on the removal and clearance of urea among all the above-mentioned uremic toxins.
 - The results of both clinical and experimental research imply that middle molecules and protein-bound solutes have a negative impact on patient survival, and they should also be considered as markers for evaluating the dosage of hemodialysis.
- **Measuring hemodialysis dose depending on urea clearance:**
 - Urea is a preferred marker due to its ease of measurement, regular testing, and well-known metabolism, generation rate, and volume of distribution.
 - Methods to measure hemodialysis dose depending on urea clearance (Figure 6.1):
 - Kt/V urea: Despite its limitations (see later), it is the most commonly used method.
 - Other methods: urea reduction ratio and solute removal index.
 - All these methods are discussed below.
- **Important note:** Hemodialysis should not only provide a good dose (i.e., Kt/V), but it must also be optimal, and we should achieve all other targets (points 1 to 15 mentioned above) to achieve adequate optimum hemodialysis.

**Figure 6.1. Methods to measure hemodialysis dose**

“Kt/V urea” to measure hemodialysis dose

- Kt/V is the most frequently applied measure of the delivered dialysis dose, although it has multiple limitations (see later).
- Multiple research shifted toward finding markers for hemodialysis dose adequacy other than urea.
- Different forms to calculate Kt/V urea are known as prescribed Kt/V, delivered Kt/V, online Kt/V, and formal urea kinetic modeling. All these forms are summarized in Figure 1 and fully discussed below.

I. Prescribed Kt/V urea

- **Definition:** It is the in vitro calculation of Kt/V by the dialyzer manufacturer. It is always higher than the delivered Kt/V.
- **What is Kt/V abbreviating for?**
 - “K” is the dialyzer clearance of urea.
 - “t” is the dialysis time (duration) in minutes.
 - “V” is the volume of distribution of urea:
 - Urea is a small molecule with a molecular weight of 60 Da, which allows it to move easily between various body compartments.
 - Additionally, urea concentration is equal in both the intracellular and extracellular compartments. This is why the volume of urea distribution is equivalent to the volume of water in the body. So, the volume of distribution of urea “V” is calculated using the same equation calculating the total body water volume:

$$V = 0.6 \times \text{body weight.}$$
- **Example of calculation:** If a patient with a body weight of 70 kg is dialyzed for 4 hours, and the urea clearance of the used dialyzer is 300 ml/min, then:
 - Kt of this patient = $300 \times 180 = 54000 \text{ ml} = 54 \text{ L}$.
 - V of this patient = $0.6 \times 70 = 42 \text{ L}$.
 - So, this patient’s Kt/V = $54 / 42 = 1.28 (\approx 1.3)$.
 - What is meant by Kt/V equals 1.3?
 - This means the total body fluids volume is cleared 1.3 times during the hemodialysis session.
 - So, if Kt/V equals 1, this means the total volume of body fluids is cleared only once during the hemodialysis session.
 - If Kt/V equals 1.5, this means the total volume of body fluids is cleared 1.5 times during the hemodialysis session.
- **Prescribed Kt/V urea pitfalls:** Using prescribed Kt/V urea to measure dialysis adequacy includes only the rate of urea clearance by dialysis, duration of dialysis, and volume of urea distribution, but it does not include ultrafiltration volume.

II. Delivered Kt/V urea

- It is the in vivo calculation of Kt/V.
- Delivered Kt/V is always lower in value than the prescribed Kt/V.
- Before discussing different forms of delivered Kt/V urea, we must describe urea movement post-dialysis. When dialysis ceases, the urea behaves as follows (Figure 6.2):
 - Immediately post-dialysis, the urea level in the blood (i.e., intravascular pool) is low because of the dialysis treatment.
 - After dialysis, by 30-60 minutes, blood urea level (i.e., intravascular pool) starts to increase because of urea distribution out of cells (i.e., extravascular pool) to the blood.
 - An example (Figure 6.2):
 - If a patient has pre-dialysis blood urea of 90 mg/dl.
 - Let us imagine that his immediate post-dialysis blood urea (i.e., intravascular pool) is 25 mg/dl after a single dialysis session.
 - After 30-60 minutes, the serum urea measurement is repeated, and it is observed that the BUN has risen to 40 mg/dl. This increase is due to the movement of urea from the "extravascular pool" to the "intravascular pool."
- The same online calculator mentioned above to calculate nPCR is used to calculate different formulas of delivered Kt/V:
 - The calculator is available at <http://ureaкинetics.org> (Daugirdas, 2009) to calculate delivered Kt/V and other data that will be mentioned in this chapter.
 - On the website, click "Solute-Solver LITE single patient calculator (Urea)." To log in to this website, use the username "solute" and the password "solver," then enter the required data to get the patient's delivered Kt/V and other data.
- Now, we will discuss the two forms of delivered Kt/V urea:
 - II-A. Single pool Kt/V urea (spKt/V).
 - II-B. Equilibrated Kt/V urea (eKt/V).
 - II-C. Standard Kt/V urea (stdKt/V).

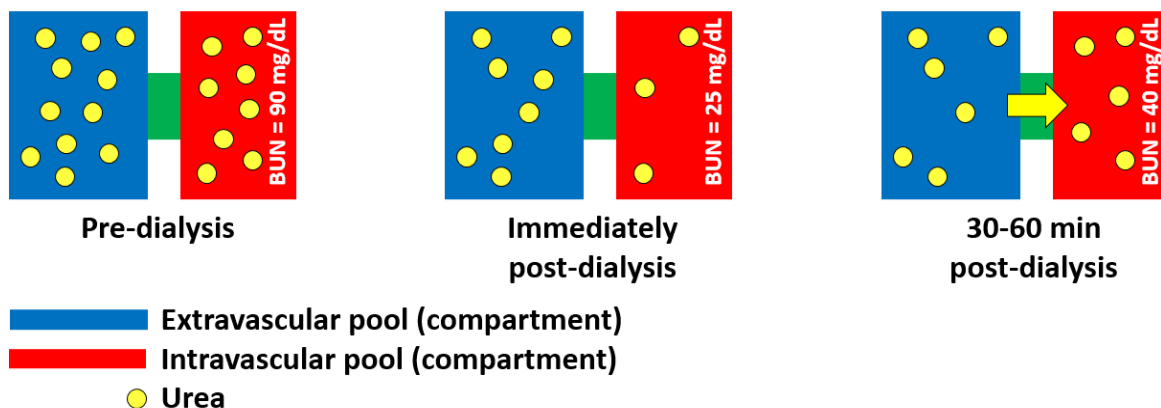


Figure 6.2. Post-dialysis urea behavior

II-A. Single pool Kt/V urea (spKt/V):

- **The following data are needed to calculate single pool Kt/V urea:**
 - Pre-dialysis blood urea.
 - Post-dialysis blood urea (immediately at the end of dialysis).
 - Ultrafiltration volume (pre-dialysis weight – post-dialysis weight).
 - Dialysis session duration in minutes.
- **Why is it called a single pool, and what is its main pitfall?**
 - Post-dialysis urea sampling for spKt/V calculation is done immediately at the end of dialysis from the blood (i.e., intravascular pool), neglecting the increase (rebound) that will occur in blood urea after 30-60 minutes of dialysis because of urea distribution out of cells (i.e., extravascular pool) to the intravascular space. That is why it is called a “single pool,” as it measures the urea level in one pool, which is the blood, neglecting the effect of the second pool (i.e., extravascular pool) on the blood urea level.
 - spKt/V overestimates the delivered dialysis dose as it depends on the immediate post-dialysis lowest blood urea level (than the higher rebound after 30-60 min), and this is considered the main pitfall of this equation.
- **Blood urea sampling precautions:** Several precautions must be followed to collect blood urea sampling accurately. These precautions are shown in Table 6.1.

Table 6.1. Blood urea sampling for calculation of Kt/V

Pre-dialysis blood urea sampling:	Sampling from arteriovenous fistula (AVF) or graft (AVG): Take the sample from the access needle before the beginning of the dialysis session.	
	Sampling from venous catheter: Discard the first 10mL of blood from the catheter hub, then take the sample.	
Post-dialysis blood urea sampling:	Sampling from AVF or AVG:	First method: Set the UF rate to zero and decrease the blood pump* speed to 50 mL/min for a minimum of 10 seconds. Following this, stop the blood pump and collect the sample within the next 20 seconds.
		Second method: Set the UF rate to zero, decrease the blood pump* speed to 100 mL/min, wait for 15-30 seconds, and then collect the sample from the arterial line.
		Third method: Pause the flow of dialysate while concurrently maintaining the blood pump rate; after a waiting period of three minutes, withdraw a blood sample from any point within the circuit.
	Sampling from venous catheter: Take blood sample 30 seconds after slowing the pump [¶] .	

* Slowing blood pump to reduce the effect of cardiopulmonary recirculation (discussed below) and AV access recirculation (it will be discussed in Chapter 10).

[¶] Slowing blood pump to decrease the effect of catheter recirculation if present. Catheter recirculation happens when blood from the venous limb of the catheter goes back to the arterial limb of the catheter without passing through the rest of the body.

- **Calculation:**

- **Formulas to calculate single pool Kt/V urea:**

- Formula 1: $\text{spKt/V} = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times 0.55 \text{ UF/V}$

Where “ln” is the natural logarithm, “R” is the ratio of post- to pre-dialysis BUN, “t” is the session length (in hours), “UF” is the ultrafiltration volume (in liters), and “V” is the post-dialysis urea distribution volume (in liters).

- Formula 2: This equation is used if “V” is not known:

$$\text{spKt/V} = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times \text{UF/W}$$

Where “W” is the post-dialysis weight. “V” can be assumed to be 55% of “W”.

- **Residual kidney function “RKF” (also called residual urea clearance “Kru”):** If the patient still urinates, measure the residual kidney function (see below to know how to measure Kru) to be added to the spKt/V:

- Patients dialyzing 3× weekly: Total combined spKt/V = spKt/V + [(5.5 × Kru)/V]
 - Patients dialyzing 2× weekly: Total combined spKt/V = spKt/V + [(9.5 × Kru)/V]

- **The online calculator by Daugirdas** mentioned before can be used to calculate spKt/V with or without Kru.

II-B. Equilibrated Kt/V urea (eKt/V) (also called two-pool or multi-pool Kt/V):

- **Main idea, and why is it called two-pool Kt/V?** As mentioned before, serum urea level increases 30-60 min after dialysis, reflecting the movement of urea from the “extravascular pool” to the “intravascular pool.” So, it is more accurate to use this raised urea blood level to get more accurate Kt/V, and this is done by using eKt/V. That is why it is called two-pool Kt/V, as it considers the urea movement from the “extravascular pool” to the “intravascular pool.”

- **Calculation:**

- **Formulas to calculate eKt/V urea:**

- Formula 1: Wait 30-60 min after dialysis to get the correct ideal urea concentration and use it in the same formulas mentioned above with spKt/V.
 - Formula 2: Due to the impracticality of waiting 30 minutes to obtain a post-dialysis blood urea sample, the eKt/V can be estimated from spKt/V. Based on urea modeling, a formula modified by Daugirdas can be used to predict the amount of rebound based on the rate of dialysis:

$$\text{eKt/V} = \text{spKt/V} \times \text{Td}/(\text{Td} + 30.7)$$

Where “Td” is the dialysis session length in minutes. 30.7 is a time constant.

- **Residual kidney function “RKF” (also called residual urea clearance “Kru”):** If the patient still urinates, measure the residual kidney function (see below to know how to measure Kru) and add it to the eKt/V by using the same formulas mentioned above with spKt/V.

- **The online calculator by Daugirdas** mentioned before can be used to calculate eKt/V with or without Kru.

- **Blood urea sampling precautions:** They are the same as those mentioned in Table 6.1.

- **Value:** The eKt/V is always significantly lower than spKt/V.

II-C. Standard Kt/V urea (stdKt/V):

- **Description:** The stdKt/V urea measures hemodialysis adequacy for one week of dialysis treatments.
- **Rationale:**
 - spKt/V and eKt/V are usually used to measure hemodialysis dose in patients with three times week dialysis. Nowadays, more frequent dialysis (maybe daily) has gained popularity. Frequent dialysis is associated with lower pre-dialysis blood urea, which leads to a lower spKt/V or eKt/V value, which does not truly reflect the correct dose of frequent dialysis.
 - The idea of the development of stdKt/V urea evolved from the need for a measure of hemodialysis adequacy that would not be influenced by the number of weekly treatments.
- **European best practice guidelines recommended that:**
 - For three times weekly dialysis, the dose should be quoted as eKt/V.
 - For hemodialysis schedules other than three times weekly, the dose should be quoted as weekly stdKt/V.
- **Calculation:**
 - **Formula to calculate stdKt/V:**

$$\text{stdKt/V} = \frac{10080 \frac{1 - e^{-\text{eKt/V}}}{t}}{\frac{1 - e^{-\text{eKt/V}}}{\text{spKt/V}} + \frac{10080}{Nt} - 1}$$

- “V” is the urea distribution volume (liters).
- “t” is the delivered treatment time (minutes): The delivered treatment time reflects the total time of administered dialysis in one week, excluding any time temporarily interrupted during the dialysis (e.g., the patient is using the bathroom in the middle of the session).
- “N” is the number of hemodialysis treatments in a week.
- **Residual kidney function “RKF” (also called residual urea clearance “Kru”):** If the patient still urinates, measure the residual kidney function (see below to know how to measure Kru) and add it to the stdKt/V by using the following formula:

$$\text{stdKt/V} = \frac{\left(\frac{10,080 \cdot \frac{1 - e^{-\text{eKt/V}}}{t}}{\frac{1 - e^{-\text{eKt/V}}}{\text{spKt/V}} + \frac{10,080}{Nt} - 1} \right)}{1 - \frac{0.74}{N} \cdot \frac{\text{UFw}}{V}} + \text{KRU} \cdot \left(\frac{0.974}{\text{spKt/V} + 1.62} + 0.4 \right) \cdot \frac{10,080}{V}$$

Where “UFw” is the number of hemodialysis treatments in a week.

- **The online calculator by Daugirdas** mentioned before can be used to calculate stdKt/V with or without Kru.

III. Online Kt/V urea

- The availability of hemodialysis machines equipped with software (online clearance monitoring [OCM] or Diascan) allows Kt/V calculation without the need for blood samples.
- Throughout dialysis treatment, the concentration of small molecular weight substances in the spent dialysate can be monitored by measuring its ultraviolet light absorbance as it exits the dialyzer.
- A blood urea concentration curve is generated during dialysis treatment and can be utilized to determine the online Kt/V.
- Online Kt/V urea must not replace the regular assessment of Kt/V by any of the previously mentioned methods.

IV. Formal urea kinetic modeling (UKM)

- Calculating Kt/V by formal urea kinetic modeling (UKM) was recommended by NKF-K/DOQI clinical practice guidelines for hemodialysis adequacy (update 2000). Unfortunately, the method of formal UKM determination is complex, and the computational software needed to calculate it is largely unavailable.
- Formal UKM is a method for describing and modeling the combined effects of urea clearance during hemodialysis sessions and urea generation (reflecting nutrition) in between dialysis sessions, hence providing a measure of both solute clearance and nutrition.
- The use of formal UKM to calculate Kt/V requires computerized software due to the complicated nature of the formulae utilized in this process.
- To calculate formal UKM, the following data are gathered from the patient across two dialysis sessions:
 - Data from the first dialysis treatment of a week:
 - Pre- and post-dialysis blood urea.
 - Pre- and post-dialysis weight.
 - Actual dialysis time in minutes.
 - Data from the second session: Pre-dialysis blood urea.
- If the patient still urinates, measure the residual kidney function “RKF” (also called residual urea clearance “Kru”) to be added to the Kt/V (see below to know how to measure Kru).
- The formal UKM computerized software proposes alterations to certain parameters (e.g., size or type of dialyzer, dialysis time) to improve solute removal and the delivered dialysis dose.

Recommended “Kt/V urea” target

- Kt/V should be done at least monthly.
- Some guidelines use spKt/V to assess dialysis adequacy, while others use eKt/V.
- Recommended targets of Kt/V in patients with no residual kidney function are described in Table 6.2, while those for patients with Kru are described in Table 6.3.

Table 6.2. Recommended Kt/V values in patients with no residual kidney function

Kt/V used	Recommendation
Guidelines using spKt/V	<ul style="list-style-type: none"> KDOQI clinical practice guideline for hemodialysis adequacy (2015 update) recommends a target spKt/V of 1.4 per hemodialysis session for patients treated thrice weekly, with a minimum delivered spKt/V of 1.2.
Guidelines using eKt/V	<ul style="list-style-type: none"> European best practice guidelines recommend that in anuric patients, treated by dialysis three times per week, the prescribed target eKt/V should be at least 1.2. Renal association clinical practice guideline recommends targeting dialysis dose to consistently achieve a minimum eKt/V of 1.2 for thrice weekly patients in the absence of a measured contribution from residual function.
stdKt/V target	<ul style="list-style-type: none"> KDOQI clinical practice guideline for hemodialysis adequacy (2015 update) recommends a target stdKt/V of 2.3 with a minimum delivered dose of 2.1.

Table 6.3. KDOQI clinical practice guidelines for hemodialysis adequacy (update 2006) recommendations for spKt/V targets in patients with residual kidney function

Dialysis frequency	Minimum (target) SpKt/V* when Kru is <2mL/min	Minimum (target) SpKt/V* when Kru is >2mL/min
2X/week	No recommendations	Kru <3: no recommendations Kru >3: 2.0
3X/week	1.2	0.9
4X/week	0.8	0.6
6X/week (short daily dialysis)	0.5	0.4

* Minimum spKt/V values recommended are corresponding to a weekly stdKt/V value of 2.0.

Limitations of Kt/V urea

Several researchers have questioned the utility of Kt/V as the preferred approach for evaluating the effectiveness of hemodialysis, given its constraints. The following are Kt/V limitations:

- The Kt/V ratio was established in a younger group of patients undergoing dialysis, with fewer comorbidities than the current dialysis patients.
- Kt/V ratio emerged during a time when cellulosic dialyzers with limited surface area and narrow pores were employed in dialysis treatments, but in the current era, high-flux dialyzers with larger surface areas and wider pores are widely used.
- Kt/V is derived from the kinetic patterns of a single solute, which is urea. Urea clearance measurement may not reflect the kinetic behavior of other potentially harmful substances.
- The measurement of Kt/V (away from stdKt/V) does not consider the missed treatments or the dialysis sessions that are shortened due to technical difficulties or other reasons.
- Kt/V overestimates the dose in small-sized or malnourished patients as they have low V.
- Kt/V does not consider other patient-specific factors that are linked to patient outcomes, such as volume control, hemodynamic instability, and alterations in biochemical parameters.

Factors affecting solute clearance and Kt/V

I- Effect of blood flow rate (QB) on solute clearance

- **Clearance of urea increases as blood flow rate (QB) increases:** If the dialyzer inlet blood urea level is 100 mg/dL and the outlet blood urea level is 40 mg/dL, the extraction ratio of urea is 60%. Therefore, a QB of 100 ml/min signifies that 60 ml of blood is cleared of urea, while a QB of 200 ml/min implies that 120 ml of blood is cleared of urea every minute.
- **The relationship between blood flow rate (QB) and solute clearance is not linear:** The clearance of urea increases as QB increases, but the relation is not linear all the way, and the clearance curve plateaus with higher QB (Figure 6.3). This means the dialyzer cannot clear plasma with the same efficiency with more increase in QB.
- **The usual blood flow rate (QB) range:** QB ranges from 200 to 500 ml/min during hemodialysis sessions (median rate about 350 ml/min).

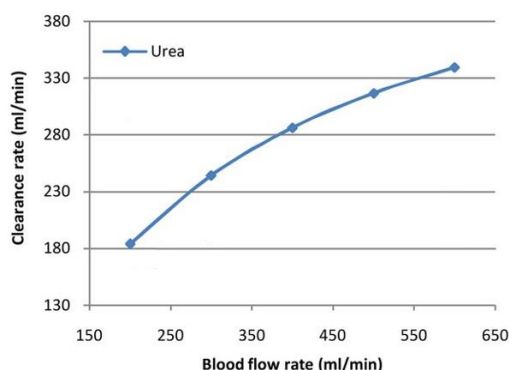


Figure 6.3. Effect of blood flow rate (QB) on dialyzer urea clearance (KD). *Derivative work (with modification) attributed to Md Shihamul Islam and Jerzy Szpunar. Reference: Open Journal of Nephrology, Vol. 3 No. 3, 2013, pp. 161-167. Doi: 10.4236/ojneph.2013.33029. Under license: CC BY 4.0 DEED. license link: <https://creativecommons.org/licenses/by/4.0/>*

II. Effect of dialysate flow rate (QD) on solute clearance

- **Clearance of urea increases as dialysate flow rate (QD) increases:** Improved efficiency in the removal and diffusion of urea from the blood is achieved with a quicker QD. (Figure 6.4).
- **The optimum dialysate flow rate (QD):** The ideal QD is 1.5 to 2 times the blood flow rate (QB), usually 500 mL/min.
- **The relationship between dialysate flow rate (QD) and solute clearance is not linear:** Clearance of urea increases as QD increases, but a greater increase in QD than the optimum rate (500 mL/min) will cause only a slight increase in clearance. As shown in Figure 6.4, raising the QD from 500 to 800 mL/min will result in a modest increase in urea clearance, ranging from 5% to 8%, when using a high-efficiency dialyzer and QB higher than 350 mL/min. So, the relation between QD and clearance is not linear as the clearance curve plateaus with higher QD.

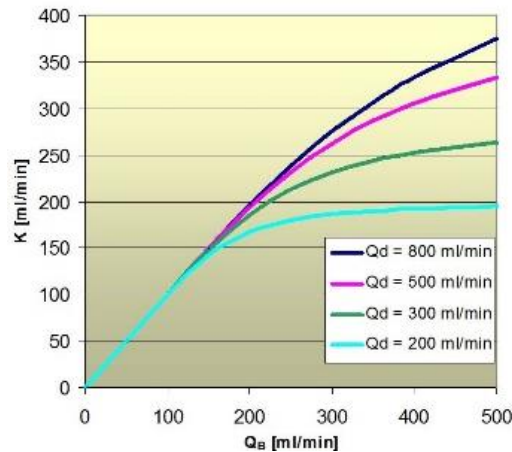


Figure 6.4. Effect of dialysate flow rates (QD) on urea clearance (K) at different blood flow rates (QB). *Attributed to Ahrenholz P, Winkler RE, Zende-Zartochti D. Reference: Updates in Hemodialysis. InTech; 2015. Available from: <http://dx.doi.org/10.5772/58878>. License type: CC BY 3.0 DEED. License link: <https://creativecommons.org/licenses/by/3.0/>*

III. Membrane efficiency

- As discussed in Chapter 5, dialyzer clearance depends on the membrane efficiency, which can be assessed by the mass transfer-area coefficient (KoA).
- Low-efficiency dialyzer membranes with low clearance have a KoA urea of <500 ml/min.
- High-efficiency dialyzer membranes with high clearance have a KoA urea of >600 ml/min.

IV. Clotted dialyzer fibers

In cases of dialyzer clotting, the dialyzer clearance of solutes decreases.

V. Duration of dialysis session

- A shorter duration of hemodialysis session will decrease solute clearance.
- Interrupted hemodialysis sessions with recurrent alarms can also affect solute clearance.

VI. Effect of erythrocytes (hematocrit) on solute clearance

- **Solute movement out of erythrocytes:** Solutes are cleared from plasma water when blood passes through the dialyzer. If a solute moves slowly from erythrocytes to plasma, the clearance of this solute decreases as hematocrit increases (since plasma volume decreases).
- **Examples:**
 - Urea is found in both plasma water and erythrocytes, and the rate at which it crosses the erythrocyte membrane is rapid (Figure 6.5). This is why the removal of urea from whole blood during dialysis is not significantly impacted by the hematocrit and is maintained at a consistent level.
 - Creatinine, phosphorus, and some other solutes slowly flux across the erythrocyte membrane. This means that their clearance decreases as hematocrit increases.

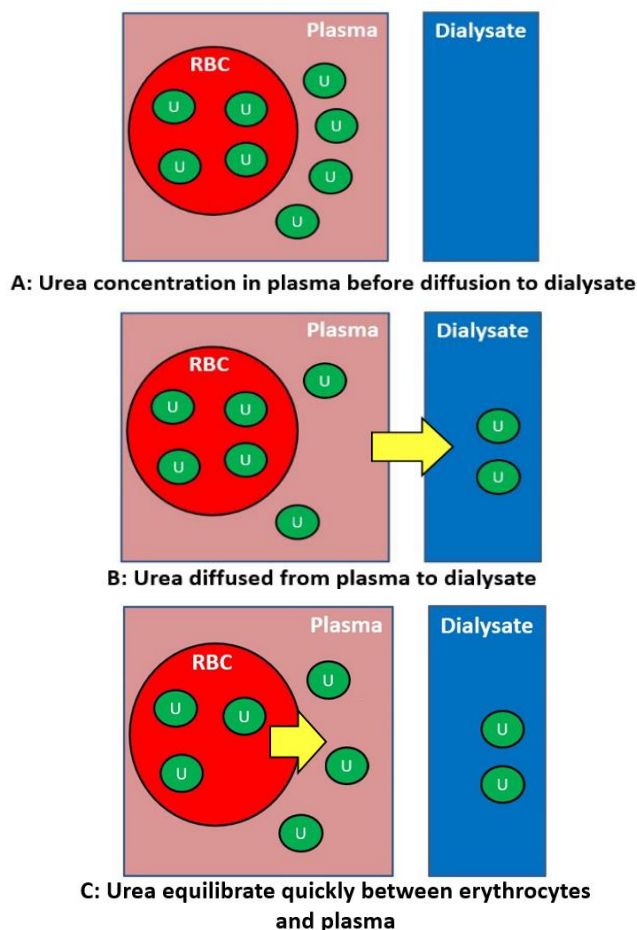


Figure 6.5. Urea equilibration between plasma and erythrocytes

VI. Effect of solute distribution on clearance

- Solutes that are mainly intracellular, such as phosphate (PO_4), can experience a rapid decline in plasma levels during dialysis but without significant overall removal from the body (even with using a dialyzer with a high PO_4 clearance). This is because the diffusion of these solutes from extravascular to intravascular space is very slow. Prolonging the duration of dialysis sessions and/or frequent dialysis sessions has a good impact on the overall removal of these solutes from the body.
- Potassium ion has the same issue of slow diffusion from extravascular to intravascular space. That explains the rebound hyperkalemia occurs after dialyzing a patient with hyperkalemia, although the potassium serum level decreases immediately after the dialysis session. So, it is advised to monitor serum potassium some hours later after dialysis of hyperkalemic patients to detect this rebound.

VII. Access recirculation

In the presence of AV access recirculation (it will be discussed in Chapter 10), the dialyzer clearance of solutes decreases.

VIII. Cardiopulmonary recirculation (arteriovenous disequilibrium)

- **In the case of arteriovenous (AV) access (arteriovenous fistula or graft) (Figure 6.6):**
 - Peripheral veins from tissues carry blood with high urea concentration and drain it into central veins.
 - The dialyzed blood (with a low urea concentration) returns to the central veins and dilutes the blood in them, causing lower urea concentration in central veins than in peripheral venous blood.
 - The diluted blood in central veins with low urea concentration is sent directly to the heart and lungs and from there to the hemodialysis access without passing through the tissues.
 - So, the blood entering the hemodialysis access has a lower urea concentration than peripheral venous blood. This is why it is important during post-dialysis urea sampling (for Kt/V calculation) to slow the blood pump to 50mL/min (Table 6.1). Slowing the blood pump decreases the urea clearance and allows its accumulation to overcome the effect of cardiopulmonary recirculation.
- **In the case of the venous catheter (Figure 6.7):** With the use of a venous catheter, cardiopulmonary recirculation cannot occur. This is because the catheter is fed with venous blood coming from tissues rich in urea blood.

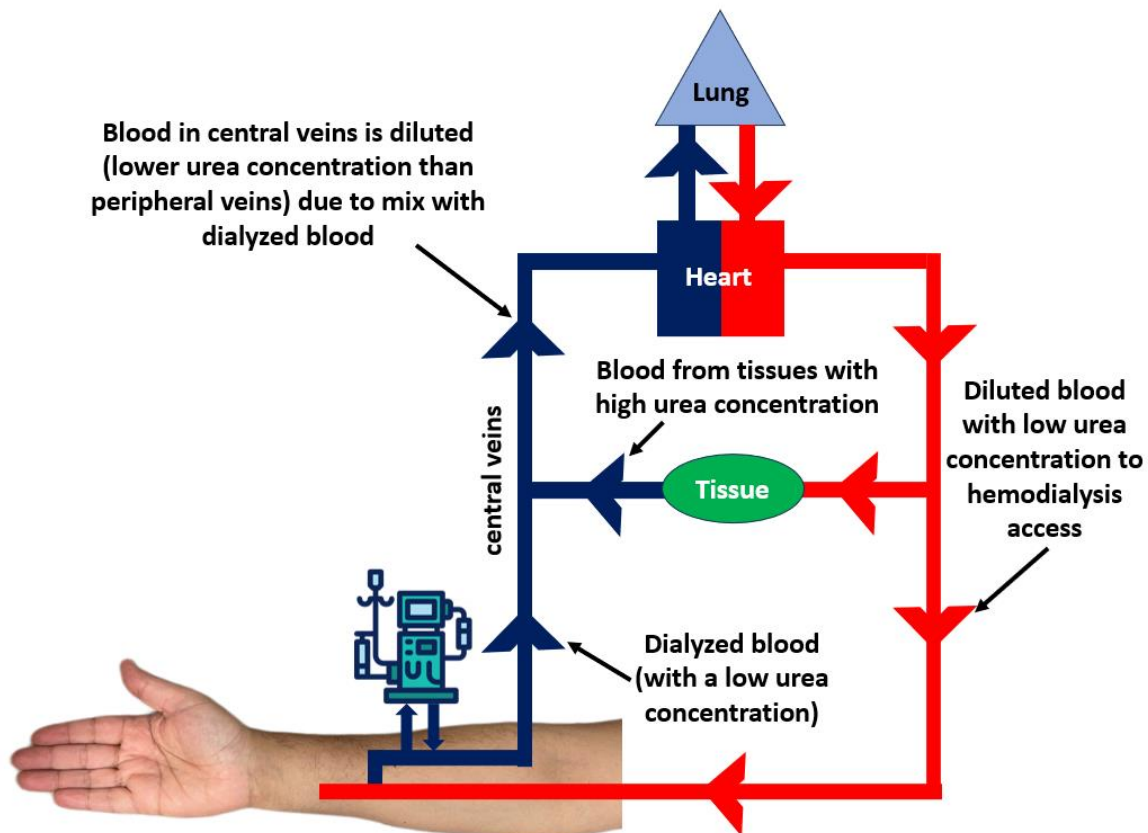


Figure 6.6. Cardiopulmonary recirculation in the case of arteriovenous (AV) access

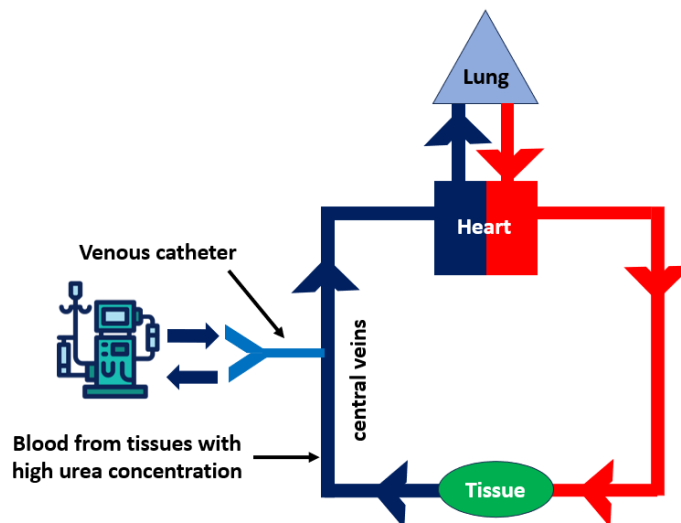


Figure 6.7. Absence of cardiopulmonary recirculation effect in the case of venous catheter

Causes of low Kt/V

From the previously discussed factors affecting solute clearance, we can conclude that the following are the causes of low Kt/V:

- 1- Low blood flow rate (QB).
- 2- Low dialysate flow rate (QD).
- 3- Clotted dialyzer fibers.
- 4- Short duration of dialysis session (e.g., early session termination due to intradialytic complications).
- 5- Access recirculation.
- 6- Error in blood sampling.

Methods to measure hemodialysis dose rather than “Kt/V urea”

I. Urea reduction ratio (URR)

- **Main idea:** Urea serum level is reduced after dialysis session. The degree to which its reduction occurs post-dialysis can be utilized to evaluate the dialysis dose.
- **Calculation:** Urea reduction ratio (URR) = $\{(pre-dialysis \text{ BUN concentration} - post-dialysis \text{ BUN concentration}) / pre-dialysis \text{ BUN concentration}\} \times 100$
- **Accepted percentage:** The minimum acceptable level of URR for adequate dialysis is generally 65% or higher.
- **URR pitfalls:** Using URR to measure dialysis adequacy only includes the rate of urea clearance by dialysis, and it does not include duration of dialysis, volume of ultrafiltration, volume of urea distribution, and rate of urea generation between dialysis sessions.

II. Solute removal index (SRI)

- SRI assesses the complete amount of urea eliminated during dialysis. It is calculated by multiplying the urea concentration in the dialysate by the volume of spent dialysate.
- Although SRI does not require blood sampling, it is not used as it has the following limitations:
 - Few studies have correlated patient outcomes with the SRI.
 - Collecting the outflow dialysate is not practical.
 - SRI is relatively inaccurate compared to the use of calculated from eKt/V .
- Some hemodialysis machines provide an online measurement of SRI.

Residual kidney function “RKF” (Residual urea clearance “Kru”) method of calculation

- **Definition:** Residual kidney function “RKF” (also called residual urea clearance “Kru”) is the remaining ability of the diseased kidneys to excrete water and uremic solutes.
- **Kru effect:** After the initiation of dialysis, some patients may have Kru that is sufficient to significantly improve overall uremic control and reduce the need for treatment.
- **Changing dialysis time or frequency based on Kru:** It is not recommended to reduce treatment time or frequency based on Kru unless its measurements are repeated monthly, as the risk of under-dialysis is high if there is an unexpected decline of Kru.
- **Collect the following for the calculation of Kru (Figure 6.8):**
 - Post-dialysis blood urea measurement of a session (BUN1).
 - When a post-dialysis blood sample is collected for blood urea, the patient must empty his bladder, and the urine is discarded. From this time, all urine must be collected and brought to the dialysis unit when the patient returns for the next dialysis.
 - Pre-dialysis blood urea measurement before the next session (BUN2).

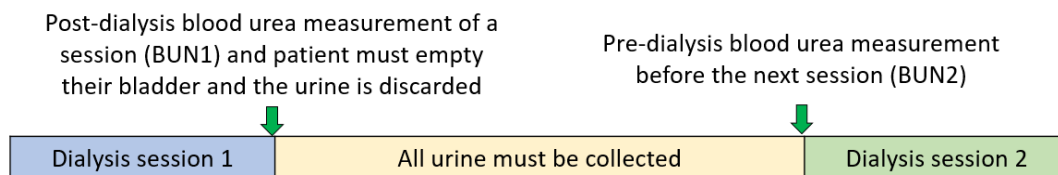


Figure 6.8. Sampling for residual renal function calculation

- **Kru calculation:**
 - Kru calculation formula:

$$\text{Interdialytic urine volume (mL)} \times \text{Urine urea concentration (mg/dL)} / \text{intradialytic period (minutes)} / \text{mean BUN between BUN2 and BUN1 (mg/dL)}$$
 - An online calculator is available to calculate Kru:
www.mdapp.co/hemodialysis-residual-renal-function-calculator-313/
- **Unit:** Kru is expressed in mL/min.



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Chapter 7

Anticoagulation For Hemodialysis Procedure

- Contact of the blood with a foreign surface leads to clotting due to the activation of the intrinsic coagulation pathway. To ensure that the dialysis process can continue, it is essential to prevent clotting from occurring.
- Clotting of the dialyzer fibers may lead to under-dialysis.
- Different methods used for anticoagulation during hemodialysis sessions are discussed in this chapter.

Heparin anticoagulation

Heparin is the most commonly used anticoagulant in dialysis. It can be administered in the form of either unfractionated or low molecular weight heparin.

Unfractionated heparin (UFH)

Mechanism of UFH anticoagulant action (Figure 7.1): Unfractionated heparin (UFH) activates antithrombin and then binds with thrombin and factor Xa to inactivate them.

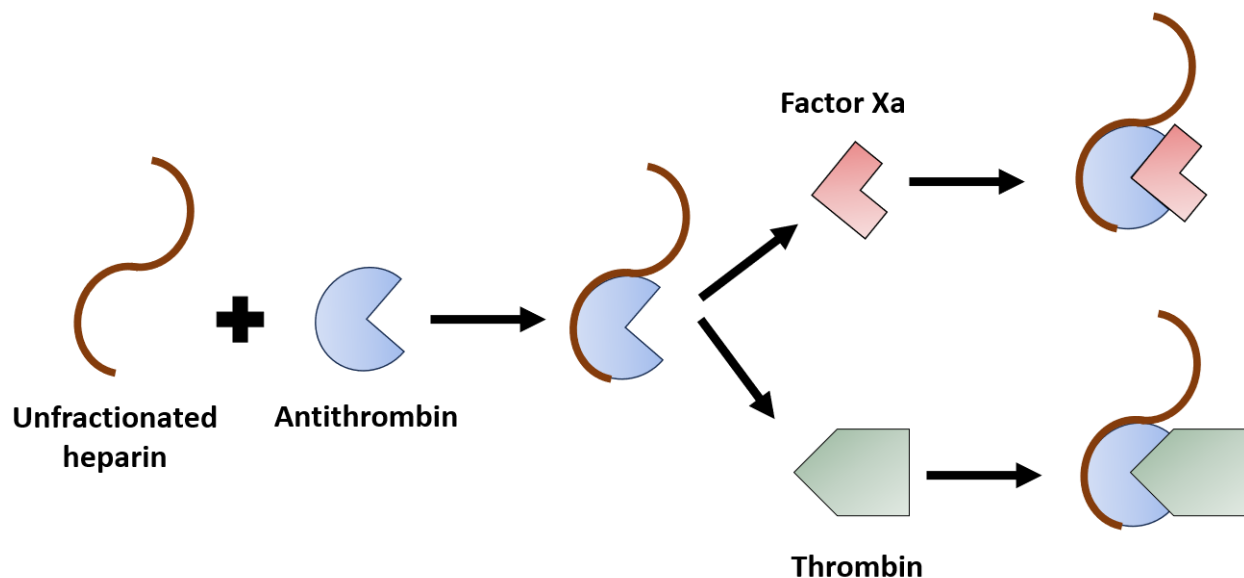


Figure 7.1. Unfractionated heparin mechanism of action

Unfractionated heparin anticoagulation dosing protocols:

- Different methods for using UFH as an anticoagulant in hemodialysis are summarized in Table 7.1, and each method is described separately in Tables 7.2 and 7.3. Some units develop their own UFH anticoagulation method that may differ from the methods discussed below.

- **Initial bolus dose administration:**

- In all methods (Table 7.1 to Table 7.3), it is preferred to administer the initial bolus heparin dose to the patient through the venous access needle of the venous limb of the dialysis catheter. Flush the venous access with saline after heparin administration, then wait for 3-5 minutes to permit heparin to disperse within the patient's vascular system before commencing dialysis.
- It is not preferred to administer heparin through the arterial line. Administering heparin into the arterial blood line requires that the non-heparinized blood from the patient be pumped through the dialyzer until the initial dose of heparin has passed through the extracorporeal circuit and reached the patient's body to anticoagulate the blood in their vascular system.

Table 7.1. Methods to use unfractionated heparin use during hemodialysis session

	Initial bolus	Followed by
Method A	Routine heparin (Initial routine bolus dose)	Constant infusion
Method B	Routine heparin (Initial routine bolus dose)	Single heparin dose
Method C	Routine heparin (Initial routine bolus dose)	Repeated heparin boluses
Method D	Routine heparin (Initial routine bolus dose)	No boluses

Table 7.2. Method A: Routine heparin (initial routine bolus dose) followed by constant infusion

Routine heparin (Initial routine bolus dose)	Followed by a constant infusion dose	When to stop heparin infusion?
2000 IU	1,200 IU/h	Stop heparin infusion one hour before the end of dialysis to reach the desired clotting time at the termination of the session (see Table 7.5 for the desired clotting time).
75–100 IU/kg	700–750 IU/h	

Table 7.3. Method B, C, and D of heparin administration during dialysis procedure

Method	Routine heparin (Initial routine bolus dose)	Followed by	When to stop heparin boluses?
Method B	4000 IU	1000-2000 IU bolus if necessary	Stop heparin boluses one hour before the end of dialysis to reach the desired clotting time at the termination of the session (see Table 7.5 for the desired clotting time).
Method C	2000 IU	1000 IU bolus at start of 2 nd , 3 rd , and 4 th hour.	
Method D	2000 IU	No repeated boluses	

Monitoring UFH efficacy:

- Clotting tests and their desired ranges for monitoring the UFH anticoagulant effect are described in Table 7.4.
- In clinical practice, UFH is typically prescribed without monitoring coagulation test, and the effectiveness of UFH anticoagulation is assessed by inspecting the dialyzer and drip chambers at the end of dialysis for any signs of clotting (see signs of clotting below).

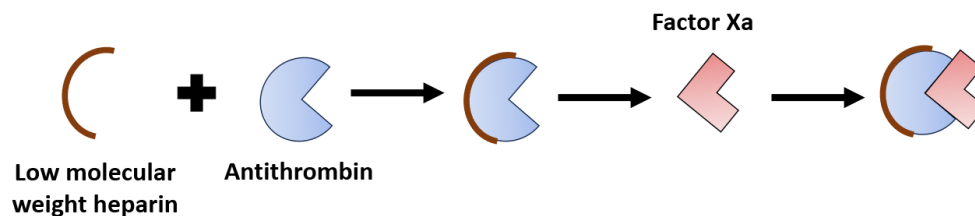
Table 7.4. Desired ranges of clotting tests for monitoring of unfractionated heparin during hemodialysis

Test	Desired ranges of clotting tests	
	During dialysis	At the end of dialysis
aPPT (activated partial thromboplastin clotting time)	2.0-2.5	1.5-2.0
ACT (activated clotting time)	+80%	+40%

UFH antidote: Reversal of the UFH effect can be done by using protamine sulfate.

Low molecular weight heparin (LMWH)

Mechanism of action (Figure 7.2): Low molecular weight heparin (LMWH) activates antithrombin and binds factor Xa to inactivate it.

**Figure 7.2. Low molecular weight heparin mechanism of action****Dose of LMWH for hemodialysis session anticoagulation:**

LMWH has a longer half-life than UFH, which allows for anticoagulation with a single bolus dose administered at the start of dialysis (Table 7.5).

Table 7.5. Low molecular weight heparin dose for hemodialysis anticoagulation

Low Molecular Weight Heparin	Bolus dose
Enoxaparin	0.5-0.8 mg/kg
Tinzaparin	1500-3500 IU
Reviparin	85 IU/kg
Nadroparin	70 IU/kg
Dalteparin	5000 IU
Logiparin	3000-4000 IU

Monitoring LMWH efficacy:

- The effectiveness of LMWH is typically determined by measuring anti-Xa activity, which is not commonly available and is not assessed routinely.
- In practice, as in the case of UFH, the efficacy of LMWH anticoagulation effect is assessed by inspecting the dialyzer and drip chambers at the end of dialysis for any signs of clotting (see signs of clotting below).

LMWH antidote: No antidote is available for LMWH.

Unfractionated heparin (UFH) versus Low molecular weight heparin (LMWH)

- Theoretically, LMWH has a longer half-life, more rapid onset of action, higher bioavailability, and more predictable effects than UFH.
- Some complications are less frequent with LMWH than with UFH (see below).
- Regarding bleeding and extracorporeal clotting risks, available evidence showed no significant differences between UFH and LMWH. As LMWH is very expensive and has generally not been found to be superior to UFH, so UFH is widely used.

Heparin dose for hemodialysis anticoagulation in patients on oral anticoagulants or antiplatelet agents

- Patients taking **coumarin** with an INR of less than 2.5 typically need anticoagulation during dialysis. Those with metallic heart valves with INR values greater than 3.0 generally do not require heparin.
- Patients who are prescribed **aspirin and other antiplatelet medications** typically need to receive standard heparin dosages. However, it is necessary to decrease or withhold heparin doses in individuals with thrombocytopenia (platelets less than $50,000 \times 10^6/L$).
- No precise data about new oral anticoagulants is available, and caution is recommended while using them.

Complications of heparinization

- **Bleeding:**
 - Heparin anticoagulation poses a risk of bleeding due to its effects on both the patient's intravascular blood and the extracorporeal circuit.
 - Thus, in the presence of active bleeding or risk of bleeding, heparin cannot be used (see indications of heparin-free dialysis below).
 - If there is post-dialysis therapy needle puncture site prolonged bleeding (>20 minutes), consider the following before deciding to stop heparin use:
 - Re-evaluate the dose of heparin.
 - Evaluate vascular access for the possibility of outflow stenosis.
 - Evaluate the needle insertion technique.
 - Check if the patient is on oral anticoagulants.

- **Heparin-induced thrombocytopenia (HIT):**
 - HIT is less with LMWH. However, LMWH must not be used in HIT as a substitution for UFH because of cross-reactive antibodies that will induce HIT.
 - HIT is of 2 types:
 - HIT type I:
 - It is a mild, transient, and self-limited drop in platelet count that typically occurs within the first two days of UFH exposure.
 - It appears to result from nonimmune platelet aggregation by a direct effect on platelets.
 - No change in dialysis-related anticoagulation management is warranted for HIT type 1.
 - HIT type II:
 - It is a clinically significant condition.
 - It results from antibodies to platelet factor 4 (PF4) complexed to UFH, referred to as "HIT antibodies" or "PF4/heparin antibodies." These antibodies can cause thrombosis and thrombocytopenia.
 - Suspected or confirmed HIT type 2 warrants anticoagulation using a non-heparin strategy and a non-heparin catheter lock at the end of a dialysis session.
- **Lipid disorders:**
 - Hypertriglyceridemia (less with LMWH use).
 - Low HDL levels (less with LMWH use).
- **Osteoporosis** (less with LMWH use).
- **Hyperkalemia:** heparin-induced suppression of aldosterone synthesis (less with LMWH use).
- **Pruritus.**
- **Alopecia.**
- **Anaphylactoid reactions (First use syndrome).**

Clotting despite anticoagulation

Signs of clotting:

- Very dark blood in the circuit.
- Visible clots in drip chambers and may be in venous line.
- Dialyzer clotting is associated with one or more of the following:
 - Streaking in dialyzer.
 - Visible clots in the arterial side header of the dialyzer.
 - Increase arterial pressure and decrease venous pressure (both occur if clotting is between dialyzer and venous pressure monitor).
- Clotting distal to the venous chamber is associated with increased venous and arterial pressure monitored by the machine.

If there is evidence of clotting despite anticoagulation, searching for the cause of clotting is mandatory. Suggested causes of clotting are:

- Incorrect heparin administration (e.g., problem with heparin pump infusion).
- Incorrect heparin dose.
- Slow blood flow.
- Excessive ultrafiltration.
- Vascular access problems (e.g., inadequate blood flow from the vascular access or excessive access recirculation)
- Kinking of blood lines.
- Air trapping inside the dialyzer, which typically results from inadequate priming.
- Multiple interruptions of dialysis sessions due to frequent alarms.

Heparin-free dialysis

Indications of heparin-free dialysis

- Bleeding disorder.
- Active bleeding.
- Intracerebral hemorrhage.
- Thrombocytopenia.
- Pericarditis.
- Recent surgery.

Steps of heparin-free dialysis method

Steps for the heparin-free dialysis method are described in Figure 7.3.

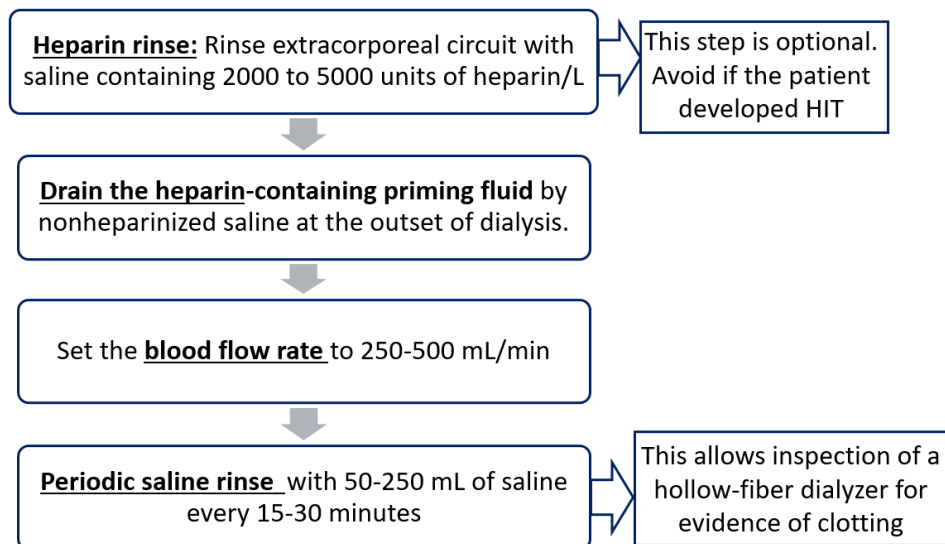


Figure 7.3. Steps of heparin-free dialysis method

Regional citrate anticoagulation (RCA)

Regional citrate anticoagulation is not usually used for conventional intermittent hemodialysis but is more frequently used for continuous kidney replacement therapy (CKRT).

Mechanism of action

Citrate binds calcium (an essential factor for clotting) in the extracorporeal circuit blood and inhibits it. Citrate anticoagulates only the extracorporeal system blood and doesn't anticoagulate the patient's intravascular blood.

Methods of regional citrate anticoagulation (RCA)

Two methods of RCA are commonly used, which are the traditional and modified methods.

I. Traditional method (Figure 7.4):

- **Steps:**
 - Citrate is infused in the extracorporeal circuit's arterial segment. Citrate binds with calcium and prevents the calcium clotting effect.
 - Infuse calcium in the extracorporeal circuit's venous segment before blood is returned to the patient to restore the ionized calcium. If blood is returned to a patient with a low calcium level, it can result in fatal cardiac arrhythmias.
 - Calcium-free dialysate is used to avoid overloading the patient with calcium in addition to the venous-infused calcium.
- **Infused citrate may be in the form of:**
 - Trisodium citrate solution (increases the risk of cardiac arrhythmia).
 - 4% citrate solution: it replaced the use of tri-sodium citrate.

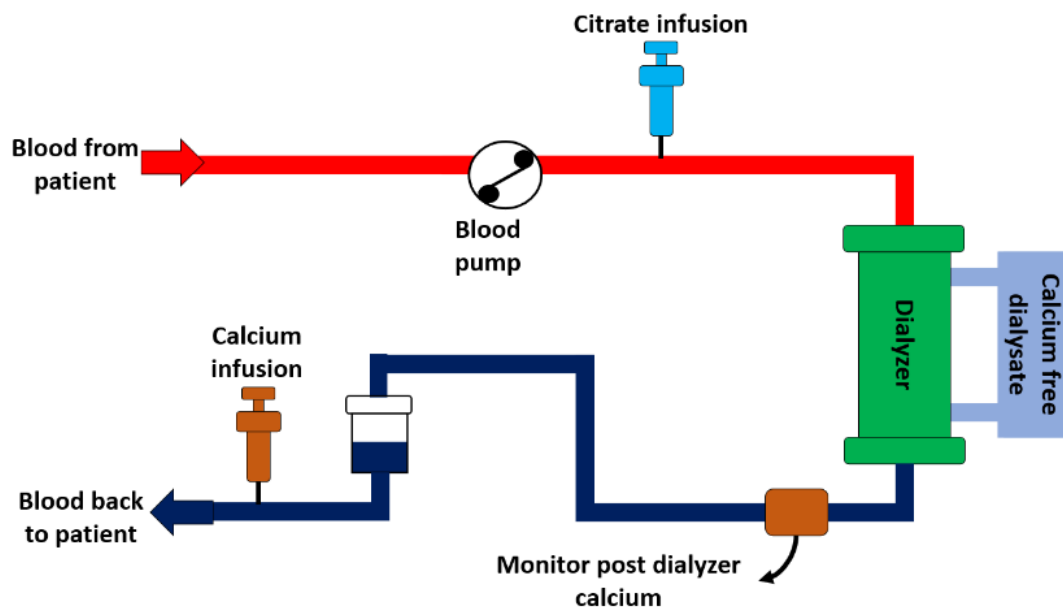


Figure 7.4. Regional citrate anticoagulation (RCA)

II. Modified method:

- Citrate anticoagulation with a calcium-containing dialysate and without calcium infusion has been successfully employed.
- The main aim of this technique is to simplify the procedure.
- The close monitoring of serum calcium levels is still essential.

Complications of regional citrate anticoagulation (RCA)

- Calcium disorder:
 - Hypocalcemia (due to calcium citrate complex).
 - Hypercalcemia (due to calcium infusion as a replacement).
- Arrhythmia.
- Hyponatremia:
 - Due to the use of hypertonic sodium citrate solution.
 - Avoid hyponatremia by making the citrate solution in aqueous dextrose solution.
- Metabolic alkalosis:
 - This is because citrate is metabolized in the liver to bicarbonate.
 - Avoid metabolic alkalosis by reducing the dialysis solution bicarbonate level to about 25 mEq/L.

Regional citrate anticoagulation (RCA) versus Heparin anticoagulation

- RCA is more expensive than heparin.
- RCA use is more complex than heparin use.
- Bleeding risk:
 - RCA reduces bleeding risk as it anticoagulates only the extracorporeal system.
 - Heparin anticoagulates both the extracorporeal system and the patient's intravascular blood.
- RCA has similar or better efficacy on circuit patency than heparin.
- RCA diminishes complement and neutrophil activation in the extracorporeal circuit.

Local citrate anticoagulation

- As discussed in Chapter 4 (Table 4.2), some dialysate contains citrate as an acidifying agent that prevents the precipitation of CaCO_3 and MgCO_3 .
- Citrate has been shown to bind with calcium at the site of the dialyzer membrane, which helps to prevent the clotting of the dialyzer capillary fibers and its pores.
- The use of citrate as an acidifying agent in dialysate has the following advantages:
 - Prevent dialyzer clotting.
 - Increase in the dialysis delivered dose.
 - Increase in solute transport.

Heparinoids (Danaparoid and Fondaparinux)

Doses and differences between danaparoid and fondaparinux are described in Table 7.6.

Table 7.6. Heparinoids used as anticoagulants during hemodialysis sessions

	Danaparoid	Fondaparinux
Mechanism of action	It acts by blocking factor Xa activity (Figure 7.5).	It binds antithrombin and accelerates its inhibition of factor Xa (Figure 7.5).
Formed of	It is a mixture of 84% heparin, 12% dermatan, and 4% chondroitin sulfates.	It is formed of synthetic pentasaccharides.
Cross-reaction with heparin-induced thrombocytopenia (HIT) antibodies	The potential for cross-reactivity with HIT antibodies exists in approximately 10% of cases. So, it is better to avoid its use in patients with HIT.	It does not cross-react with HIT antibodies. So it can be used in patients with HIT.
Pre-dialysis loading dose	In patients >55 kg: 750-IU. In patients ≤55 Kg: 500 IU.	2.5–5.0 mg.
Maintenance dose	Subsequent doses are titrated to achieve an anti-Xa activity of 0.4–0.6 post bolus.	It has an extended half-life, so there is no need for a maintenance dose.
Monitoring	The half-life of both substances is prolonged in renal failure due to their renal excretion, which increases the risk of bleeding. Monitoring is often employed to evaluate anti-Xa activity before the subsequent dialysis session to achieve a predialysis anti-Xa level of ≤0.2 IU/mL.	

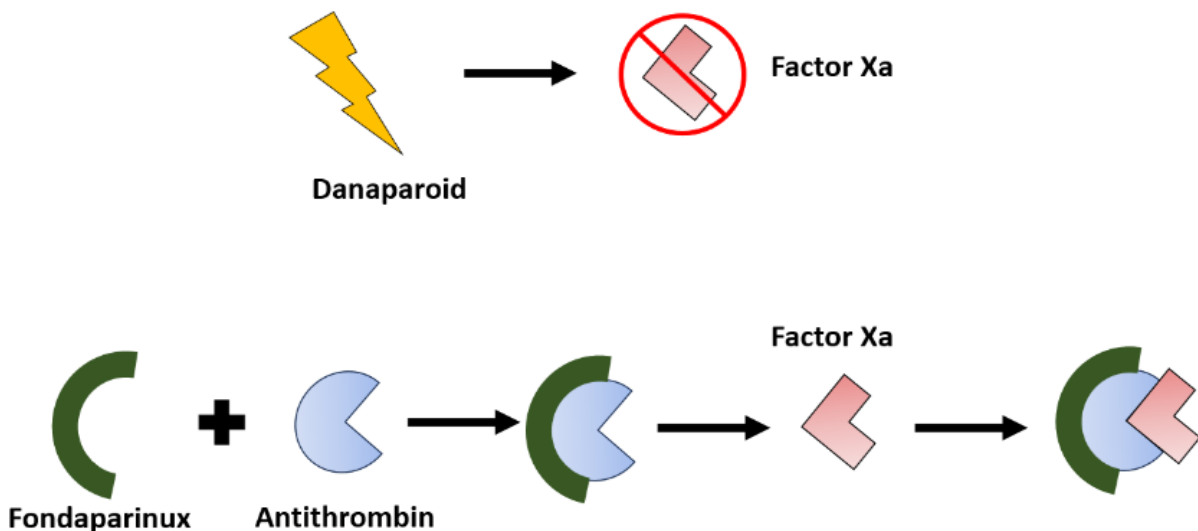


Figure 7.5. Heparinoids mechanism of action

Direct thrombin inhibitors

- Direct thrombin inhibitors are mainly used in patients who develop heparin-induced thrombocytopenia (HIT).
- They act by directly inhibiting thrombin. Different direct thrombin inhibitors are discussed below.

I. Argatroban

- **Dose:**
 - Initial bolus dose of 250µg/kg.
 - Followed by an infusion at a rate of 2µg/kg/min or 6–15 mg/hour.
- **When to stop:** 30 minutes before the end of the dialysis session.
- **Monitoring (target):** aPPT 2.0–2.5 times normal during the dialysis session.
- **Precaution:** This synthetic compound is metabolized in the liver and cannot be safely administered to patients with liver failure.

II. Lepirudin (recombinant hirudin)

- **Dose:** It is given as a single dose of 0.08-0.1 mg/kg at the beginning of dialysis treatment.
- **Monitoring (target):**
 - aPPT < 1.5 times normal pre-dialysis.
 - Around one-third of patients have been found to develop hirudin antibodies, which enhance its anticoagulant action.
- **Disadvantages:**
 - It has a prolonged half-life in dialysis patients because it is renally excreted. This carries a high bleeding risk.
 - It is more expensive than heparin.
 - No antidote is available for recombinant hirudin.

III. Bivalirudin

- **Dose:** It is given as an infusion at 1.0–2.5 mg/hour (0.009–0.023 mg/kg/hour).
- **Monitoring (target):** aPPT of around 1.5–2.0 times normal during dialysis session.

Other anticoagulants

I. Prostacyclin (PGI₂) and its synthetic derivative Epoprostenol

- It inhibits platelet aggregation and adhesion.
- PGI₂ is a potent vasodilator.
- It may cause hypotension.

II. Nafamostat mesylate

- Synthetic serine protease inhibitor.
- It does not cause hypotension.
- Several side effects have been reported, such as anaphylaxis, agranulocytosis, and hyperkalemia.

III. Heparin-coated dialyzers

Heparin is a negatively charged molecule that can adsorb to the surface of dialyzer membranes. This helps the development of heparin-coated dialyzer membranes, which have been reported to allow dialysis without the use of heparin or with the use of reduced heparin levels.

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Chapter 8

Complications During Hemodialysis

This chapter discusses complications that occur during the hemodialysis session or immediately after it.

Intradialytic hypotension (IDH)

Definitions of intradialytic hypotension (IDH)

No single definition of intradialytic hypotension is known; multiple definitions exist. Below are two commonly used definitions:

- **K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients (2005) and European Best Practice Guidelines (2007)** define IDH as a decrease in systolic BP ≥ 20 mmHg or a decrease in mean arterial pressure (MAP) by 10 mmHg associated with clinical events and need for nursing interventions.
- **Another definition** considers IDH if there is a reduction in systolic blood pressure to below 90 mmHg. This definition has the most pronounced correlation with an elevated risk of death.

Incidence of IDH

- IDH is the most common intradialytic complication.
- It has been observed that the incidence of IDH in various patient populations with end-stage kidney disease (ESKD) ranges from 5 to 40 percent.

Manifestations of IDH

- **Common symptoms:**
 - Dizziness.
 - Light-headed.
 - Nausea.
 - Vomiting.
 - Muscle cramps.
 - Lack of alertness.
 - Visual impairment.
 - Complete collapse and unresponsiveness.
- **There may be no symptoms present:**
 - Some patients may have no symptoms until their blood pressure drops to dangerously low levels.
 - Therefore, blood pressure must be consistently monitored during the hemodialysis session.

Consequences of IDH

Long-term prognosis is unfavorable in individuals with IDH:

- IDH is associated with increased mortality.
- IDH can cause organ stunning:
 - Organ stunning is defined as ischemia and oxygen starvation of organs and tissues.
 - Organ stunning has bad consequences in the long term.
 - Myocardial stunning is associated with cardiac wall motion abnormalities.
- Vascular access thrombosis is an additional complication caused by IDH.

Mechanisms responsible for the development of IDH

I. Factors related to blood volume changes:

1. Rapid ultrafiltration (UF) rate:

- **Normal effect of UF (Figure 8.1-A):**
 - During hemodialysis, UF removes the fluid excess from the plasma space, leading to a decrease in plasma volume.
 - When there is a drop in plasma volume, water moves from the extravascular compartment into the plasma to re-fill it.
- **Effect of rapid UF rate (Figure 8.1-B):**
 - In the case of rapid UF, the rate of fluid removal from the plasma compartment (UF rate) exceeds the rate at which fluid re-fills the plasma from the extravascular compartment. This will cause hypovolemia and hypotension.
 - The accepted UF rate is 10-13 mL/kg/h (0.5 to 1.2 L/h).

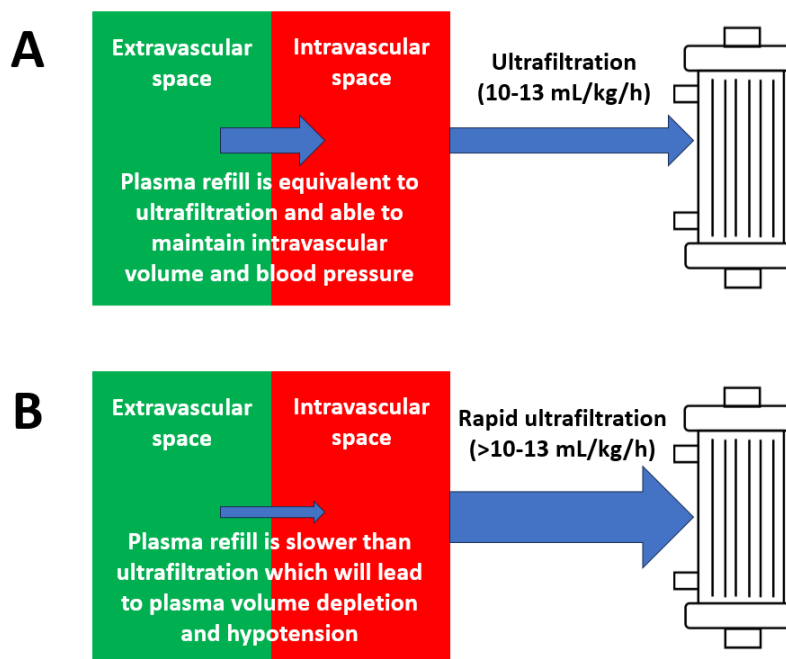


Figure 8.1. Effect of ultrafiltration rate on plasma refill and blood pressure

2. Large interdialytic weight gains (IDWG):

- Rapid UF rate, as discussed above, is primarily caused by large IDWG.
- This large IDWG, if removed by rapid UF on a 4-hour dialysis session, will cause a UF rate greater than the rate of vascular space re-fill from ECF, so the plasma volume is decreased, which causes hypotension.

3. Ultrafiltration (UF) below the patient's dry weight: If there is more UF, although the patient's dry weight is reached, hypovolemia and hypotension will occur.

4. Dialysate sodium level and its effect on blood volume:

- **Low dialysate sodium level (Figure 8.2):** A dialysate sodium concentration below that of plasma will result in hypotonic blood returning from the dialyzer compared to the extracellular space fluid. This osmotic difference will cause water to move from the vascular to the extracellular space, which will decrease the blood volume.
- **High dialysate sodium level:** This will lead to increased post-dialysis thirst and water intake, which will increase IDWG.
- **A recent randomized control study (Miskulin et al. 2024) showed that:**
 - The use of a dialysate sodium of 135 mEq/L as compared with 138 mEq/L was associated with:
 - Small reduction in interdialytic weight gain.
 - No difference in the rate of IDH.
 - No difference in the predialysis blood pressure (BP) level.
 - Increase in IDH-related symptoms.
 - Raising dialysate sodium from 135 to 140mEq/L was associated with:
 - Small increase in interdialytic weight gain.
 - Reduction in the rate of IDH.
 - Marked increase in predialysis BP level.

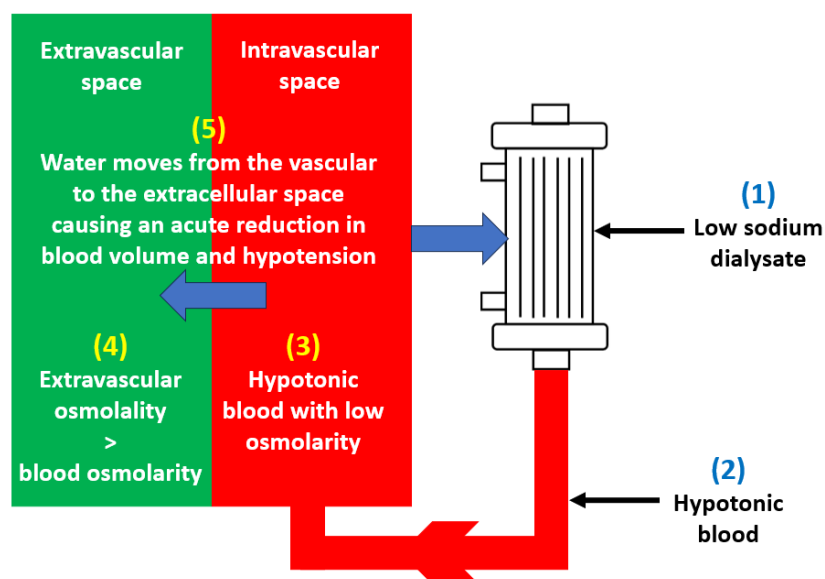


Figure 8.2. Effect of low dialysate sodium level on blood volume and blood pressure

II. Lack of vasoconstriction:

Total peripheral resistance (TPR) is determined by the degree of arteriolar constriction, which is essential because it determines blood pressure. A decrease in TPR (due to vasodilatation) will cause a reduction in blood pressure. Factors decreasing TPR in hemodialysis patients are discussed below.

1. **High dialysate temperature:** Cutaneous vasodilation occurs when the dialysate temperature exceeds the ideal range (35–38°C). This vasodilation reduces vascular resistance and predisposes the patient to hypotension.
2. **Low dialysate potassium level:** IDH is more prevalent in dialysate with a potassium concentration of 1 mEq/L.
3. **Food ingestion:**
 - Eating while undergoing hemodialysis causes vasodilation of arterioles in the splanchnic area; this results in a decrease in TPR and an increase in splanchnic venous capacity.
 - The increase in splanchnic venous capacity steals blood from the systemic circulation, causing volume depletion and hypotension.
 - The effect of eating on blood pressure likely persists for a minimum of two hours. Individuals at risk for IDH should avoid consuming food immediately before or during the hemodialysis procedure.
4. **Anemia:** It induces vasodilation and increases the risk of hypotension.
5. **Autonomic dysfunction:**
 - Autonomic dysfunction affects the ability to increase vascular resistance and heart rate.
 - This is observed in more than half of dialysis patients. Individuals who have diabetes mellitus are especially susceptible to developing autonomic neuropathy.
6. **Antihypertensive medications:** The administration of antihypertensive drugs before dialysis may inhibit the body's normal physiologic response to volume contraction that occurs during ultrafiltration.

III. Cardiac factors:

1. **Diastolic dysfunction:**
 - Diastolic dysfunction refers to abnormalities in myocardial relaxation, compliance, and filling, which will cause a reduction in cardiac output.
 - Patients undergoing dialysis frequently experience diastolic dysfunction as a result of hypertension, coronary artery disease, and uremia.
2. **Low dialysate calcium concentration:** A low dialysate calcium concentration of 1.25 mmol/L is associated with lower cardiac contractility.
3. **Abnormal cardiac compensatory mechanisms:** Normal compensatory mechanisms for plasma volume reductions include increased heart rate, cardiac contraction, and vascular resistance. However, these responses are abnormal and inadequate in response to ultrafiltration in dialysis patients.

IV. Adenosine release:

- **Adenosine release:** Adenosine is released from tissues secondary to ischemia that occurs during hypotension.
- **Adenosine causes the following:**
 - It blocks the release of norepinephrine from sympathetic nerve terminals, which leads to vasodilation and hypotension.
 - Adenosine itself has a vasodilator effect.

V. Vasopressin level:

- Vasopressin constricts splanchnic vessels preferentially.
- Typically, vasopressin level rises in response to hypotension; however, this rise is usually inadequate in patients on dialysis.

VI. Other serious medical conditions that can cause IDH:

1. Pericardial tamponade.
2. Myocardial infarction.
3. Occult hemorrhage.
4. Septicemia.
5. Dialyzer reaction (see later).
6. Hemolysis (see later).
7. Air embolism (see later).

Management of the acute IDH episode

1. **Patient position:** It is recommended that the patient be placed in the Trendelenburg position.
2. **Restoration of plasma volume:**
 - Administer a bolus (100 mL or more if required) of 0.9% saline.
 - Albumin is expensive and provides a minimal advantage over 0.9% saline.
 - It appears that hypertonic saline is not more effective than 0.9% saline.
 - According to the results of a small study, 20% hypertonic glucose may be effective in restoring plasma volume.
3. **Decrease UF rate:**
 - Reduce the ultrafiltration rate as much as possible or stop it.
 - When the patient regains stable pressure, continue ultrafiltration again (start with a low UF rate).
4. **Nasal oxygen administration:** There is evidence that intradialytic hypoxemia is associated with intradialytic hypotension, which may also lead to arrhythmias.
5. **Discontinuation of dialysis:**
 - Dialysis should be terminated if hypotension is resistant to management and severe complications have occurred.
 - Severe resistant hypotension rarely happens and requires searching for an underlying cause.

- 6. No need to reduce the rate of blood flow:** Blood flow rate slowing is a common practice in the treatment of IDH; however, it is of questionable benefit:
- Slowing blood flow rate only had a role with non-volumetric-controlled machines and acetate dialysate used in the past. When the blood flow rate is reduced in these older dialysis machines, the pressure on the blood side decreases (i.e., decreasing TMP), which will reduce the UF rate. Also, a lower blood flow rate reduces acetate (which has a vasodilator effect) transfer to the patient.
 - With the currently used volumetric control machines (volumetric control was discussed in Chapter 4), the desired TMP and UF are maintained independent of blood flow rate. So, a reduction in the blood flow rate will not reduce UF.

Prevention of IDH occurrence

- It is essential to exclude other serious medical conditions mentioned above that can cause IDH (e.g., pericardial tamponade, myocardial infarction, occult hemorrhage...etc.)
- The following are the suggested measures to prevent the occurrence of IDH, especially in patients with recurrent attacks after exclusion of other serious medical conditions.

I. Preventive measures related to hemodialysis procedure: Ultrafiltration control:

1. Ultrafiltration-related measure that showed a good benefit:

Ultrafiltration rate:

- The accepted UF rate is 10-13 mL/kg/h.
- Weekly dialysis time must be extended in individuals whose required ultrafiltration rate is greater than 10-13 mL/kg/h. This will reduce the frequency of IDH by decreasing the needed ultrafiltration rate per hour (i.e., the same amount of weight loss but over an extended period of time).

2. Ultrafiltration-related measures that showed good benefits but are not widely available:

a. Blood volume control devices with feedback loop: Recently, some hemodialysis machines contain software that analyzes blood volume variations during hemodialysis sessions and, through a feedback mechanism, continuously adjusts the ultrafiltration rate.

b. Isonatric hemodialysis (the new automated dialysate sodium control biosensor):

- Main idea: To prevent intradialytic patient hypotension, excessive sodium removal by diffusion is avoided using isonatric dialysis, in which sodium is removed by convection alone.
- Isonatric hemodialysis: Some recently available dialysis machines contain an automated Na balancing module that provides online monitoring of serum sodium and can align dialysate sodium concentration to serum sodium concentration, which will prevent loss of sodium by diffusion.
- Benefits: Isonatric hemodialysis reduces intradialytic serum sodium changes as it effectively prevents excess sodium loss during hemodialysis and excessive sodium gain.

3. Ultrafiltration-related measures that showed no additional benefit and are not commonly used:

a. Ultrafiltration (UF) profile:

- Urea and waste products removal from blood by diffusion during dialysis:
 - As shown in Figure 8.3, the urea serum level decreases throughout the dialysis session and becomes lower and lower as the session time passes. This low serum urea causes decreased serum osmolality, and fluid shifts from the intravascular space into cells, precipitating hypovolemia and hypotension.
 - The highest serum urea level is at the beginning of the hemodialysis session, with little effect on serum osmolality and fluid movement from intravascular space into cells.
- UF profiling is a practice of removing the greatest amount of fluid at the beginning of a hemodialysis session, followed by a gradual decrease of the UF rate through the session time. The removal of high fluid volume at the beginning depends on the idea that the serum urea level at this time is still high, which maintains the serum osmolality.
- UF profiling can be used alone or is often used concomitantly with sodium profiling (see later) due to their intrinsic connection.

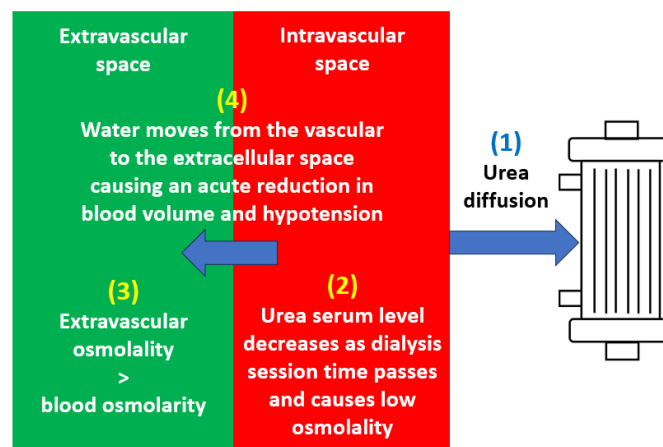


Figure 8.3. Urea removal from blood by diffusion during dialysis and its effect on serum osmolality and water movement

b. Sequential ultrafiltration (UF) and dialysis:

- Main factors causing hypovolemia during hemodialysis session:
 - As previously stated, urea and waste products clearance during dialysis reduces serum osmolality that induces a shift of intravascular fluid into cells and precipitates hypovolemia and hypotension (Figure 8.3).
 - It is well-known that UF reduces ECF, which precipitates hypovolemia and hypotension.

- Thus, separating UF and diffusion by sequential UF may be a solution to avoid their combined effect of decreasing intravascular volume. In sequential UF, pure ultrafiltration is done alone first (i.e., by stopping dialysate flow to stop diffusion → so no removal of urea → so plasma osmolarity is maintained during UF → this prevents hypotension), then it is followed by dialysis with diffusion to remove excess urea.
- Main disadvantage: Sequential UF extends the period of treatment.

II. Preventive measures related to hemodialysis procedure: Dialysate characteristics:

1. Dialysate-related measures that showed good benefit:

a. Use cool dialysate:

- One approach is to adjust the temperature of the dialysate to 35–36°C.
- Another approach is to individualize dialysate temperature:
 - Method A: Empiric fixed reductions of dialysate temperature: The dialysate temperature is adjusted to 0.5°C below the patient's average pre-dialysis tympanic membrane temperature, which may result in a reduction of body temperature of around 1°C.
 - Method B: Isothermic dialysis: A feedback temperature-controlled device measures the core body temperature and reduces the dialysate temperature accordingly.

b. Dialysate calcium concentration: Avoid low calcium dialysate. It is advisable to consider using a dialysate calcium concentration of 1.50 mmol/L.

c. Dialysate magnesium concentration: Do not use low-magnesium (0.25 mmol/L) dialysate. It is suggested to use dialysate magnesium of ≥ 1.0 mmol/L.

2. Dialysate-related measure that showed no additional benefit and is not commonly used:

Sodium modeling:

- Again, as previously stated, urea and waste products clearance during dialysis reduces serum osmolarity that induces a shift of intravascular fluid into cells and precipitates hypovolemia (Figure 8.3). To prevent this shift, increasing the sodium concentration of the dialysate (by sodium modeling) can reestablish the osmotic gradient in the serum and facilitate plasma refill.
- Sodium modeling:
 - As shown in Figure 8.4, the use of high dialysate sodium concentration (145–155 mmol/L) early in the dialysis session makes the returning blood from the dialyzer hypertonic, which prevents the decline in serum osmolarity (caused by urea and solutes clearance from plasma). Following this, the sodium content of the dialysate is progressively decreased to 135–140 mmol/L by the end of the treatment.
 - The primary disadvantage of this approach is the possibility of developing hypertension, increased thirst, and water consumption due to a positive sodium balance. It is not highly recommended for use.

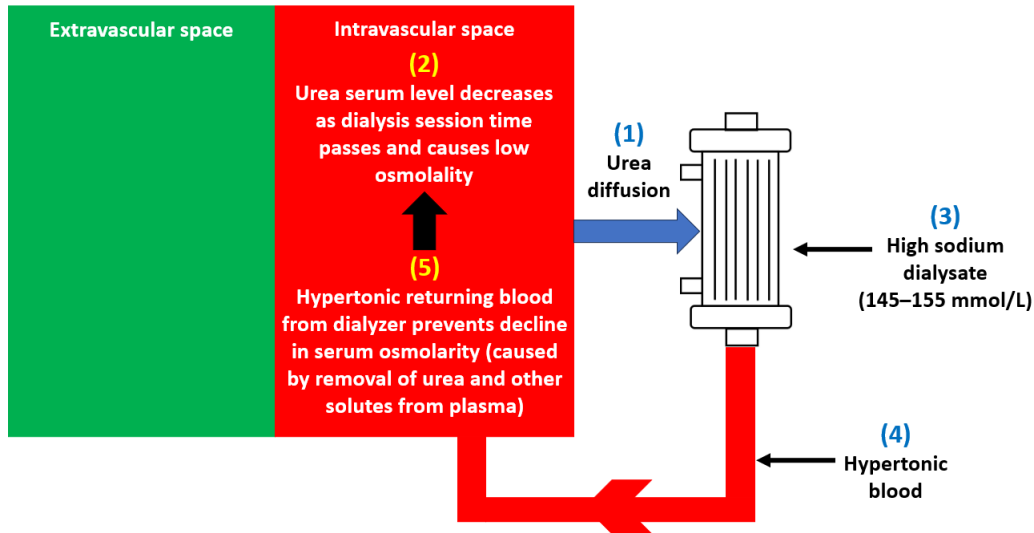


Figure 8.4. Sodium remodeling: The use of high dialysate sodium early in the dialysis session

III. Preventive measures related to hemodialysis procedure: Change dialysis modality:

For patients with chronic debilitating intradialytic hypotension, an alternative mode of dialysis may be considered, such as peritoneal dialysis, hemodiafiltration (HDF), daily dialysis, or nocturnal hemodialysis.

IV. Preventive measures related to the patient:

1. Preventive measures related to the patient's weight:

a. Intradialytic weight gain (IDWG) control:

- Large IDWG can be prevented with patient education regarding its bad effects.
- Fluid intake should ideally be <1 L daily in anuric patients.
- Salt restriction (2 g per day) is more effective than fluid restriction at reducing IDWG.

b. Maintain the urine volume: Maintaining urine volume (by using diuretics) in hemodialysis patients with residual kidney function decreases the requirement for UF during dialysis and reduces the risk of IDH.

c. Consider raising the patient's dry weight:

- The optimal dry weight is often determined empirically by trial and error. It usually depends on a clinical basis:
 - Measuring blood pressure.
 - Examine for edema.
 - Tolerance of ultrafiltration to the chosen weight: The dry weight is marginally higher than the weight at which adverse responses manifest, including cramping, nausea, vomiting, or hypotension.
- Clinical decision-making about dry weight can be assisted by bioimpedance, serum atrial natriuretic factor levels, or assessment of the inferior vena cava or lungs by ultrasound.

2. Other patient-related preventive measures:

- a. Food intake:** Patients should not eat during or immediately before dialysis.
- b. Hemoglobin level:** Assess the predialysis hemoglobin level and correct anemia.
- c. Antihypertensive medications modification:**
 - Administer antihypertensive drugs following dialysis, not before it.
 - It is advisable to avoid prescribing blood pressure drugs that require dosing twice daily or more. It is preferred to prescribe drugs that can be administered once daily and instruct patients to take the dose at night following dialysis.
- d. Full cardiovascular assessment:** This should be done in cases with recurrent episodes of IDH.
- e. Intradialytic exercise:** There is evidence that combined aerobic and anaerobic exercise training during dialysis has a beneficial effect on intradialytic hypotension and physical health status.

V. Use of medications to prevent IDH:

1. Midodrine:

- **Mechanism of action:** It is an orally acting α -adrenergic agonist.
- **Dose:**
 - Pre-dialysis dose:
 - Oral administration of 2.5-5 mg 15-30 minutes before hemodialysis.
 - If the response is inadequate, escalate the dosage to 10 mg (40 mg has been reported) 15-30 minutes before the subsequent hemodialysis session.
 - Intradialytic dose: If hypotension still occurs near the end of hemodialysis, give an additional 2.5-5 mg dose mid-dialysis, provided it is administered ≥ 3 hours after the pre-dialysis dose.
- **Side effect:** Supine hypertension is the major dose-limiting side effect.
- **Contraindication:** It is contraindicated in cases of active cardiac ischemia (not just coronary artery disease).
- **No benefit of midodrine in the following cases:**
 - Concomitant use of α -adrenergic blockers.
 - Existing data do not support its utility in patients with autonomic insufficiency (who are about half of the dialysis population).
- **Midodrine versus using cool dialysate:** The midodrine effect to prevent IDH does not appear to be additive to that of cool dialysate.

2. Sertraline:

- It is a selective serotonin reuptake inhibitor.
- It improves autonomic function.
- Four to six weeks of therapy with sertraline reduces the frequency of IDH.
- The sertraline effect to prevent IDH does not appear to be additive to that of cool dialysate.

3. **Fludrocortisone:** It is only effective if there is a low random aldosterone level. Fludrocortisone did not induce any improvement in patients with hypotension who have normal levels of adrenal hormones.
4. **Verapamil:** Limited data suggest that verapamil may reduce the incidence of IDH in patients with diastolic dysfunction.

VI. Suggested stepwise approach to prevent IDH:

We discussed all the available preventive measures for IDH occurrence above (from point I to point V). Table 8.1 shows a suggested stepwise approach for the prevention of IDH using the widely available measures that showed good benefits.

Table 8.1. Stepwise approach to prevent IDH occurrence

Step	Measures
First step	<ul style="list-style-type: none"> • Reassess the dry weight. • Limit interdialytic sodium and fluid intake. • Avoid food intake during dialysis. • Withhold antihypertensive medications before dialysis and prescribe drugs that can be administered once daily. • Correction of anemia to target levels.
Second step (if the first step fails)	<ul style="list-style-type: none"> • Cardiac evaluation.
Third step (if cardiac evaluation is normal)	<ul style="list-style-type: none"> • Use cool dialysate ± midodrine trial.
Fourth step (if cool dialysate fails)	<ul style="list-style-type: none"> • Increase in dialysis time and/or frequency.
Fifth step (if the fourth step fails)	<ul style="list-style-type: none"> • Switch the patient to other forms of dialysis (e.g., peritoneal dialysis, hemodiafiltration (HDF), daily dialysis, or nocturnal hemodialysis).

Intradialytic hypertension (ID-HTN)

Definition of intradialytic hypertension (ID-HTN)

Many definitions for intradialytic hypertension are available:

- It is defined as a sustained increase of blood pressure (BP) during a dialysis session, with BP values during and at the end of the dialysis session exceeding BP values at dialysis onset.
- Another definition considers intradialytic hypertension as systolic blood pressure rise ≥ 10 mmHg with hemodialysis.

Incidence of ID-HTN

Intradialytic hypertension occurrence is estimated to be about 5-15%.

Causes of ID-HTN

- **Dry weight and ultrafiltration-related causes:**
 - **Dry weight overestimation:** This means that the actual dry weight is lower than that which was prescribed. This leads to less UF, and the patient will not reach the actual dry weight and will have excess water volume. Dry weight overestimation is the predominant factor contributing to intradialytic hypertension.
 - **Rapid ultrafiltration with hypovolemia or too much ultrafiltration:** This may exacerbate the compensatory mechanisms, such as the sympathetic nervous system and renin-angiotensin-aldosterone system, which will cause hypertension.
- **Medication-related causes:**
 - Removal of antihypertensive medications during dialysis.
 - Giving erythropoietin stimulating agents (ESAs) intravenously before the end of hemodialysis causes an increase in endothelin-1 (ET-1), which induces hypertension.
- **Endothelin-1 (ET-1):** Elevated levels of ET-1 could potentially contribute to the development of intradialytic hypertension.
- **Dialysate related causes:**
 - High dialysate sodium or calcium concentration.
 - Dialysate potassium:
 - Rebound hypertension is reported one hour after dialysis at dialysate potassium concentrations of 1 and 2 mmol/L. However, this was not detected at a dialysate potassium concentration of 3 mmol/L (Dolson et al. 1995).
 - However, another study (Vongchaiudomchoke et al. 2023) showed that dialysate potassium concentration of 2 or 3 mmol/L did not affect the incidence of intradialytic hypertension in chronic hemodialysis patients who frequently developed intradialytic hypertension.
- **Arterial oxygen saturation:** There is evidence that low intradialytic arterial oxygen saturation may induce intradialytic hypertension.

Management of ID-HTN

- **Dry weight and ultrafiltration:**
 - Reassess the patient's dry weight.
 - Reduce large IDWG to avoid rapid ultrafiltration.
- **Anti-hypertensive medications modification:**
 - Carvedilol:
 - It is non-dialyzable.
 - It is a non-selective beta-blocker with additional blockades of alpha 1-adrenoceptors, so it reduces sympathetic overactivity during dialysis session.
 - It has an ET-1 antagonistic effect.
 - ACE-I and ARBs reduce the activity of the renin-angiotensin-aldosterone system.
 - Use other non-dialyzable medications.

- **ESAs:** Don't give ESAs before or during the hemodialysis session.
- **Dialysate changes:** Using a dialysate sodium concentration that is lower than the patient's serum sodium.
- **Monitor oxygen saturation level** during hemodialysis sessions and give oxygen to patients with low intradialytic arterial oxygen saturation.

Muscle cramps

Timing of muscle cramps during hemodialysis session

Muscle cramps are commonly observed near the end of the dialysis session.

Pathogenesis of muscle cramps during hemodialysis session

- **Hypotension and hypo-osmolality:**
 - **Hypotension and hypovolemia** are important predisposing factors.
 - **Hypo-osmolality:**
Cramps that occur independently of obvious volume depletion or hypotension and respond in a positive manner to hypertonic solutions suggest a role for hypo-osmolality in the pathogenesis of cramps.
- **Electrolyte disturbance:**
 - **Low-sodium dialysate** may precipitate cramps.
 - **Hypocalcemia** may be the cause of the cramps.
 - **Hypomagnesemia** may cause dialysis-related cramps to be resistant to treatment.
 - **Pre-dialysis hypokalemia**, if present, will be more severe and may induce cramping if the potassium concentration in the dialysate is below 2 mmol/L.
- **Peripheral vascular disease** may be the precipitating cause of muscle cramps.

Management of muscle cramps

- **Intravenous solutions:**
 - **0.9% saline:** When hypotension and muscle cramps occur concomitantly, treatment with 0.9% saline can be used, but it does not always resolve the cramp, and hypertonic solutions are preferred.
 - **Hypertonic solutions:**
 - These solutions have greater efficacy in the acute therapy of muscle cramps compared to saline due to their superior ability to dilate muscle blood vessels.
 - Which hypertonic solution to use:
 - Administration of hypertonic glucose is the best method for muscle cramp therapy in nondiabetics.
 - Hypertonic saline administration may induce thirst and IDWG.
 - Mannitol may accumulate in dialysis patients, and it is not preferred.

- **Physical therapy:**
 - **Forced stretching:** Muscle cramping may be relieved with forced stretching of the affected muscle (e.g., ankle flexion for calf cramping).
 - **Massage:** Its effect is variable and not effective in all cases.
 - **Local heat application** may be beneficial.
- **Oxygen:** Nasal administration of oxygen has shown benefit in the treatment of cramps.
- **Nifedipine:**
 - Oral 10 mg sometimes can reverse cramping.
 - It should be used in hemodynamically stable patients.

Prevention of muscle cramps

- **Prevent hypotensive episodes:** This will eliminate most cramping (see preventive measures of IDH mentioned before).
- **Physical therapy:**
 - **Stretching exercises:** It is the first line used for the prevention of cramps associated with dialysis and nocturnal cramps.
 - **Compression devices:** Sequential compression devices may be of benefit.
- **Dialysate related measures:**
 - **Dialysate sodium:** Raising dialysate sodium is beneficial but may increase IDWG and blood pressure.
 - **Dialysate magnesium:** A reduced incidence of cramps was observed in patients who received magnesium dialysate at a concentration of 0.5 mmol/L. Dialysate with low magnesium should be avoided.
- **Avoid low predialysis levels of serum electrolytes:** Check serum calcium, potassium, and magnesium and correct any abnormal low levels (extreme caution should be taken while administering magnesium supplements to dialysis patients).
- **Medications:**
 - **Carnitine:**
Intravenous administration of 1g carnitine after each dialysis has proven helpful; however, a higher dose is occasionally used.
 - **Oxazepam:**
5–10 mg, given 2 hours before dialysis.
 - **Vitamin E:**
400 IU at bedtime reduces the incidence and severity of leg cramps. The safe dose of vitamin E in hemodialysis patients is 800 IU/d (it is not safe to use doses of vitamin E that exceed 1000 IU/d).
 - **Quinine sulfate is contraindicated:**
It is currently regarded as contraindicated due to its adverse effects despite its efficacy in avoiding intradialytic cramping.
- **Rule out peripheral vascular disease.**

Hemolysis

Causes of hemolysis during hemodialysis session

- **Faulty roller pump.**
- **Obstruction and/or narrowing in bloodline, needle, or catheter:**
 - Kinks in the arterial bloodline.
 - Hemolysis (usually subclinical) may also appear when the blood flow rate is high and relatively small needle sizes are used.
- **Problems with dialysis solution:**
 - Overheated dialysate.
 - Hypotonic dialysate due to insufficient concentrate-to-water ratio.
 - Dialysate is contaminated with chloramines, chlorine, copper, or nitrates.

Manifestations of hemolysis

- **In cases of acute massive hemolysis:**
 - Back pain, chest tightness and shortness of breath.
 - Port-wine appearance of blood in the venous bloodline and a pink discoloration of the plasma in centrifuged blood samples.
 - Severe decrease in hematocrit.
 - Hyperkalemia occurs, causing muscle weakness, electrocardiographic changes, and may be cardiac arrest.
- **Chronic mild subclinical hemolysis** diagnosis is challenging, and diagnostic investigations are usually needed to identify hemolysis.

Management of hemolysis

- **Stop dialysis and hospitalize the patient:**
 - **Stop dialysis:** Dialysis should be stopped immediately, and the bloodlines should be clamped. Blood in the blood circuit must not be returned as the hemolyzed blood has a very high potassium content and should not be reinfused.
 - **Hospitalization:** The patient must be admitted for observation, as there is a possibility of delayed hemolysis of injured red blood cells following dialysis termination.
- **Order:**
 - **Laboratory tests:** Order serum potassium, complete blood count, reticulocyte count, and lactate dehydrogenase (LDH).
 - **Electrocardiogram (ECG).**
- **Manage as the following:**
 - Blood should be obtained for transfusion.
 - Treat the resultant hyperkalemia.
- **Search for the cause:** Dialysis water quality needs to be assessed.

Air embolism

Air embolism during hemodialysis sessions is an extremely rare yet life-threatening complication.

Sites of air entry during hemodialysis session

The most common sites of air entry are:

- The arterial needle.
- The pre-pump arterial tubing segment.
- The heparin line.
- Accidentally opened end of a central venous catheter.

Manifestations of air embolism

- **Foam** is observed in the venous bloodline of the extracorporeal circuit.
- **The manifestations are position-dependent:**
 - ***In seated patients:***
 - Air travels to the cerebral venous system and obstructs it without entering the heart.
 - This causes convulsions, coma, and maybe death.
 - ***In recumbent patients:***
 - The air enters the heart (an unusual churning sound may be detected during auscultation) and obstructs the right ventricular outflow, causing acute right ventricular failure, pulmonary arterial hypertension, and arrhythmias
 - Further air passage to the lungs obstructs pulmonary capillaries, causing dyspnea, cough, chest tightness, pulmonary edema, and respiratory failure.
 - Further passage of air across the pulmonary capillary bed into the left ventricle can result in air embolization to the arteries of:
 - The brain, which causes acute neurologic.
 - The heart, which causes cardiac dysfunction.

Management of air embolism

- Stop the blood pump.
- Clamp the venous bloodline.
- Don't return the blood in the extracorporeal circuit to the patient.
- Quickly position the patient in a left-sided recumbent position, with the head and chest bent downward.
- Administer 100% oxygen by mask or endotracheal tube.
- It may be necessary to evacuate air from the ventricle or atrium by the use of any one of the following
 - Cardiac catheterization
 - Percutaneous needle insertion.

Disequilibrium syndrome

Dialysis disequilibrium syndrome is an abnormal condition that affects the central nervous system.

Manifestations of disequilibrium syndrome

- **Milder forms of the syndrome and early manifestations of the severe form:** nausea, vomiting, restlessness, and headache.
- **More severe manifestations** include seizures, obtundation, and coma.

Disequilibrium syndrome in acute and chronic dialysis

- Disequilibrium syndrome occurs more in acutely uremic patients who are dialyzed aggressively.
- Patients undergoing chronic dialysis may still develop milder manifestations of the disease.

Pathogenesis of disequilibrium syndrome

1. **Rapid lowering of plasma osmolarity (Figure 8.5):** A rapid reduction in plasma urea and solute levels during dialysis results in hypotonicity of the plasma relative to the brain cells, which causes water osmosis from the plasma to the brain tissue. This contributes to the development of brain edema and an increase in intracranial pressure.
2. **Change in cerebrospinal fluid (CSF) pH: Paradoxical CSF acidosis (Figure 8.6):**
 - Rapid correction of severe acidosis leads to a rapid elevation of serum bicarbonate in blood, which will combine H^+ and cause a high rapid rise in plasma CO_2 :
$$(HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O)$$
 - The high level of plasma CO_2 rapidly diffuses into the CSF and is converted to H^+ . This, together with the failure of the higher plasma bicarbonate to enter the CSF (because of the low permeability of the blood-brain barrier to bicarbonate), results in a fall in the CSF pH.
 - The decrease in CSF pH causes the protein-bound sodium and potassium to dissociate (as protein will bind to excess hydrogen to buffer it). Free sodium is osmotically active and osmose water into the brain cells.
3. **Idiogenic osmoles effect (Figure 8.7):**
 - Intracellular idiogenic osmoles (e.g., myoinositol, glutamine, and glutamate) are produced as a compensatory mechanism to maintain intracerebral osmolality in conditions of hyperosmolality (e.g., uremia). During dialysis, urea serum concentration declines, and the plasma becomes hypotonic in relation to idiogenic osmoles in the brain cells. These idiogenic osmoles cause water to move into brain cells, causing brain edema.
 - Also, retention of these acidic osmoles causes a fall in intracellular pH and contributes to the “paradoxical CSF acidosis” mentioned above.

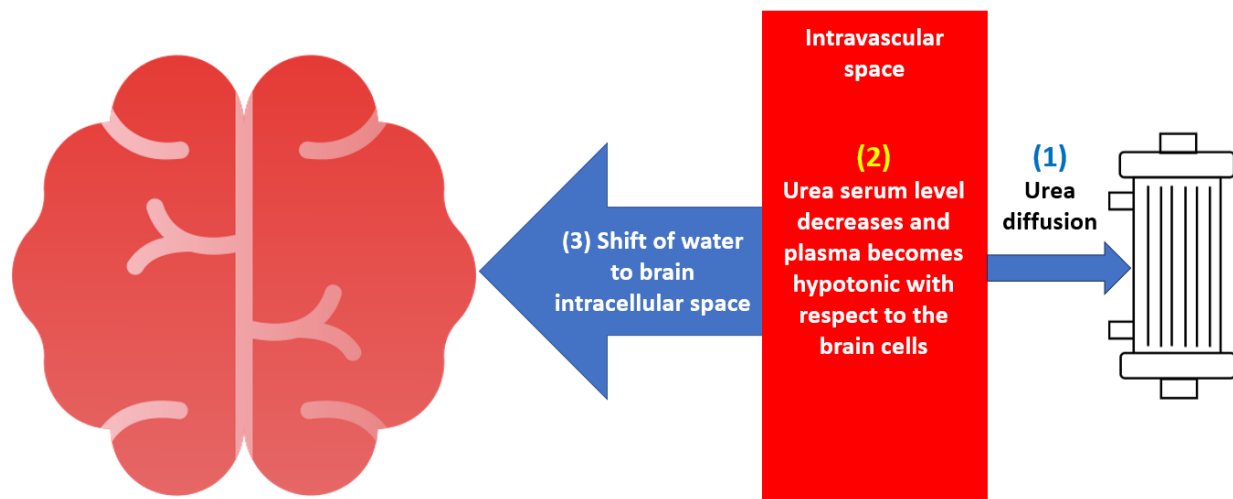


Figure 8.5. Role of rapid lowering of plasma osmolarity in the development of disequilibrium syndrome

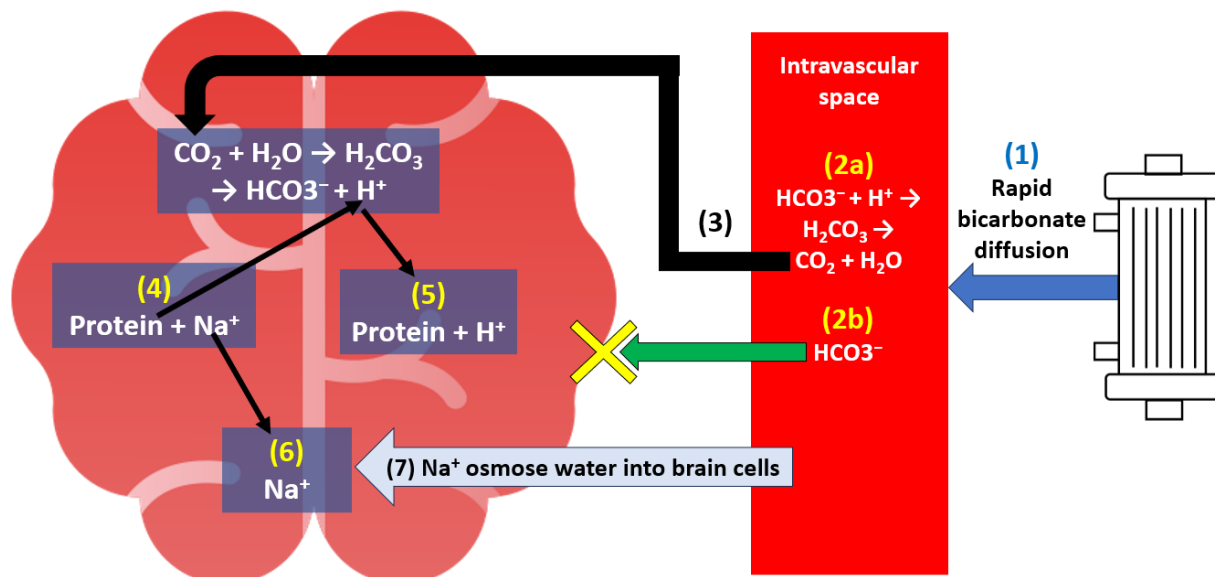


Figure 8.6. Role of paradoxical CSF acidosis in the development of disequilibrium syndrome

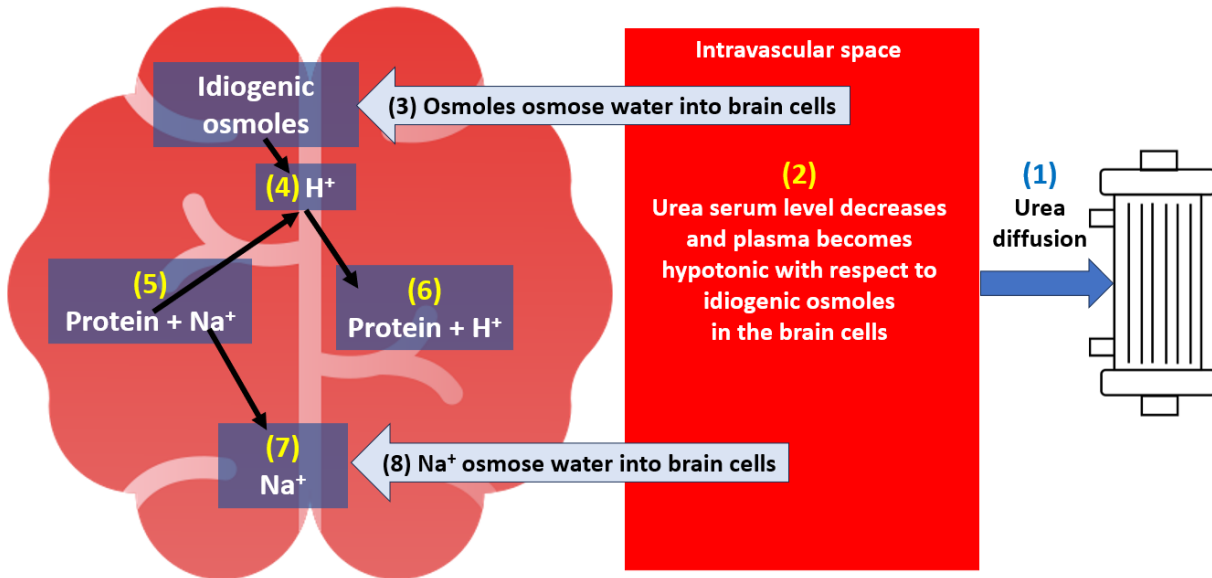


Figure 8.7. Idiogenic osmoles effect in developing disequilibrium syndrome

Diagnosis of disequilibrium syndrome

Dialysis disequilibrium syndrome lacks a definitive diagnostic test. Its diagnosis depends on clinical presentation. The diagnosis is suspected in patients who present with typical symptoms during their first acute dialysis treatment or in chronic dialysis patients while resuming dialysis after a period of nonadherence to treatments.

Management of disequilibrium syndrome

- **Mild disequilibrium:**
 - Symptomatic treatment.
 - The blood and dialysate flow rates should be reduced.
 - The ultrafiltration rate should be reduced too.
 - Glucose or hypertonic sodium chloride solutions may be given.
 - Early termination of the dialysis session should be considered, especially in acutely uremic patients.
- **Severe disequilibrium (seizures and coma):**
 - Dialysis should be stopped.
 - First aid measures for seizure management must be taken (see later).
 - Intravenous mannitol, hypertonic saline, or glucose may be of benefit.
 - If seizures and coma are due to disequilibrium syndrome, the patient should improve within 24 hours.
- **Exclude other causes of seizures:** Other causes of seizures in dialysis patients rather than disequilibrium syndrome should be excluded as early as possible (see later), especially if the patient does not improve within a 24-hour period.

Prevention of disequilibrium syndrome

- **In case of acute dialysis for a patient with acute uremia:**
 - **Avoid prescribing aggressive dialysis sessions:** It is better to use the following parameters in the first dialysis sessions of acute dialysis:
 - Make a short dialysis session (1.5 to 2h).
 - Use a small-size dialyzer.
 - Low dialysate flow rate (QD).
 - Low blood flow rate (e.g., QB of 200ml/h).
 - **Urea reduction ratio (UUR) target:** The target reduction in the plasma urea nitrogen level should be limited to about 30-40%.
 - **Severely acidotic patients:** In these patients, initial dialysis treatments should be with reduced dialysate bicarbonate to prevent paradoxical CSF acidosis, as mentioned before.
 - **Don't use dialysate with low sodium concentration:** Avoid using low dialysate sodium (>2–3 mmol/L less than the plasma sodium level) to avoid rapid changes in serum sodium.
 - **Hypernatremic patients:**
 - In these patients, uremia and hypernatremia correction should not be attempted simultaneously.
 - It is advisable to initiate dialysis treatment for a patient with hypernatremia using a dialysate containing a sodium concentration similar to that of plasma. Later, hypernatremia can be gradually corrected after dialysis by 5% dextrose.
- **In case of chronic dialysis:**
 - **Sodium dialysate:** Using sodium dialysate of at least 140 mmol/L can minimize the incidence of disequilibrium syndrome.
 - **Sodium modeling:** Although it decreases the occurrence of disequilibrium syndrome, it has many drawbacks, as discussed before.

Seizures

Causes of seizures during hemodialysis session

- Disequilibrium syndrome.
- Severe hypotension.
- Hypertensive encephalopathy.
- Metabolic causes: hypoglycemia, hypocalcemia, hypernatremia, or hyponatremia.
- Intracranial hemorrhage.
- Air embolism.
- Aluminum encephalopathy.
- Drugs that lower the seizure threshold.

Immediate urgent management of seizures during hemodialysis session

- **Immediate management:**
 - Terminate the dialysis session.
 - Secure vascular access throughout the seizure to prevent its damage.
 - Ensure the patient is not in danger of injury and is in a secure setting.
 - Administer intravenous fluids and oxygen as required.
 - The majority of seizures resolve spontaneously within five minutes.
- **If a patient continues to seize:**
 - Achieve airway protection and patient stabilization.
 - Administering intravenous benzodiazepines is the treatment of choice to terminate the seizures.
 - Refer the patient for neurology consultation.
- **After the seizure has been remitted, try to find the cause:**
 - Assess vital signs to detect any blood pressure abnormality that may be the cause.
 - Blood should be sampled for serum levels of glucose, calcium, sodium, magnesium, and other electrolytes, trying to diagnose if there is a metabolic cause of the seizures.
 - Brain imaging may be needed to exclude intracranial hemorrhage.
 - In the case of air embolism, foam is observed in the venous bloodline.
 - If aluminum encephalopathy is suspected:
 - Identification of aluminum accumulation on a bone biopsy provides the definitive diagnosis; however, bone biopsies are seldom performed in practice.
 - When a bone biopsy is not performed, the diagnosis is established using the unstimulated baseline serum aluminum concentration. In selected patients, this is followed by the deferoxamine-stimulated serum aluminum level.
 - Revise the patient's medications for any drug that lowers the seizure threshold.
 - Exclude recent star fruit ingestion.
 - Dialysis disequilibrium syndrome, as mentioned before, is a diagnosis of exclusion.

Headache

Incidence of headache

Headache is a very common complication that occurs during hemodialysis. The incidence of dialysis headaches ranged from 28% to 73% of patients during dialysis.

Causes and management of headache during hemodialysis session

- Table 8.2 shows the probable causes of headaches during hemodialysis sessions and how to deal with them.
- Besides management lines mentioned in Table 8.2, acetaminophen can be given during dialysis.

Table 8.2. Causes and management of intradialytic headache

Cause	Management
Hypotension	Correct hypotension and hypovolemia (see preventive measures of IDH above).
Accelerated/severe hypertension	See management and prevention of intradialytic hypertension above.
In patients who consume coffee, blood caffeine concentration is sharply lowered during dialysis, and headache may be a sign of caffeine withdrawal.	Caffeine withdrawal symptoms may be avoided or treated with a strong cup of coffee.
Hypoglycemia	Check random glucose level and manage hypoglycemia if present.
Hyponatremia or hypernatremia	Check serum sodium level and manage accordingly.
Magnesium deficiency may precipitate headaches during dialysis.	Correct hypomagnesemia (extreme caution should be taken while administering magnesium supplements to dialysis patients).
In patients with a history of migraine, dialysis may precipitate migraine headaches.	Re-evaluate migraine therapy.
Disequilibrium syndrome	Management discussed before.
Neurologic cause (e.g., bleeding precipitated by anticoagulation): This should be considered in patients with atypical or severe headaches.	Brain imaging.
Dialysis-associated changes in vasoactive substances such as nitric oxide: This is characterized by a bifrontal or temporal headache starting after initiation of dialysis, worsening over the duration of the treatment, with resolution over 72 hours.	In patients with recurring and severe dialysis-associated headaches, a trial of shortened, more frequent hemodialysis sessions may be effective in alleviating the headache.

Nausea and Vomiting

Incidence of nausea and vomiting

Nausea or vomiting occurs in 9.8%–18.2% of dialysis treatments.

Causes of nausea and vomiting during hemodialysis session

- Hypotension.
- Vomiting is an early manifestation of disequilibrium syndrome (discussed before).
- Type A and type B dialyzer reactions (see later).
- Gastroparesis, if present, is aggravated by hemodialysis and may have a role. Gastroparesis is frequently observed in those with diabetes; however, it can also manifest in those without diabetes.
- Hemodialysis may aggravate gastric acid secretion in some patients.
- High sodium or calcium dialysate solution (due to contamination or incorrect formulation).

Management of nausea and vomiting

- Treat associated hypotension or any other associated cause.
- Antiemetics can be prescribed to treat vomiting for reasons other than hypotension.

Prevention of nausea and vomiting

- Prevent the occurrence of IDH (mentioned above).
- In patients with excessive gastric acid secretion during dialysis treatment, the use of H₂ receptor antagonists or proton pump inhibitors before the beginning of dialysis treatment is effective.
- Metoclopramide (5–10 mg orally before dialysis session) can be used if symptoms persist.

Dialyzer reactions

- Historically, it was believed that adverse responses occurring with newly used dialyzers are more prevalent than with reused dialyzers; this phenomenon is known as "first-use syndrome."
- However, similar reactions occur with reused dialyzers, which has made the term "first-use syndrome" obsolete. Nowadays, reactions from dialyzers are discussed under the more general category "dialyzer reactions," which can occur with the use of both new and reused dialyzers.
- There are two types of dialyzer reactions, which are discussed in Table 8.3:
 - Anaphylactic type (type A) reaction.
 - Nonspecific type (type B) reaction.

Table 8.3. Dialyzer reaction types

	Type A (Anaphylactic type)	Type B (Nonspecific type)
Incidence	Rare: 5/100000 dialyses.	Common: 3-5/100 dialyses.
Onset	It typically occurs during the initial minutes of dialysis. However, its occurrence may be delayed for ≥ 30 minutes.	It typically occurs 20–40 minutes after starting dialysis.
Presentation	<ul style="list-style-type: none"> • Mild type: Facial flushing, urticaria and pruritus, sneezing, watery eyes, cough, and abdominal cramps or diarrhea. • Severe type: Anxiety, a burning sensation at the access site or over the entire body, dyspnea, chest tightness, angioedema, laryngeal edema, respiratory failure, cardiac arrest, and may result in death. 	Chest pain, sometimes accompanied by back pain.
Causes	<ul style="list-style-type: none"> • At first, it was thought that the reactions were occurring to the cellulose membrane. • Ethylene oxide (Eto) sterilization. • Use of AN69 membranes (formed of polyacrylonitrile [PAN] material—see Chapter 5, Table 5.2) in patients receiving angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors amplify the activation of the bradykinin system by the PAN membrane. It is not known to what extent ACE inhibitor–associated reactions occur with other PAN-based membranes or with other non–PAN–based membranes. • Heparin: <ul style="list-style-type: none"> ○ Heparin may be the cause of type A reaction. ○ Try heparin-free dialysis or citrate anticoagulation when a patient is allergic to multiple dialyzers (regardless of the sterilizing method employed). ○ LMWH cross-reacts with UFH and is not a safe substitute. • The use of high-flux dialyzers increases the risk of bacterial contamination of dialysate. 	The pathogenesis is unclear. However, activation of the complement by the membrane material is a possibility.

	<ul style="list-style-type: none"> • Bacterial contamination of reused dialyzers due to inadequate disinfection. • Eosinophilia: Patients with mild to moderate eosinophilia are more prone to Type A reactions. This could result from eosinophil degranulation with the secretion of bronchoconstrictive mediators and other mediators. 	
Management	<ul style="list-style-type: none"> • The exact etiology is often difficult to be determined. • In case of anaphylaxis: <ul style="list-style-type: none"> ○ Stop dialysis. ○ Clamp bloodlines, and don't return extracorporeal blood to the patient. ○ Antihistaminics, steroids, and epinephrine. ○ Cardiopulmonary resuscitation if needed. • In mild forms: <ul style="list-style-type: none"> ○ Stop dialysis. ○ Administer antihistaminics and oxygen. 	<ul style="list-style-type: none"> • Diagnosis is by excluding other causes of chest pain. • Supportive treatment. • Nasal oxygen supply. • Continue hemodialysis.
Outcome	<ul style="list-style-type: none"> • It could be fatal. 	<ul style="list-style-type: none"> • It is much less severe than type A reaction. • Symptoms usually resolve after 30-60 minutes.
Prevention	<ul style="list-style-type: none"> • Avoid Eto sterilization. Use γ-irradiated, steam-sterilized, or electron beam-sterilized dialyzer. • Rinse dialyzers and blood tubing (including the connecting side branches as the heparin pump branch) very well to eliminate residual Eto and other putative allergens. • Avoid AN69 membrane dialyzers if the patient is on ACE inhibitors, or replace ACE inhibitors with other drugs (e.g., angiotensin receptor blockers "ARBs") • Change membrane type. • Try heparin-free dialysis or citrate anticoagulation. 	<ul style="list-style-type: none"> • Change from cellulose to modified cellulose or synthetic membranes. • Reusing dialyzers may help.

Chest pain

Chest pain during dialysis is one of the serious complaints that needs urgent intervention.

Causes of chest pain during hemodialysis session

- Angina due to obstructive coronary artery disease.
- While angina is typically a sign of obstructive coronary artery disease, individuals on hemodialysis may potentially develop angina without any coronary obstruction. Mechanisms explaining this theory are:
 - It is common for hemodialysis patients to have hypertrophied cardiomyopathy with inadequate capillary perfusion, which can cause angina-like symptoms
 - Hemodialysis patients may develop high cardiac output (due to anemia or high-flow arteriovenous fistula). The combination of high cardiac output and the physiologic stress of the hemodialysis session itself can aggravate angina-like symptoms.
- Hemolysis (discussed before).
- Air embolism (discussed before).
- Dialyzer reaction (discussed before).

Stepwise approach to deal with chest pain during hemodialysis session

I. Step 1: Immediate measures:

- **Do the following at first:**
 - Stop ultrafiltration and decrease the blood flow rate to ≤ 200 mL/min.
 - Put the patient in a recumbent position.
 - Give oxygen.
 - Record blood pressure, heart rate, and other vital signs.
- **Exclude serious causes:**
 - **Exclude air embolism:** Observe the venous bloodline for any air foam and manage immediately (discussed before).
 - **Exclude hemolysis:**
 - Observe the venous bloodline for a port-wine appearance of the blood and manage immediately (discussed before).
 - Check whether any other dialysis patients in the unit are having the same symptoms. This is common if hemolysis is due to an issue of the water treatment unit.
 - **Exclude coronary disease:**
 - Do an electrocardiogram (ECG).
 - Do the following laboratory tests:
 - Electrolytes.
 - Troponin levels.
 - Complete blood count.

II. Step 2: In the absence of air embolism or hemolysis, and the chest patient is proven to be of cardiac origin (as approved by ECG and troponin levels), the continuing steps of management depend on whether the patient is hypotensive or not:

- **In patients with chest pain and hypotension:**
 - **Manage hypotension:**
 - Place the patient in the Trendelenburg position.
 - Reduce the ultrafiltration rate as much as possible or stop it.
 - Administer a 200–300 mL intravenous bolus of isotonic fluid.
 - Nasal oxygen administration: As mentioned before, there is evidence that intradialytic hypoxemia is associated with intradialytic hypotension.
 - Observe the patient and follow blood pressure measurements and vital signs.
 - **If both the hypotension and chest pain resolved:**
 - Continue dialysis.
 - Don't resume ultrafiltration initially till the patient is observed to be still stable with no chest pain.
 - Cardiac evaluation should be done after the dialysis session.
 - **If the patient has persistent chest pain and/or persistent hypotension with evidence of cardiac ischemia (e.g., arrhythmia or ischemic changes on ECG):**
 - Dialysis should be discontinued.
 - Drug use in patients with suspected cardiac pain:
 - Administer aspirin 81 mg.
 - Nitrates: They can cause hypotension. Patients on hemodialysis who are hypotensive or hypovolemic should avoid using nitrates since it has the potential to decrease venous tone and exacerbate hypotension rapidly.
 - Transfer the patient to the hospital by ambulance.
 - Cardiac evaluation should be done.
- **In patients with chest pain without hypotension with evidence of cardiac ischemia (e.g., arrhythmia or ischemic changes on ECG):**
 - Dialysis should be discontinued.
 - Drug use in patients with suspected cardiac pain:
 - Administer aspirin 81 mg.
 - Nitrates: It can be used in the absence of hypotension provided that the patient has venous access (if the patient becomes hypotensive, this can be easily managed with intravenous saline through the venous access).
 - Transfer the patient to the hospital by ambulance.
 - Cardiac evaluation should be done.

III. Dialyzer reaction:

Diagnosis of dialyzer reaction (usually type B) is one of exclusion after excluding other causes of chest pain, as shown above in step 1.

Dyspnea

Dyspnea may appear after the initiation of hemodialysis with or without chest pain. The causes and management of this acute dyspnea are described below.

Causes of dyspnea during hemodialysis session

- Isotonic saline, which is typically given at the beginning of HD (even in small doses), might cause dyspnea.
- Angina.
- Acute severe hypertension.
- Pericardial effusion with or without tamponade.
- Pulmonary embolism (this should be suspected in patients who have had therapy for thrombosed vascular access recently).
- Bacteremia (often associated with catheter infection).
- Hemolysis.
- Air embolism.
- Allergic reaction to heparin.

Management of dyspnea

- **Supply oxygen** if there is evidence of hypoxia.
- **Try to find the cause and treat it:**
 - In patients with dyspnea and chest pain, manage chest pain as mentioned above.
 - If severe hypertension is the suspected cause, more ultrafiltration is needed.
 - Do chest X-ray and cardiac evaluation for diagnosis of pericardial effusion.
 - Pulmonary angiography should be done if pulmonary embolism is suspected.
 - Check markers of infection if bacteremia is suspected.
 - Exclude air embolism: Observe the venous bloodline for any air foam and manage immediately (discussed before).
 - Exclude hemolysis:
 - Observe the venous bloodline for a port-wine appearance of the blood and manage immediately (discussed before).
 - Check if other dialysis patients in the unit have the same symptoms. This is common if hemolysis is due to an issue of the water treatment unit.
 - Allergic reaction to heparin is a diagnosis of exclusion.
- **Dialysis continuation:**
 - If the patient's vital signs are unstable or there is persistent hypoxia or a life-threatening condition:
 - Stop dialysis:
 - Transfer the patient to the hospital by ambulance.
 - Continue dialysis if the patient is stable and there is no hypoxia.

Cardiac arrhythmia

Acute cardiac arrhythmia during dialysis sessions is a common cause of sudden death in dialysis patients.

Risk factors of cardiac arrhythmia in hemodialysis patients

- In patients receiving hemodialysis, coronary artery disease, and left ventricular hypertrophy are the primary causes of cardiac arrhythmias.
- Arrhythmia is precipitated by the following.
 - Dialysate related factors:
 - Arrhythmia is common when the dialysate potassium is <3 mEq/L. Avoid low potassium dialysate (less than 2 mEq/L).
 - Arrhythmia is also common when the dialysate calcium is low, especially in patients with higher serum calcium levels.
 - Long interdialytic period: Patients receiving thrice-weekly hemodialysis have a significant risk of sudden death after the long interdialytic period. This indicates that volume or electrolyte disorders that are common to happen in the long interdialytic period might be the cause.
 - Intradialytic hypotension.
 - Anemia.

Management of cardiac arrhythmia

- Stop dialysis.
- Blood should be carefully returned.
- Urgent cardioversion is indicated for all patients with an unstable rhythm.
- Airway management and cardiac monitoring are essential.
- Administration of antiarrhythmic drugs (caution should be taken while administering procainamide and other class Ia antiarrhythmics to dialysis patients, as they may induce QT prolongation and torsades de pointes).
- Cardiology consultation.

Syncope

Causes of syncope during hemodialysis session

Syncope may manifest during hemodialysis secondary to any of the following:

- Severe hypotension.
- Arrhythmia.
- Myocardial infarction.
- Stroke.

Management of syncope

- Stop dialysis.
- Elevate the patient's legs.
- Give oxygen.
- Record blood pressure and other vital signs.
- Administer a bolus (200 to 300 mL) of isotonic fluid for hypotensive patients.
- Order an ECG.
- Do laboratory tests for electrolytes, troponin levels, and complete blood count.
- Refer for syncope evaluation.

Itching (Pruritus)

- Itching that appears only during hemodialysis, especially if associated with allergic symptoms, usually indicates a reaction to heparin, dialyzer, or blood circuit components.
- More commonly, itching is present chronically and unrelated to the dialysis procedure. It is caused by the disturbance of chronic kidney disease-associated mineral-bone disorders (CKD-MBD), which is beyond the scope of this book.

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Chapter 9

Arteriovenous Fistula and Graft: Basics, Creation, Use, and Examination

Arteriovenous fistula (AVF) and graft (AVG) are the permanent vascular accesses for hemodialysis. AVF and AVG are considered the lifeline of the patient.

Upper extremity arteriovenous fistula (AVF)

Main idea

AVF formation occurs via subcutaneous anastomosis. Venous segment pressure increases as it receives an increased inflow from artery. The venous segment wall then undergoes arterIALIZATION and dilation. Blood for dialysis can be obtained from this venous segment via dialysis needles.

Vessel preservation

Preservation of upper limb veins for fistula preparation should be done in patients where dialysis access is expected in the future (CKD G3-G5):

- **Venipuncture:** Venipuncture is preferred to be from the non-dominant arm. For venipuncture in either arm, only the most distal small veins should be used. If larger veins must be used, only a highly experienced individual should operate on them.
- **Use of venous catheters for dialysis:** This is better avoided, so it is important to send the patient to have his fistula as early as possible before reaching dialysis.

When should AVF be created?

- Patients with non-dialysis chronic kidney disease and GFR below 30 mL/min per 1.73 m² must receive comprehensive education regarding all available kidney replacement therapies (KRT).
- KDIGO Clinical Practice Guideline for Chronic Kidney Disease (2024) recommend considering planning for dialysis access in adults when the GFR is <15–20 mL/min per 1.73 m² or risk of KRT is >40% over 2 years. You can calculate risk of KRT using the following calculators:
 - Kidney failure risk equation - 4 variable:
https://qxmd.com/calculate/calculator_308/kidney-failure-risk-equation-4-variable
 - Kidney failure risk equation - 8 variable (more accurate results):
https://qxmd.com/calculate/calculator_125/kidney-failure-risk-equation-8-variable
- Earlier referral should occur in patients with unstable and/or rapid rates of eGFR decline (e.g., >10 mL/min/year).



AVF preoperative evaluation

Patient history: A complete history is required. Ask about the following:

- **Previous** venous catheter insertion or intravenous pacemaker/cardiovascular implantable electronic device (CIED) implantation, prior use of peripherally inserted central catheter (PICC) lines, and prior vascular surgery.
- **Comorbidities:** Peripheral vascular disease, diabetes mellitus, or congestive heart failure.
- **History of previous failed AVF** and the cause of failure.

Preoperative physical examination:

- **Pulses:** Assess all pulses in the upper limb.
- **Blood pressure:** Measure the blood pressure in both extremities. Blood pressure is considered normal if the difference is less than 10 mm Hg, borderline if it is between 10 and 20 mm Hg, or problematic if it is greater than 20 mm Hg.
- **Allen test (test of palmar arch patency):**
 - **Main idea:** The Allen test measures collateral flow between the radial and ulnar arteries at the palmar arch.
 - **Steps: Do the following for the ulnar artery and repeat them for the radial artery:**
 1. Compress both the radial and ulnar arteries at the wrist simultaneously.
 2. With the arteries compressed firmly, instruct the patient to create a fist repetitively to cause the palm to blanch.
 3. When the patient's hand is blanched, release the compression of the ulnar artery and watch the palm to determine if it becomes pink. Then, release all compression.
 - **Interpretation:**
 - When colour returns to the blanched palm upon release of the arterial compression, it indicates arterial patency and flow adequacy.
 - Blanching that persists for ≥ 5 seconds after release of the ulnar or radial artery is a positive sign of insufficiency.
- **Examine for the evidence of heart failure:**
 - Severe heart failure patients might be unable to tolerate the increased cardiac output necessary for blood circulation through the access.
 - Low cardiac output may cause AVF maturation failure.
- **Examine neck, chest, and upper limbs:**
 - Check for any scar from a previously inserted central catheter or an old AV access.
 - Check for any signs of central vein stenosis such as arm edema or the appearance of venous collateral (central vein stenosis will be discussed in Chapter 12).
 - Check for any evidence of previous neck, chest, or upper limbs surgery.
- **Evidence of infection:** KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to identify infection risks that should first be managed before proceeding with AV access creation (e.g., dental infection, osteomyelitis, etc.).

Preoperative imaging:

I. Doppler ultrasonography:

- **Minimal vein and artery size:**
 - Generally, a minimum lumen diameter of 2.5 mm in the vein and 2 mm in the artery is required for a successful surgical anastomosis.
 - However, the KDOQI Vascular Access Guideline (2019 Update) mentioned that there is no minimum-diameter threshold to create an AVF and that arteries and veins of <2 mm in diameter should undergo careful evaluation for feasibility and quality to create a functioning AVF.
- **Mapping:** Assess both the ulnar and cephalic veins for:
 - Depth.
 - Continuity.
 - The absence of strictures.
- **Doppler limitation:** The main drawback of Doppler ultrasonography is the inadequate visualization of central vessels.

II. Venography:

- It is used to assess central veins if there is any evidence of central vein stenosis or a previous central vein procedure (e.g., pacemaker placement).
- KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to use the smallest volume of iodinated contrast or non-iodinated contrast agents (e.g., CO₂ gas) in all patients with CKD to preserve residual kidney function.

III. Arteriography:

- It is used when pulses are significantly diminished or absent at the desired access site or when there is a difference in mean arterial pressure of more than 20 mmHg between the two limbs.
- Use the smallest volume of iodinated or non-iodinated contrast agents (e.g., CO₂ gas) as mentioned above.

AVF types and possible locations

Conventional, transposed, and translocation fistula:

- **Conventional AVF:** In this procedure, an anastomosis is created between a superficial artery and vein.
- **Transposed AVF:** In this procedure, a deep vein is moved into a subcutaneous tunnel and anastomosed with an artery. Transposed AVF is usually done as a two-stage surgery.
- **Vein translocation AVF:** A vein is surgically extracted from its anatomical site in order to establish a connection between an artery and another vein:
 - To accomplish this, venovenous and venoarterial anastomosis must be formed with the translocated vein.
 - In order to reposition the vein, this method necessitates the development of a subcutaneous tunnel.

Generally rules:

- It is preferred to create an AVF in the nondominant arm. The dominant arm may be utilized only if all possible locations in the nondominant arm have been used.
- It is preferred to create the AVF distally in the upper limb. When distal areas fail, then go proximally.

Locations:

Multiple sites for AVF can be accessed in the upper limb (the most commonly used locations are shown in Figure 9.1):

- **Conventional AVFs:**
 - Snuffbox (distal-most site).
 - Radiocephalic (radial artery to forearm cephalic vein at the wrist).
 - Ulnar artery to forearm basilic vein (uncommon).
 - Brachial artery to upper arm cephalic vein (at the elbow).
- **Transposed AVFs:**
 - Forearm basilic vein to radial or artery at the wrist.
 - Forearm basilic vein to the brachial artery (loop configuration).
 - Forearm cephalic vein to the brachial artery (loop configuration).
 - Transposed basilic vein in the upper arm to the brachial artery.
 - Perforating veins in the proximal forearm to the proximal radial artery (Konner modification of the Gracz fistula).
- **Vein translocation AVFs:**
 - In general, the great saphenous vein is the most frequently utilized due to its straightforward harvesting process.
 - Femoral vein harvesting is infrequently done due to the extensive surgical procedure involved and the potential for severe complications that may arise.

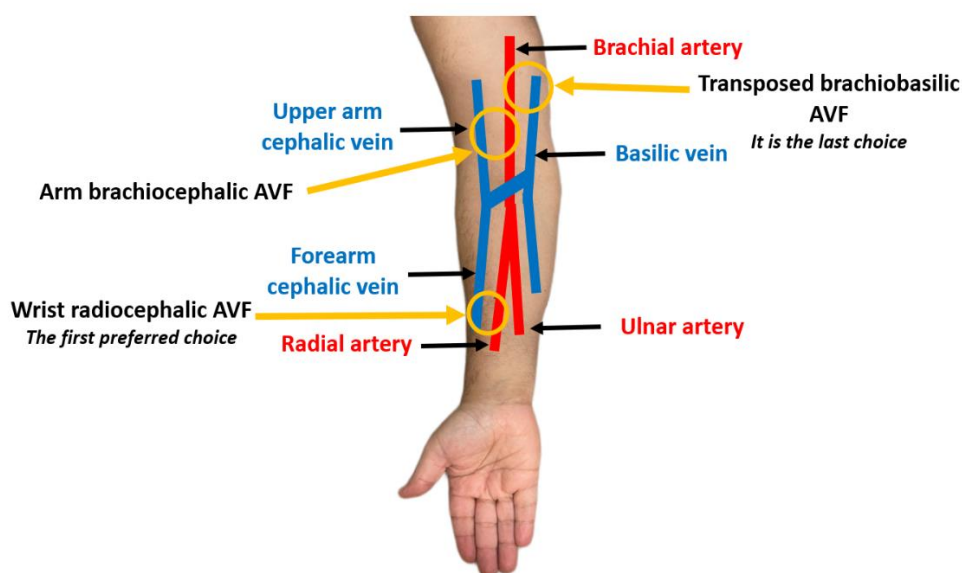


Figure 9.1. Most commonly created AVF sites

Techniques of anastomosis

- **Two techniques for anastomosis are used (Figure 9.2):**
 - **The side-to-side technique:** It may cause venous hypertension, which would manifest as hand edema and discomfort (referred to as "red hand syndrome").
 - **The side-to-end technique:** Venous hypertension doesn't occur in this technique as the vein is tied distally.
- **Anastomosis technique in relation to fistula site:**
 - Radiocephalic fistula can be done side-to-side or side-to-end anastomosis.
 - Brachiocephalic fistula is usually done side-to-side anastomosis.
- **The European Best Practice Guidelines - ERBP (2019)** mentioned that there is insufficient evidence to support side-to-end over side-to-side anastomosis for AVF creation.



Figure 9.2. Techniques of anastomosis

ERBP (2019): Perioperative prophylactic antibiotics for preventing AVF infection

- They suggest giving preoperative antibiotic prophylaxis for complex AVF procedures.
- They suggest not giving preoperative antibiotic prophylaxis for simple AVF (e.g., creation of a native radiocephalic or native brachiocephalic AVF) procedures.

Creation of AVF

- Surgical technique (under regional block or local anaesthesia) is the standard technique for AVF creation. The European Best Practice Guidelines (2019) suggest using regional block anaesthesia rather than local anaesthesia.
- Nowadays, endovascular techniques are available for creation of AVF connections.
- There is inadequate evidence for the KDOQI Vascular Access Guideline (2019 Update) to make a recommendation on the preferred use of surgical or endovascular techniques for postoperative maturation.

AVF post-operative instructions

- The arm should initially be kept **elevated**.
- Check the AVF daily for the presence of **thrill and bruit**.
- **Avoid the following:**
 - Compression of the fistula during sleeping.
 - Tight circumferential dressings.
 - Venipuncture from the fistula.

- **KDOQI Vascular Access Guideline (2019 Update) statements for the AVF post-operative period:**
 - **Post-operative exercise:**
 - There is inadequate evidence to make a recommendation on the use of upper extremity exercise to facilitate postoperative AVF maturation.
 - Use the whole arm rather than finger exercise if exercise is used to facilitate AVF maturation.
 - The use of **adjuvant far-infrared therapy** to improve AVF primary patency should be based on individual circumstances, feasibility, and the clinician's best judgment and expertise.
 - **AVF should be evaluated by a surgeon/operator:**
 - Within 2 weeks of creation for early detection of any postoperative complications
 - Within 4–6 weeks of creation for signs of maturation (see below).

Post-operative mature AVF (rule of sixes)

KDOQI Vascular Access Guideline (2019 Update) recommends that all new AVFs should be examined by an appropriate member of the vascular access team within **4–6 weeks** of creation for signs of maturation. The following criteria and signs “**rule of 6**” are indicators of AVF maturation:

- Maturation should typically occur **6** weeks following surgery.
- The venous segment should be less than **6** mm below the skin.
- The venous segment should be **6** mm in diameter.
- A straight venous segment with a minimum length of **6** cm is required for cannulation.
- A minimum blood flow rate of **600** mL/min (500–800 mL/min through forearm AVF).

AVF first use (cannulation)

- AVF must be allowed to mature before cannulation, as premature cannulation trials can be associated with infiltration, vessel compression, and permanent fistula loss.
- The longer the wait before use, the better the fistula outcome.
- The first cannulation is a source of anxiety for the patient and often for the cannulator as well.
- The following are the recommendations of KDOQI Vascular Access Work Group (2006) for first cannulation.

I. Day of the week:

- It is optimal to try the initial cannulation on a **day without dialysis**. This helps to avoid any heparin administration-related complications.
- If trial cannulation on a non-dialysis day is not possible, the initial trial cannulation can be done at a **midweek treatment**. This decreases the possibility of complications related to the dialysis after a long weekend interval (e.g., volume overload and high blood chemistries).

II. Use “wet needle” technique:

- **Steps**

- Attach a 10-mL syringe filled with 8 mL of normal saline solution to the AVF needle, but do not prime the needle until immediately before the cannulation.
- Grasp the fistula needle by the butterfly wings and prime the needle with normal saline until all the air is purged. Clamp the needle closed. Remove the protective cap and immediately proceed with the cannulation technique.
- When the needle has advanced into the vessel, a blood flashback will be visible (the needle may need to be unclamped to see the blood flashback). When blood is visible, aspirate back 1 to 5 mL with the 10-mL syringe. Flush the needle with the normal saline solution and clamp. The syringe must aspirate and flush with ease. Monitor for signs or symptoms of infiltration. Patients usually experience sharp pain upon infiltration of saline or blood into the tissues.
- Blood return from the needle alone is insufficient to indicate proper needle placement; therefore, before connecting the needles to the blood pump, needle placement should be confirmed with a normal saline flush.

- **Advantages of “wet needle” techniques:**

- If saline infiltration occurs, the normal saline is less harmful to the surrounding AVF tissue than if it was infiltrated by blood.
- The use of a “wet needle” eliminates the potential for blood to leak or spill from the needle when the caps are opened.

III. Needle with a “backeye”:

A needle with a backeye is consistently recommended to optimize flow from the access site and minimize the need for needle rotation.

IV. Needle size selection:

- It is recommended to use a small size needle (**preferred 17G**) for initial cannulation trials.
- Increasing the needle size later on subsequent dialysis depends on the fistula's performance.

V. Use ultrasound:

KDOQI Vascular Access Guideline (2019 Update) and ERBP (2019) consider it reasonable to use ultrasound for proper needle placement in AVF of selected patients as needed and performed by trained operators to prevent cannulation complications. The use of ultrasound is recommended for both the first cannulation and regular cannulations later.

General instructions for regular cannulation of AVF

1. Educate the patient on washing the access arm using antiseptic to clean the skin before every cannulation.

2. Skin preparation: An aseptic technique must be used.

3. Anesthesia with a topical cream: This is suggested to be used, however rarely needed, in patients with high pain sensitivity.

4. Use of tourniquets for AVF: Tourniquet enlarges the vein and facilitates AVF cannulation.

5. Ultrasound use: As mentioned above, KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to use ultrasound in the AV access of select patients to prevent cannulation complications.

6. Needle size (Table 9.1):

- As mentioned before, during the initial cannulation trials, it is recommended to use small needles (preferred 17G).
- In subsequent hemodialysis sessions, larger needles are used to allow a high blood flow rate (>350 mL/min).

Table 9.1. Hemodialysis needle size, colour, and maximum blood flow rate

Needle wings color	Needle gauge	Maximum blood flow rate
Red	17G	< 300 mL/min
Green	16G	300-350 mL/min
Blue	15G	150-450 mL/min
White	14G	> 450 mL/min

7. Arterial and venous needles positioning: These two needles are placed into the venous segment (discussed in Table 9.2 and illustrated in Figure 9.3).

Table 9.2. Position characteristics of arterial and venous needle of arteriovenous access

	Arterial “inlet or upstream” needle	Venous “outlet or downstream” needle
Definition	This is the needle that withdraws blood from the patient to the dialyzer.	This is the needle that returns the blood to the patient.
Position and spacing	It is placed in the upstream segment (near the blood inlet into the fistula) at ≥ 3 cm away from the site of arterial anastomosis.	It is placed 5-6 cm downstream (proximal) to the arterial needle to minimize recirculation.
Orientation (pointing)	<ul style="list-style-type: none"> • The arterial needle may point either upstream (toward the fistula) or downstream (toward the heart). • Arterial needle pointing in a downstream direction is a popular approach. This is because the “flap” left behind when the needle is withdrawn tends to close more naturally with blood flow. 	It should be inserted pointing downstream (pointing toward the heart) to minimize recirculation.

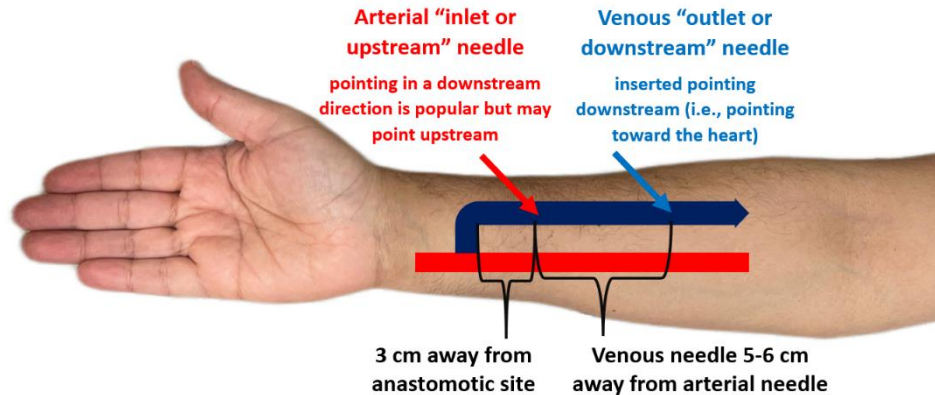


Figure 9.3. Position characteristics of arterial and venous needle of arteriovenous access

8. Needle insertion angle: KDOQI Vascular Access Work Group (2006) suggests inserting the needle at approximately 25° angle with the bevel up.

9. Needle axis rotation: It is suggested to rotate the needle 180 degrees along its axis following insertion in order to reduce the risk of needlepoint injury to the back wall of the vessel.

10. Cannulation techniques:

a. First technique: The "rope ladder" technique (rotational cannulation approach):

- This approach means using the entire length of the access for cannulation without localizing needle sticks to fixed two areas (Figure 9.4).
- Cannulating needle sticks in fixed specific areas with every hemodialysis session weakens the fistula wall and forms an aneurysm.

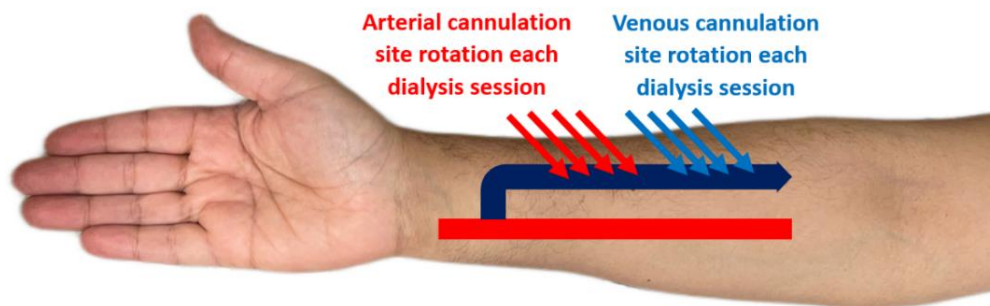


Figure 9.4. "Rope ladder" technique (rotational cannulation approach)

b. Second Technique: Buttonhole cannulation technique:

- **Technique:**
 - The AVF is always punctured by sharp needles in the exact same spot, at the same angle, at the same needle track, and at the same penetration depth every time.
 - After the creation of the buttonhole tract by sharp needles, blunted needles can now be used through this tract.

- **Disadvantages of the buttonhole technique:**
 - It increases the risk of infection. Strict antiseptic measures must be followed while using the buttonhole technique.
 - The degree of its success may be highly technique-dependent.
- **KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to limit AVF buttonhole cannulation (because of infection risk) only to special circumstances, such as:**
 - AVF has only a short or small segment for cannulation.
 - Enlarging or large aneurysm (to prevent its further expansion).
 - Failure of rope-ladder cannulation for cannulators (e.g., home hemodialysis) who have established excellent hygiene and cannulation technique.

11. Preventing of infiltration:

- Lifting the needle up should be avoided after its insertion.
- Use of proper taping helps to prevent infiltration.
- Proper needle removal prevents post-dialysis infiltration:
 - Before removing the needle, apply the gauze dressing over the needle site, but do not apply pressure yet.
 - Next, carefully remove the needle at approximately the same angle as it was inserted. This prevents dragging the needle across the patient's skin.
 - Avoid a steep angle during needle removal as it may result in a vein wall puncture by the needle's cutting tip.
 - Don't apply any pressure (whatever its strength) to the puncture site until the needle has been fully extracted.
- Monitor closely for any signs of infiltration.
- If infiltration happens, a prompt response is required. How to deal with infiltration is discussed later in the "complications" section.

12. Hemostasis post-dialysis:

- After removing the needle, apply firm pressure to the puncture site using one or two fingertips. Ensure the pressure is not too strong, which may obstruct the AV access flow.
- Pressure must be maintained for a minimum of 10 minutes before assessing for bleeding at the puncture site.
- If prolonged bleeding >20 minutes, consider the following to detect the cause (also mentioned before in Chapter 7):
 - Re-evaluate the dose of heparin.
 - Evaluate vascular access for the possibility of outflow stenosis.
 - Evaluate the needle insertion technique.
 - Check if the patient is on oral anticoagulants.
- It is not advisable to apply any adhesive bandages until complete hemostasis has been accomplished.

Upper extremity arteriovenous graft (AVG)

Main indication and when should AVG be created?

- AVG is indicated **if an AVF cannot be created** due to narrow or non-distensible vessels.
- In contrast to AVF, AVG does not require a long maturation time. AVG can be created when the patient is expected to start hemodialysis within **2-4 weeks**.

AVG preoperative evaluation

Generally, the preoperative evaluation for AVG is similar to that of AVF.

AVG material

- Polytetrafluoroethylene (PTFE) grafts are the most commonly used.
- Biologic grafts (more likely to become aneurysmal than PTFE grafts).
- Other grafts (tapered, elastic, and heparin-bonded grafts) showed no extra benefit over PTFE.

AVG possible locations

AVG can be created anywhere in the arm (preferably the nondominant). Examples:

- Looped forearm (brachial artery to cephalic vein, or brachial artery to the basilic vein).
- Straight forearm (radial artery to cephalic vein).
- Looped upper arm (axillary artery to axillary vein).
- Straight upper arm (brachial artery to axillary vein).

ERBP (2019): Perioperative prophylactic antibiotics for preventing AVG infection

They recommend giving preoperative antibiotic prophylaxis for AVG insertion.

AVG post-operative instructions

These are similar to that of AVF. There is no role for arm exercises to help AVG maturation.

AVG first use (cannulation)

- After placement, a PTFE graft **should not be cannulated before two weeks**. This duration is essential to ensure AVG maturation, which is indicated by the following:
 - Resolution of edema and erythema, which makes the graft easily and freely palpable.
 - Adhesion between the graft and the subcutaneous tunnel is developed, which prevents hematoma formation.
 - Flow through a mature forearm AVG is about 1,000 mL/min.
- **Premature AVG cannulation** before 2-3 weeks may lead to infection and blood extravasation into the tunnel, which compresses the graft and causes its loss.
- For AVG first use, follow the **same steps mentioned before for AVF first use**.

General instructions for regular cannulation of AVG

These instructions are the same as those for AVF, except for the following:

- **No need for the use of a tourniquet** in cases with AVG.
- **Needle insertion angle:** KDOQI Vascular Access Work Group (2006) suggests inserting the needle at approximately 45° angle with the bevel up.
- **The buttonhole cannulation technique**
 - It is not recommended in synthetic PTFE graft cannulation because of the high risk of infection of both the buttonhole and the AVG.
 - However, the buttonhole can be used for the cannulation of some other certain AVG materials.

Improving AVG patency: KDOQI Vascular Access Guideline (2019 Update) suggestions

- **The use of a combination of dipyridamole (200 mg) and aspirin (25 mg) twice daily** to improve AVG primary unassisted patency after careful consideration of potential individual patient benefits, risks, and circumstances.
- **Oral fish oil:**
 - It can be used in patients with newly created AVGs to reduce patient morbidity (i.e., reduce the frequency of thrombosis and related corrective interventions).
 - There is inadequate evidence to make a recommendation on the use of oral fish oil supplementation to prolong AVG cumulative patency.

AVF versus AVG:

KDOQI Vascular Access Guideline (2019 Update) Considerations: Change in concepts from “fistula first” to “patient first”

- Historically, guidelines strongly promoted AVFs as the first option because of lower complication rates. However, several observations challenged this “fistula first” approach. That’s why the KDOQI (2019 Update) has adopted a new patient-centered approach that considers multiple aspects of a patient’s needs and dialysis access eligibility, as there is often not a simple one-size-fits-all answer for the ideal dialysis access to all patients. **The main concept is changed by KDOQI (2019 Update) from “fistula first” to “patient first” or, in other terms, “the right access, in the right patient, at the right time,”** as KDOQI considers it reasonable to choose the site of the AV access after careful consideration of the patient’s ESKD Life-Plan. Table 9.3 shows KDOQI (2019 Update) considerations regarding the choice of vascular access location.
- Check KDOQI Vascular Access Guideline (2019 Update) (from page S36 to page S39) for several algorithms discussing patients’ different pathways. Also, check (page S44) for case examples of different ESKD Life-Plans.

Table 9.3. KDOQI Vascular Access Guideline (2019 Update) paths for the AV access location (AVF or AVG) choice after careful consideration of the patient's ESKD Life-Plan

Path	Patient's ESKD Life-Plan	Site (location) of AV access
A	Anticipated long duration (e.g., >1 year) on hemodialysis (HD).	<ul style="list-style-type: none"> Forearm AVF (snuffbox or distal radiocephalic or transposed radiobasilic). Forearm loop AVG or proximal forearm AVF (e.g., proximal radiocephalic, proximal vessel, and perforator combinations) or brachiocephalic, per operator discretion. Brachio basilic AVF or upper arm AVG, per operator discretion.
B	Anticipated limited duration (e.g., <1 year) on HD.	<ul style="list-style-type: none"> Forearm loop AVG or brachiocephalic AVF (with a high likelihood of unassisted maturation). Upper arm AVG.
C	A patient urgently starts HD without prior sufficient time to plan for and/or create an AV access and has an anticipated limited duration (e.g., <1 year) on HD.	<ul style="list-style-type: none"> Early or standard cannulation loop AVG (forearm or upper arm location) or central venous catheter (CVC), per operator discretion and patient's clinical needs.
D	A patient urgently starts HD without prior sufficient time to plan for and/or create an AV access and has an anticipated long duration (e.g., >1 year) on HD.	<ul style="list-style-type: none"> Peritoneal dialysis (PD) catheter, and follow path (A) if PD is not a long-term option or Forearm early cannulation loop graft; when AVG fails, follow path (A) or CVC if there is a high likelihood of rapid AVF maturation and usability success, then follow path (A).
General considerations suggested by KDOQI (2019 Update) for AV access creation: <ul style="list-style-type: none"> KDOQI suggests an AV access (AVF or AVG) in preference to a CVC in most incident* and prevalent[¶] HD patients, if possible, due to the association with lower vascular access-related events (e.g., infection, thrombotic, and non-thrombotic complications). KDOQI suggests that if sufficient time and HD patient (incident* and prevalent[¶]) circumstances are favorable for a mature, usable AVF, such a functioning AVF is preferred to an AVG due to fewer long-term vascular access events (e.g., thrombosis, loss of primary patency, interventions) associated with unassisted[‡] AVF use. 		

* Incident HD patients are newly diagnosed ESKD patients initiating HD.

¶ Prevalent HD patients are those who receiving HD for > 3 months.

‡ Unassisted AVF use refers to an AVF that matures and is used without the need for endovascular or surgical interventions, such as angioplasty. A preplanned vessel superficialization is acceptable and not considered an additional intervention.

“Lower extremity AVF or AVG” or “HeRO Graft”

- The HeRO graft is a vascular access that comprises a hybrid PTFE graft–catheter system.
- The KDOQI Vascular Access Guideline (2019 Update) suggests that if all arteriovenous access options in the upper extremity have been exhausted and the patient’s ESKD Life-Plan includes a long duration (e.g., >1 year) on hemodialysis, “lower extremity AVF or AVG” or “HeRO Graft (Merit Medical)” may be considered based on individual patient circumstances and the operator’s best clinical judgment and expertise.
- AV access in the lower extremity has a high complication rate and poor outcome.

Clinical monitoring (physical examination) of AVF and AVG

- Clinical monitoring (physical examination) is noninvasive and cost-effective for evaluating AV access. Multiple studies have shown that physical examination can detect and localize stenotic lesions in most patients with AV access.
- KDOQI considers it reasonable for nephrology trainees and health practitioners involved with clinical HD patient care to be properly trained in physical examination of the AV access.
- KDOQI Vascular Access Guideline (2019 Update) recommends assessing the vascular access and surrounding area by physical exam **before every cannulation** to detect clinical indicators of flow dysfunction or any potential complication.

I. Inspection (Look)

1. Vascular access scar site helps to know the site of the anastomosis, for example (Figure 9.5):

- Wrist radiocephalic AVF scar is longitudinal in shape above the wrist.
- Brachiocephalic AVF scar is transverse over the antecubital fossa.
- Transposed brachiobasilic AVF scar is longitudinal in the inner side of the arm.

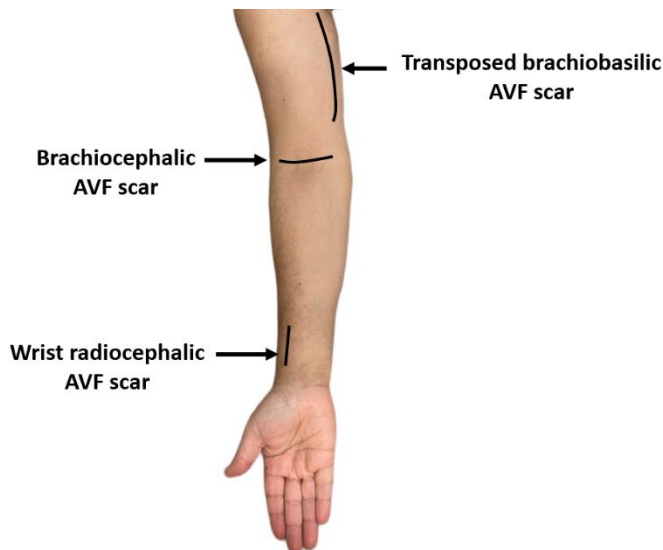


Figure 9.5. Arteriovenous fistulas scar site

2. Signs of infection/inflammation:

- Redness.
- Swelling.
- Induration.
- Drainage.
- Pus.
- Skin rash may be due to allergic reaction to:
 - Betaine.
 - Antibiotic cream.
 - Any other locally administered material.
- It may be associated with pain and fever

3. Infiltration and/or hematoma: Due to improper cannulation technique.**4. Signs of hand ischemia (steal syndrome)** (more details about steal syndrome will be discussed in chapter 10):

- Blue hands.
- Cold hands.
- Pain.
- Paresthesia.
- Skin ulcers in very severe cases.
- Some terminal cases may develop dry gangrene.

5. Aneurysm/Pseudoaneurysm (more details about aneurysm/pseudoaneurysm will be discussed in chapter 10):

- **Criteria of stable aneurysm/pseudoaneurysm:**
 - Overlying skin is intact without any change in pigmentation.
 - The fistula has no evidence of outflow obstruction on physical examination by arm elevation test (see arm elevation test below).
 - Stationary aneurysm size.
- **Criteria of unstable aneurysm/pseudoaneurysm “impending rupture” (it is considered a surgical emergency, and access must be ligated):**
 - Thin and shiny overlying skin.
 - Depigmentation of overlying skin.
 - Ulceration of overlying skin.
 - Rapid enlargement in size.
 - Prolonged leaking after needle removal.

6. Signs of central vein stenosis (more details about central vein stenosis will be discussed in chapter 12):

- The presence of edema in the face, neck, upper extremities, or breasts.
- Increased arm circumference at the ipsilateral side of central vein stenosis than the other arm
- Presence of collaterals on chest wall and shoulders.

7. Notice any scars on the chest wall for evidence of previous catheter insertion sites.

II. Palpation (Feel)

1. **Palpate AV access pulse and thrill characters:** Normal and abnormal AV access pulse and thrill characters are described in Table 9.4.
2. **Access versus non-access extremity:** Items to compare between the two upper extremities are discussed in Table 9.5.

Table 9.4. AV access pulse and thrill characters in normal and abnormal conditions

AV access pulse		AV access thrill (Examine the thrill from the site of anastomosis all the way to the chest wall)
Normally	Soft pulse that is easily compressed by the application of gentle pressure.	The thrill is continuous (i.e., systolic and diastolic) except at the arterial anastomosis, where it is normally discontinuous.
Outflow (downstream) stenosis*	<ul style="list-style-type: none"> • Hyper-pulsatile, water-hammer pulse. • The clinical history that goes with this scenario is the presence of prolonged bleeding after removal of the access needles. 	Thrill becomes discontinuous (frequently systolic) and can be felt immediately downstream (i.e., proximal near to heart) from a stenosis.
Inflow (upstream) stenosis*	<ul style="list-style-type: none"> • Hypo-pulsatile, feeble, flat. • The clinical history that goes with this scenario is the inability to aspirate blood from the arterial needle (needle pulling negative pressure). 	Thrill is weak or absent.

* More details about AV access stenosis will be discussed in Chapter 10.

Table 9.5. Compare access versus non-access upper extremity

Test	Suspected Abnormality
Temperature	<ul style="list-style-type: none"> • Warm + swelling = infection • Cold = steal syndrome
Grip strength	
Range of motion	To detect steal syndrome
Sensory loss	

III. Auscultation (Listen)

1. AV access auscultation:

Auscultate the AV access to assess the bruit. Auscultate AV access from the site of anastomosis all the way to the chest wall:

- **Normally:** Continues bruit (systolic and diastolic).
- **Outflow (downstream) stenosis:** High pitched loud, discontinuous bruit immediately downstream (i.e., proximal near to heart) from stenosis.
- **Inflow (upstream) stenosis:** Low-pitched quiet bruit.

2. Heart auscultation:

- Heart auscultation is essential for early detection of newly formed murmurs, which may suggest infective endocarditis.
- If there is a murmur heard over the heart, compress and occlude AV access by your finger:
 - If the murmur disappears, it is a sound transmitted from AV access (i.e., not an actual heart murmur).
 - If the murmur doesn't disappear, it is actually a heart murmur.

IV. AV access specific tests

1. Arm elevation test (Figure 9.6):

- **Importance:** It assesses the possibility of outflow (downstream) stenosis.
- **Method of the test:** Elevate the patient's AV access limb, then observe whether the AV access or the aneurysm has collapsed.
- **Results:**
 - **Normally (Figure 9.6-A):** The AV access collapses.
 - **Outflow (downstream) stenosis (Figure 9.6-B):** After arm elevation, the access remains distended and does not undergo collapse.

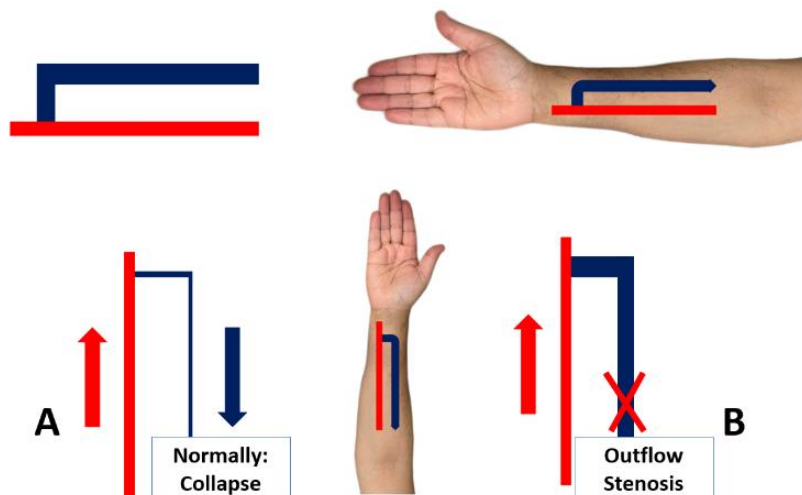


Figure 9.6. Arm elevation test

2. Augmentation test (Figure 9.7):

- **Importance:** It assesses the possibility of inflow (upstream) stenosis.
- **Method of the test:**
 - Place one of your fingers on the outflow venous segment several centimeters beyond the arterial anastomosis, and press down to occlude the access till no blood is flowing through the access.
 - Feel the pulse strength by the other finger distally to the point of occlusion.
- **Results:**
 - **Normally (Figure 9.7-B):** In well-functioning AV access, the thrill disappears, and the pulse distal to occlusion is strong and bounding (i.e., augmented pulse), and this may cause the distal finger to rise and fall with each beat, indicating good inflow to the fistula.
 - **Inflow (upstream) stenosis (Figure 9.7-C):** No pulse augmentation happens, and no thrill is felt by the distal finger.
 - **Accessory veins (collaterals) in case of AVF (Figure 9.7-D):**
 - If no pulse augmentation happened, but the distal finger feels a thrill, this indicates the presence of multiple collaterals (accessory veins) causing “siphon off” (i.e., draining of) the blood out from the main venous segment).
 - These accessory veins can cause early maturation failure of the AVF (this will be discussed in Chapter 10).
 - To determine the accessory veins (collaterals) level, do the sequential occlusion test (see next).

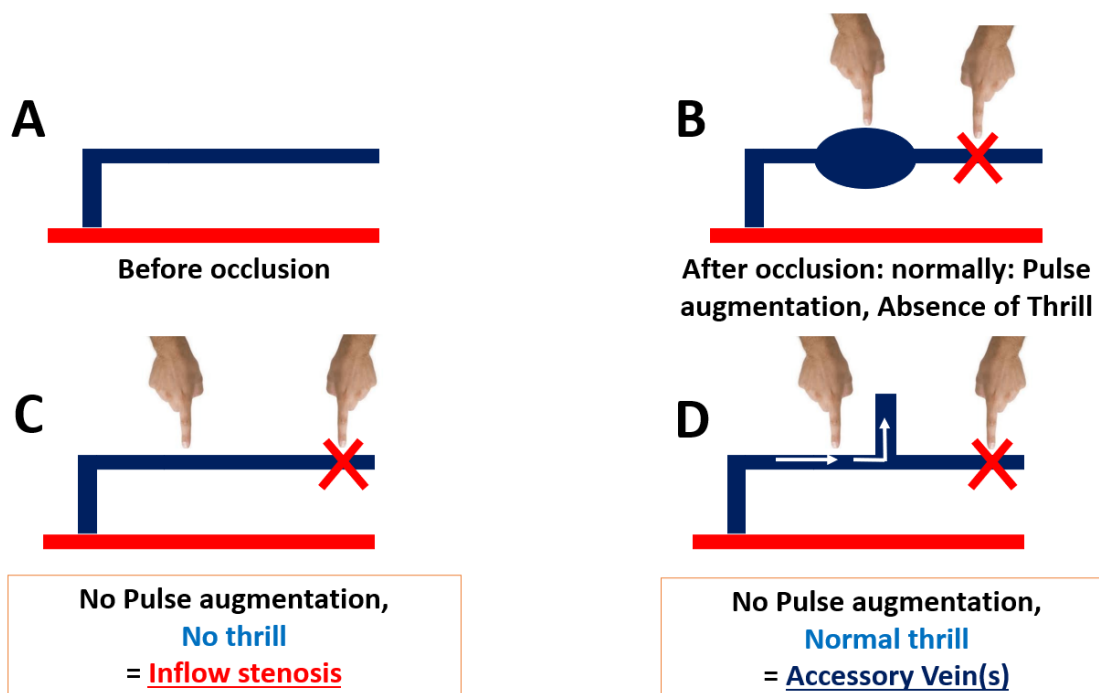


Figure 9.7. Augmentation test

3. Sequential occlusion test:

- **Importance:** To determine the level of the accessory veins (collaterals) in cases of AVF.
- **Method of the test and results (Figure 9.8):**
 - Move the occluding finger toward the anastomosis of the fistula.
 - When the thrill disappears and the access augments, so the examiner's occluding finger has just passed the site of the collateral.
 - Moving the occluding finger away again from the anastomosis should bring the thrill back.

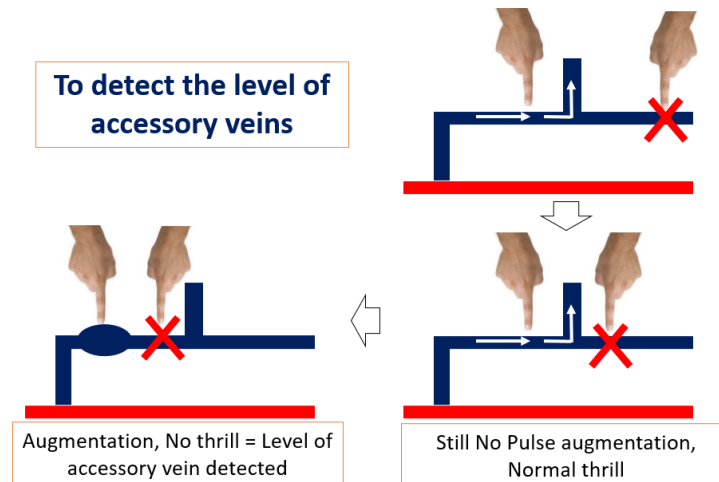


Figure 9.8. Sequential occlusion test

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Chapter 10

Arteriovenous Fistula and Graft (AVF and AVG): Complications (Diagnosis and Management)

Postoperative swelling, edema, and pain

- These are frequently occurring and typically resolve within a few days.
- Generally, elevating the arm serves to relieve these symptoms.

Primary maturation failure of AVF

Definition of AVF primary maturation failure

It is the failure of the AVF venous segment to mature at six weeks after creation.

Incidence of AVF primary maturation failure

Primary AVF maturation failure is a common problem, occurring in about 10% to 35% of AVFs.

Possible reasons for AVF primary maturation failure

- **Poor surgical technique** with poor anastomosis.
- **Poor vessels:** Pre-existing vascular calcification or sclerosis.
- **Stenosis close to anastomosis (juxta-anastomotic):** present in >70% of non-maturation cases.
- **Early thrombosis soon after fistula construction results from:**
 - Surgical technical factors.
 - Compression of the AVF while the patient is asleep.
- **Several collaterals (accessory veins)** from the main venous segment drain (siphon off) the blood out from the main venous segment; this causes a decreased pressure in the main venous segment. Accessory veins can be detected by augmentation test and sequential occlusion test (discussed before in Chapter 9).

Diagnosis of AVF primary maturation failure

Every fistula that fails to mature at six weeks should undergo a **fistulogram**.

Treatment of AVF primary maturation failure

- **Stenosis after fistula construction:** see stenosis treatment later.
- **Thrombosis after fistula construction:** see thrombosis treatment later.
- **Accessory veins:** An obliteration procedure of these collaterals helps the fistula to mature.

Venous hypertension

- Following AV access creation, a slight increase in the circumference of the arm with the access (two to three centimeters) is typical; however, an increase in arm circumference more than this is usually an indicator of venous hypertension or stenosis of the central veins.
- As mentioned in Chapter 9, venous hypertension is common after side-to-side anastomosis.
- Venous hypertension and extremity swelling are most commonly due to central vein stenosis secondary to previous central catheters (this will be discussed in Chapter 12).

Needle infiltration

Prevention of infiltration was discussed in Chapter 9. An immediate reaction to needle infiltration prevents access damage. The following are the lines to deal with infiltration once it has happened.

- **Dealing with the needle at the site of filtration:**
 - **Needle removal:**
 - Remove the needle and apply compression. Care must be taken to clot the needle tract, not the AV access, then:
 - Temporary AV access rest is suggested (see next).
 - If dialysis cannot be postponed and AV access rest is not an option, re-cannulate the AV access (see next the instructions for re-cannulation).
 - Some experts suggest leaving the needle in place and re-cannulating the AV access at another new site; if dialysis cannot be postponed and AV access, rest is not an option (see next the instructions for re-cannulation).
 - **Application of ice:** A 10-minute application of ice to the affected area helps to reduce the bleeding and the extent of the infiltration.
- **AV access rest:**
 - Temporary AV access rest is suggested by some experts for ≥ 1 dialysis session, whatever the size of the infiltration. However, the KDOQI Vascular Access Guideline (2019 Update) suggested rest only in cases of significantly large infiltration.
 - If dialysis cannot be postponed and AV access rest is not an option, re-cannulate the AV access. The following instructions must be followed for re-cannulation:
 - Cannulate the AV access at a new site downstream (proximal) to the infiltration site.
 - If there is no more proximal site for cannulation, the KDOQI Vascular Access Guideline (2019 Update) states that a reattempt at the area of injury should not proceed until local pressure and ice are applied for 30 min.
- **If a hematoma develops, a close assessment should be made, including:**
 - Measurement of swelling.
 - Assessment of flow in the access proximal and distal to the hematoma.
 - Assessment of the circulation to the extremity.

AV access stenosis

Site of AV access stenosis

Stenosis can occur in any area of AVF or AVG. The most common sites:

- **AVG:** The most common cause of stenosis in AVG is neointimal hyperplasia, which usually occurs at or just distal to the graft–vein anastomosis. The cause of accelerated neointimal hyperplasia in AVG is thought to be:
 - Turbulence downstream to the graft–vein anastomosis.
 - A compliance mismatch between the relatively rigid graft and the more flexible vein.
- **AVF:** The juxta-anastomotic region is the frequent site of stenosis.

Outflow versus inflow stenoses

- **Inflow stenosis:** This is common in both AVF and AVG.
- **Outflow stenosis:**
 - It is more common with AVG than AVF.
 - In AVF:
 - In upper arm fistulas, outflow stenosis is not uncommon.
 - In the forearm fistulas, outflow stenosis is not common because:
 - The degree of neointimal hyperplasia is low.
 - Presence of accessory outflow collateral veins compensates for obstruction of the main AVF segment.

AV access stenosis consequences

AV access stenosis has bad consequences:

- Vascular access stenosis leads to thrombosis.
- Stenosis reduces access blood flow and can lead to under-dialysis.

Clinical indicators of AV access stenosis (AVF and AVG monitoring)

1. Physical examination:

- Physical examination is useful in detecting isolated inflow or outflow access stenoses but is less effective in detecting combined inflow and outflow lesions.
- Clinical tests to diagnose stenosis are the arm elevation and augmentation tests (discussed before in Chapter 9).

2. Hemodialysis machine pressure changes:

Outflow and inflow stenoses can affect venous and pre-pump arterial pressures during hemodialysis sessions. Therefore, measuring these pressure changes over time (trending or dynamic pressure changes) can be an indirect method of diagnosing stenosis.

- **Trending (dynamic) venous pressure changes to diagnose access outflow stenosis:**
 - Access outflow stenosis should be suspected when there is a progressive rise in venous pressure on three or more treatments in succession without a change in needle size or blood flow.
 - Access outflow stenosis should also be suspected when there is an increased venous pressure of >120mmHg for 15-gauge needles and >150mmHg for 16-gauge needles at a low blood flow of 200 ml/min for three dialysis sessions. The main concept for using a blood flow rate of 200 ml/min in this method is that at high blood flow rates, much of the resistance to flow is from the needle and not the vascular access.
- **Trending (dynamic) pre-pump arterial pressure changes to diagnose access inflow stenosis:** Access inflow stenosis should be suspected when there is a progressive increase of pre-pump arterial pressure (in a negative direction) on three or more treatments in succession.

3. Post-dialysis prolonged bleeding (>20 minutes) at needle puncture site: Vascular access outflow stenosis should be one of the causes to be evaluated to diagnose the cause of prolonged bleeding (other causes were mentioned in Chapter 7).

4. Dialysis dose: Reduced dialysis clearance suggests stenosis in the absence of other known causes.

Diagnosis of AV access stenosis (AVF and AVG surveillance)

- KDOQI Vascular Access Guideline (2019 Update) mentioned that there is inadequate evidence to make a recommendation on routine AVF or AVG surveillance by measuring access blood flow, intra-access pressure monitoring, or imaging for stenosis, that is additional to regular clinical indicators (mentioned above), to improve access patency. In other words, clinical access monitoring is primary, while surveillance is supplementary.
- Randomized controlled trials have shown that:
 - In AVG: Surveillance to detect stenosis and correction with angioplasty has not been shown to improve graft survival.
 - In AVF: Surveillance has been shown to decrease the incidence of thrombosis but may not improve fistula survival.
- The following are the methods used for AV access surveillance and detection of stenosis.

1. Measuring intra-access pressure:

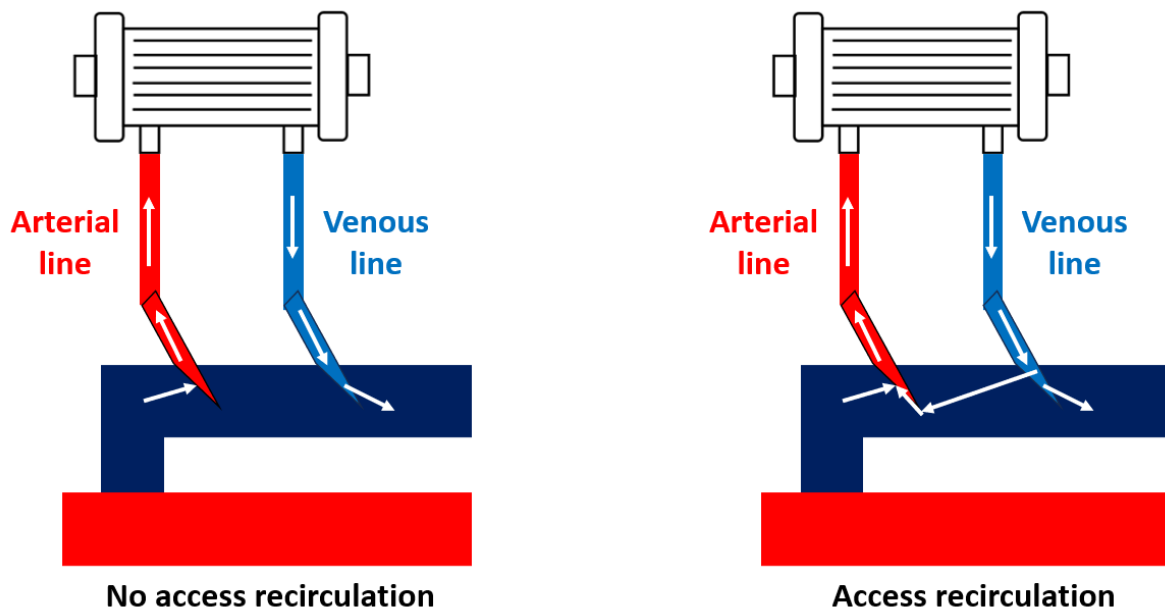
- Increased intra-access pressure can be used as an indicator of access stenosis.
- Normally:
 - In AVG, the pressure decreases continuously throughout the graft, generally less than 50% of the mean arterial pressure (MAP).
 - AVF intra-access pressure is, on average, lower than in an AVG. The pressure decreases suddenly in the venous segment of the fistula soon after the AV anastomosis, and it equals approximately 20% of the pressure in the feeding artery.
- Abnormalities of intra-access pressure in relation to stenosis are discussed in Table 10.1.

Table 10.1. Measuring intra-access pressure to diagnose stenosis

Problem	Effect on intra-access pressure
Outflow stenosis due to neointimal hyperplasia at or downstream from the vein anastomosis	<p>AVG outflow stenosis:</p> <ul style="list-style-type: none"> Intra-access pressure rises $>50\%$ MAP (i.e., intra-access pressure/MAP >0.50), and flow decreases. When intra-access pressure exceeds 50% of MAP, graft flow typically drops to 600–800 mL/min, making the AVG susceptible to thrombosis. AVG intra-access pressure may not increase with outlet stenosis and is less valuable as a surveillance tool. <p>AVF outflow stenosis:</p> <ul style="list-style-type: none"> In AVF, blood entering the venous segment may return via multiple collateral veins and bypass the stenosis, so intra-access pressure in an AVF may not increase with outlet stenosis and is less valuable as a surveillance tool.
Inflow stenosis	This causes decreased intra-access pressure all through the access.
If a stenosis develops in the body of an AVG between the areas used for arterial and venous limb cannulation	<ul style="list-style-type: none"> Intra-access pressure at the arterial end increases. Intra-access pressure at the venous needle remains normal or can even decrease.

2. Access recirculation:

- Definition:** Dialyzed blood returning through the venous needle re-enters the extracorporeal circuit through the arterial needle rather than returning to the systemic circulation (Figure 10.1).

**Figure 10.1. Access recirculation**

- **Causes:**

1. **Low access blood flow rate due to stenosis:** Recirculation does not occur until stenosis is enough to decrease access blood flow to a level near or less than the prescribed pump flow (around 350–500 mL/min).

2. **Other causes of access recirculation rather than stenosis:**

- Reversed needle placement causes recirculation by 20 percent or more.
- Misdirection of the venous needle by placing it pointing upstream (i.e., pointing toward the anastomosis site).
- Placing needles too closely together: Recirculation does not result from placing needles too closely together as long as access blood flow exceeds the machine blood flow rate.

- **Methods to assess access recirculation:**

1. **Two-needle urea-based (chemical) method:**

- Steps to do the two-needle urea-based method (Figure 10.2):
 - Turn off ultrafiltration 30 minutes after the initiation of hemodialysis.
 - Obtain arterial (A) and venous (V) line samples.
 - Reduce blood flow to 50 mL/min (reduces the entry of dialyzed cleared blood into the arterial access), wait for 10–20 seconds, then obtain another blood sample from the arterial blood line (P).
 - Use the formula $[(P - A) \div (P - V)] \times 100$ to detect the percent of recirculation.
- If access recirculation exists (Figure 10.3): The blood urea concentration in the blood entering the arterial line (A) will be lower than that in the blood sample from the arterial blood line (P), indicating that dialyzed blood re-enters to the arterial line rather than returning to the systemic circulation. For example, if (P) is 100 mg/dl, (A) is 80 mg/dl, and (V) is 30 mg/dl. Using the formula mentioned above, the percentage of access circulation is 28%.
- Recirculation percentage: Recirculation exceeding 10% using the two-needle urea-based method should prompt investigation to diagnose the cause.

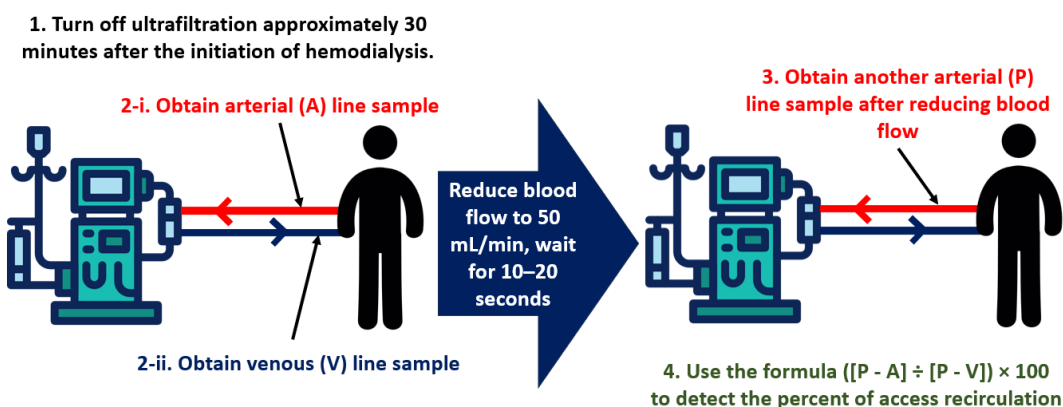


Figure 10.2. Two-needle urea-based (chemical) method

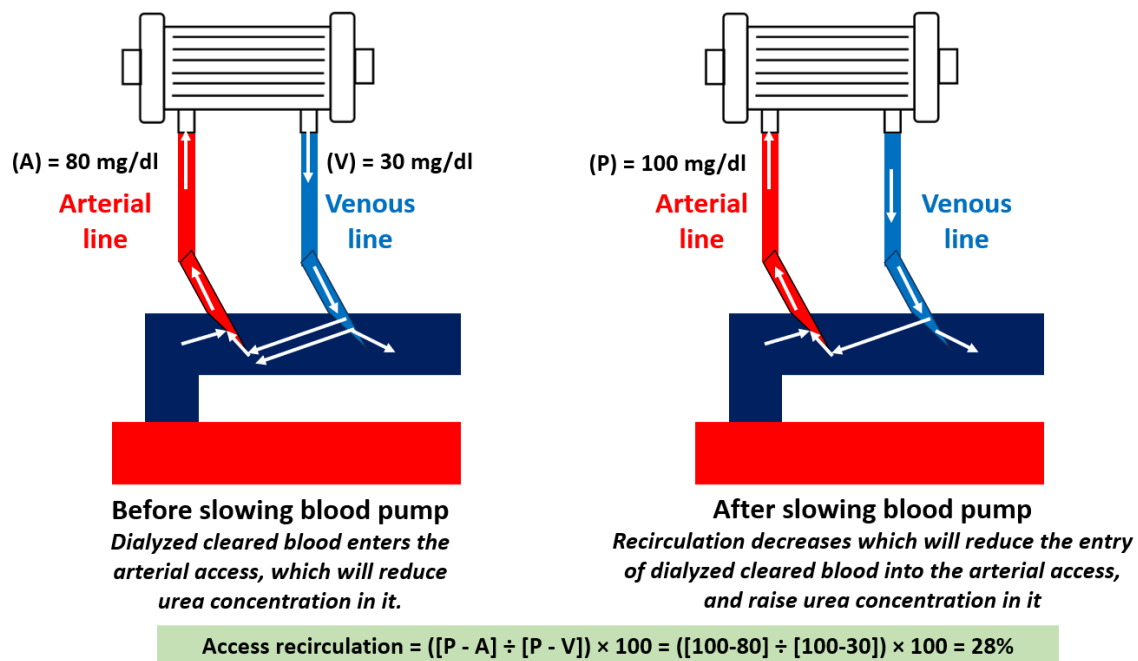


Figure 10.3. Access recirculation calculation in the two-needle urea-based (chemical) method

2. Three-needle urea-based (chemical) method:

- This method uses the same formula mentioned above for the two-needle urea-based method, but the difference is in (P).
- In the three-needle urea-based method (Figure 10.4), a blood sample is obtained from the patient contralateral (non-access) arm instead of getting a blood sample from the arterial line after slowing the blood pump.
- Blood urea sample from the contralateral arm represents (P) in the formula.
- KDOQI Vascular Access Work Group (2006) mentioned that the three-needle urea-based approach should not be used to measure recirculation because of the following:
 - This method overestimates recirculation as the BUN obtained from a peripheral vein in the contralateral (i.e., non-access) arm is often higher than the BUN in the blood entering the access, even in the absence of recirculation. BUN is more elevated in blood obtained from the non-access arm because of cardiopulmonary recirculation (discussed before in Chapter 6) and venovenous disequilibrium. Venovenous disequilibrium means that urea removal in the contralateral limb is reduced due to decreased perfusion of the contralateral arm (and other tissue beds) during dialysis.
 - This method requires that peripheral blood from the contralateral non-access limb be drawn from an extra separate needle stick, which may irritate the patient.

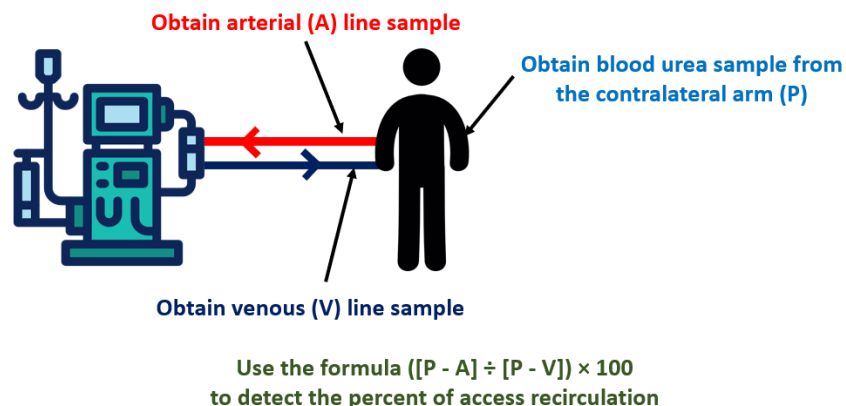


Figure 10.4. Three-needle urea-based (chemical) method

3. Ultrasound dilution method (UDM):

- In this method, two ultrasound sensors are attached to venous and arterial lines, and they are also connected to a monitor. Isotonic saline is quickly injected into the venous line to dilute the blood.
- If there is no access recirculation (Figure 10.5-A): The arterial sensor will not detect any saline-diluted blood.
- If access recirculation exists (Figure 10.5-B):
 - The arterial sensor measures the diluted concentration of recirculated blood. The ratio of dilution in the venous and arterial lines provides the percentage of access recirculation.
 - Recirculation percentage: Recirculation exceeding 5% using the ultrasound dilution method should prompt investigation.

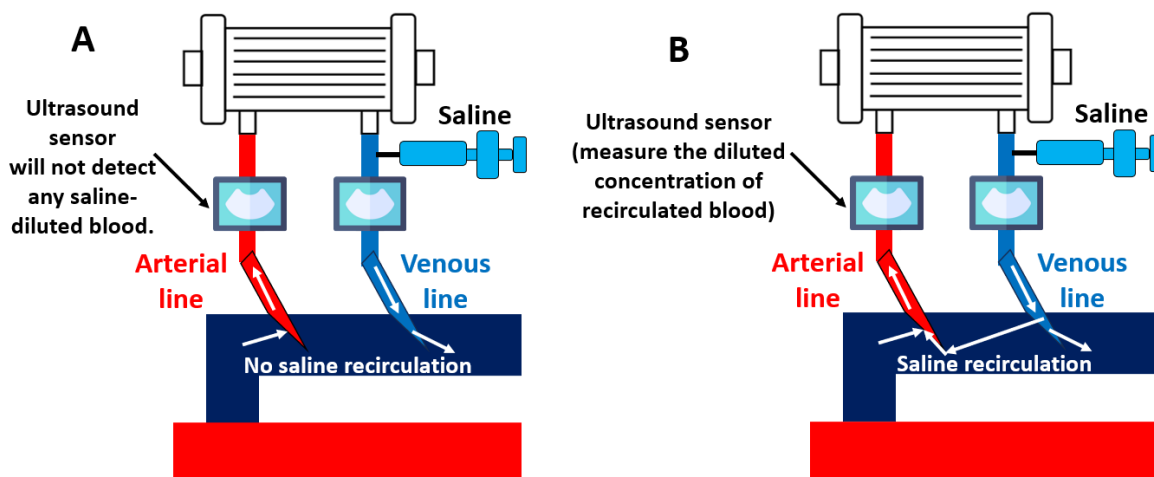


Figure 10.5. Ultrasound dilution method (UDM)

- ### 4. Other methods to detect access recirculation:
- Thermal dilution (using a blood temperature module), optical dilution, conductivity dilution, and potassium dilution.

3. Measurement of access flow by saline dilution (Krivitski method):

- It is well known that a low access flow rate reflects stenosis. So, measuring flow access is a method to diagnose stenosis.
- Method (Figure 10.6):
 - Reverse the arterial and venous lines to make access recirculation intentionally.
 - Two ultrasound saline dilution sensors are clamped onto the bloodlines, one on the arterial and one on the venous bloodline.
 - A bolus of isotonic saline is administered into the venous line.
 - The ultrasound saline dilution sensors action:
 - The ultrasound saline dilution sensors sense the diluted blood to calculate saline recirculation (R).
 - Besides sensing dilution, the ultrasound sensors simultaneously measure blood flow in the bloodlines (Qb).
 - Access flow (Qa) can now be calculated with the formula $Q_a = Q_b \times ((1R)/R)$.

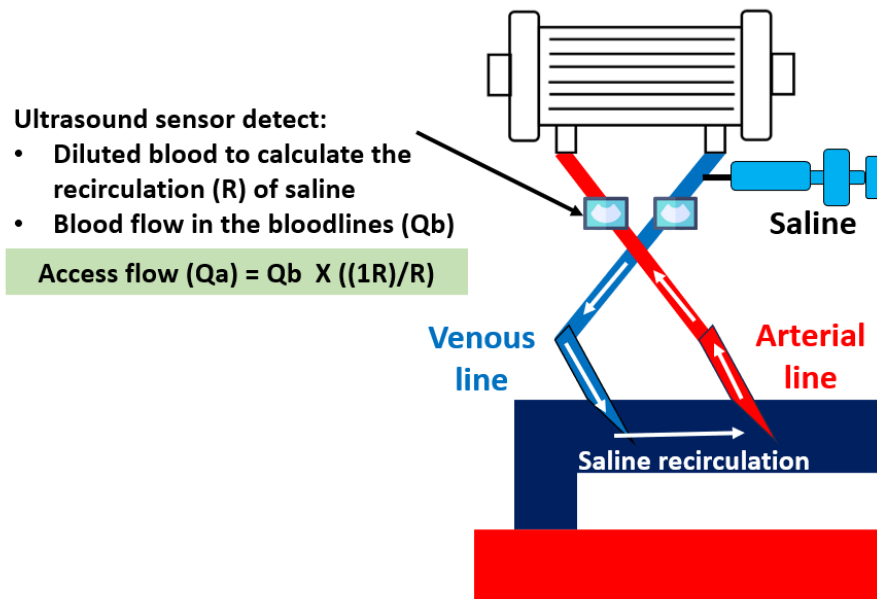


Figure 10.6. Measurement of access flow by saline dilution (Krivitski method).

Notice that the arterial and venous lines are intentionally reversed.

4. Imaging:

- It is the most used method to diagnose stenosis.
- KDOQI Vascular Access Guideline (2019 Update) considers it reasonable that when clinical monitoring suspects clinically significant AV access stenosis, further timely and confirmatory evaluation should proceed within less than two weeks, including imaging of the dialysis access circuit.
- The following are the different imaging procedures that can be used to diagnose access stenosis.

a. Doppler ultrasonography:

- ***Doppler ultrasonography can be used to:***
 - Detect stenotic lesions directly.
 - Measure the rate of flow through vascular access. As mentioned before, it is well known that a low access flow rate reflects stenosis.
- ***Where to measure access blood flow (venous segment versus arterial segment of the access)?***
 - Flow measurement by Doppler depends on an accurate measurement of both:
 - Velocity.
 - Vessel diameter.
 - The diameter of the venous segment of the AV access is not uniform all the way, so it is not recommended to measure the access flow in the venous segment.
 - Flow is better measured at the arterial segment of the AV access, where the vessel is a uniform, smooth cylinder with a fixed diameter.
- ***Average flow through AVF and AVG:***
 - Flow through a forearm AVF averages 500–800 mL/min.
 - Flow through a forearm AVG is about 1,000 mL/min.
 - Flow in upper arm fistulas or grafts may be considerably higher.
- ***When to assess for access stenosis?*** KDOQI Vascular Access Work Group (2006) stated that the patient has to be referred for access visualization by fistulogram if:
 - AVG flow rate is <600 mL/min.
 - AVF flow rate is <400 to 500 mL/min.
 - AV access flow is <1,000 mL/min and has decreased by >25% over the preceding four months.
- ***N.B.*** AVF can sustain patency at access flows as low as 200 mL/min, whereas AVG initiates thrombus formation at flows ranging from 600 to 800 mL/min.

b. Access angiography:

- Most centers refer patients with a high probability of stenosis as determined by low-cost methods directly for angiography, bypassing Doppler altogether (the Doppler study does not provide as much anatomical detail of the access as angiography).
- An angiogram is perhaps the most dependable diagnostic procedure, but it is invasive and requires x-ray exposure.
- Angiography has a limited evaluation role of the arterial tree.

c. Magnetic resonance angiography (MRA):

- The 2007 European Best Practice guidelines recommend the use of MRA when there is the need to image both the arterial and venous circulation.
- The main fear of using gadolinium in hemodialysis patients is the possibility of the development of nephrogenic systemic fibrosis. However, using newer gadolinium agents (type II and type III) decreases the incidence of nephrogenic systemic fibrosis in renal patients.

AV access stenosis treatment

When to treat AV access stenosis?

- **KDOQI Vascular Access Guideline (2019 Update) recommendations:**
 - **If AV access stenosis is not associated with clinical indicators:** Pre-emptive angioplasty or pre-emptive surgical intervention are not recommended to improve access patency.
 - **Patients with persistent clinical indicators of underlying AV access stenosis:** In this situation, pre-emptive treatment of AV access stenosis is reasonable to reduce the risk of thrombosis and AV access loss.
- **Some experts suggest AV access stenosis treatment if there is a narrowing of the vascular lumen ≥ 50 percent, and associated with** clinical symptoms, abnormal physical findings, and/or abnormal blood flow measurements.

Percutaneous (endovascular) balloon angioplasty versus surgical approach

- **KDOQI Vascular Access Guideline (2019 Update):**
 - KDOQI considers it reasonable to use a careful, individualized approach to treating stenosed AVF and AVG (surgical or endovascular balloon angioplasty) based on the operator's best clinical judgment and considering the patient's ESKD Life-Plan.
 - However, KDOQI considers it reasonable to use balloon angioplasty as the primary treatment (see next).
- **KDOQI Vascular Access Work Group (2006)** stated that if angioplasty of the same lesion is required more than two times within three months, the patient should be considered for surgical revision if the patient is a good surgical candidate.

Percutaneous balloon angioplasty:

- Although it is fast and convenient, the **primary patency rate** of this technique at 12 months is relatively low, ranging from 26% to 62%.
- In order to further enhance the durability of therapy, **several types of angioplasty balloon have been explored**, such as high-pressure balloon angioplasty, ultra-high-pressure balloons, drug-coated balloon angioplasty drug-coated balloon angioplasty:
 - **High-pressure balloons:** They are the standard typical angioplasty balloons used for treating dialysis vascular access stenosis.
 - **Ultra-high-pressure balloons:**
 - More expensive than high-pressure balloons.
 - They are very useful for extremely resistant venous lesions.
 - **Drug-coated balloons:**
 - An example of drug-coated balloons is the paclitaxel-coated balloons.
 - Drug-coated balloons versus thigh-pressure balloons:
 - Evidence is contradictory and further multi-center, large-scale, and well-designed randomized clinical trials comparing different balloon types are needed to prove outcomes.

- KDOQI Vascular Access Guideline (2019 Update) mentioned that there is inadequate evidence to make a recommendation regarding the use of drug-coated balloons versus standard high-pressure balloons.
- Several trials have compared drug-coated balloons with standard high-pressure balloon angioplasty. In general, these have shown improved lesion patency with drug-coated balloons at six months and one year.
- However, a recent systematic review and network meta-analysis of 20 randomized controlled trials (Xin Chen et al. 2023) showed that in failing AVF and AVG stenosis, high-pressure balloon angioplasty might be a preferential option than drug-coated balloons as it has numerically higher primary patency and is related to a lower risk of complications.
- **Cutting balloons:**
 - No high-quality studies have been published evaluating the effectiveness of cutting balloon angioplasty on the treatment of access stenosis.
 - Data from a limited number of studies suggest that cutting balloon angioplasty may provide some benefit for selected types of lesions.

Stents to treat stenosis:

- **Stent types: KDOQI Vascular Access Guideline (2019 Update) recommendations:**
 - **Stent-graft:** It is a metal stent with PTFE covering its internal and/or external surfaces. KDOQI recommends its use.
 - **Bare metal stents:** KDOQI considers it reasonable to avoid its use.
- **Indications for stent use:**
 - **KDOQI Vascular Access Guideline (2019 Update):**
 - KDOQI suggests the following as indications for the use of stent-grafts in preference to angioplasty alone:
 - Recurrent clinically significant graft-vein anastomotic stenosis in AVG.
 - In-stent re-stenosis in AVF and AVG.
 - Treatment of ruptured venous stenotic segment of AVF and AVG.
 - Note that the above mentioned indications are relevant to AV accesses stenosis in the absence of central vein occlusion.
 - **There is also evidence to use stents if:**
 - The stenotic lesion is elastic.
 - There are several coexisting stenoses.

AV access thrombosis

Incidence of AV access thrombosis

Thrombosis is the most common complication of arteriovenous access and accounts for 80%–85% of access loss.

Causes of AV access thrombosis

- Stenosis.
- Fistula compression.
- Hematoma formation from cannulation injury.
- Vascular endothelial injury.
- Hypovolemia.
- Hypotension.
- Hypercoagulable states.

Physical examination of AV access with thrombosis

There is absence of access thrill and bruit.

Prevention of AV access thrombosis

- In case of recurrent thrombosis, it is essential to investigate for causes of thrombosis other than stenosis.
- KDOQI Vascular Access Guideline (2019 Update) does not suggest the use of heparin, clopidogrel, or clopidogrel-prostacyclin (iloprost) as adjuvant therapies in the perioperative period to improve primary patency or initial use of AV access (AVF or AVG).

Treatment of AV access thrombosis

1. Percutaneous endovascular thrombolysis (mechanical and/or pharmacologic) versus surgical thrombectomy:

- The choice is based on the operator's best clinical judgment and expertise.
- KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to treat surgically in the following circumstances:
 - Endovascular treatment failures.
 - Clinically significant lesions not amenable to endovascular treatment.
 - Situations in which the surgical outcomes are deemed markedly better.

2. Indication for stent-graft use: Recurrent graft-vein anastomotic thrombosis in AVG.

3. Correct associated stenosis: Any venous stenosis associated with the clot needs to be corrected to prevent re-clotting.

4. Lines with no benefit: Early attempts to dissolve clots with the use of streptokinase and urokinase were not very successful.

Secondary AVF (Sleeves up protocol)

- If AVG thrombectomy and thrombolysis have been unsuccessful, a trial should be attempted to create a secondary fistula from the AVG venous drainage.
- Secondary AVF is possible because of the venous enlargement and thickening caused by the previous graft and has the advantage of being usable much sooner after creation.

Steal syndrome (Dialysis access–associated hand ischemia)

Incidence of steal syndrome

Steal syndrome complicates 1%-20% of accesses.

Mechanisms of steal syndrome

- **Arterial steal:** Anastomosis causes a low resistance flow from the artery to a vein, and blood may be diverted straight from the artery to the vein rather than through the distal arteries to the hand (i.e., the vein steals the blood from the hand), causing ischemia of the hand.
- **Other mechanisms:** Arterial stenosis or distal arteriopathy involving small vessels.

Risk factors of steal syndrome

- | | |
|---|--|
| <ul style="list-style-type: none"> • Advanced age. • Female sex. • Diabetes mellitus. • Peripheral vascular disease. • Large outflow conduits. | <ul style="list-style-type: none"> • Multiple prior permanent access procedures. • Upper arm access. • Distal brachial artery–based procedures (i.e., near antecubital fossa). • Prior episode of AV access steal. |
|---|--|

Onset of steal syndrome

Steal syndrome could occur at one of two onsets:

- Immediately after access creation.
- Insidiously over days to weeks.

Manifestations of steal syndrome

- | | |
|--|---|
| <ul style="list-style-type: none"> • Pain • Coldness. • Paresthesias of distal extremity, especially during dialysis. • Cyanosis • Pulselessness. | <ul style="list-style-type: none"> • Ischemic ulcers. • Dry gangrene. • Compare the access arm's temperature, pulse, and function versus the opposite hand. • Rarely, loss of the limb. |
|--|---|

Differential diagnosis of steal syndrome

- Carpal tunnel syndrome.
- Peripheral vascular disease.
- Neuropathy.
- Nerve trauma.
- Ischemic monomelic neuropathy due to the loss of blood supply to nerves.

Imaging to diagnose steal syndrome

Confirm steal syndrome diagnosis by arteriogram, duplex Doppler ultrasound evaluation with finger pressures, and waveform analysis.

Management of steal syndrome

- KDOQI Vascular Access Guideline (2019 Update) defines the treatment options according to the grade/severity of the steal syndrome, shown in Table 10.2.

Table 10.2. Management of steal syndrome according to presentation grade/severity

Grade	Severity	Clinical presentation	Treatment
1	Mild	Cool extremity with few symptoms	None (manage expectantly with close monitoring for progression of ischemia and worsening of signs and symptoms).
2	Moderate	Intermittent symptoms during dialysis, claudication	Surgical intervention sometimes.
3	Severe	Ischemic rest pain, tissue loss	Surgical intervention mandatory.

- Surgical intervention options for treatment of steal syndrome:
 - Ligation (if symptoms are severe, risk of limb loss, or no other available option).
 - Correction of arterial inflow stenosis.
 - Flow limiting or banding.
 - Proximalization of the arterial inflow.
 - Revision using distal inflow.
 - Distal revascularization and interval ligation (DRIL) (Figure 10.7). DRIL technique has two steps:
 - Step 1: Ligation of the artery immediately distal to the origin of the AV access.
 - Step 2: Construction of a reversed saphenous vein or PTFE graft from the artery proximal to the origin of the fistula to the artery distal to the site of ligation.

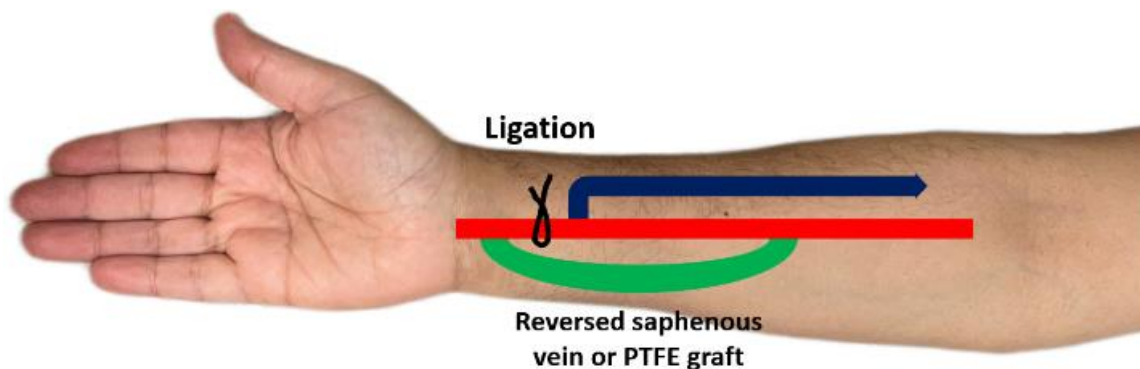


Figure 10.7. Distal revascularization and interval ligation (DRIL)

Aneurysm and Pseudoaneurysm

Difference between aneurysm and pseudoaneurysm

- True aneurysm is an area of localized bulging or dilation involving all vessel wall layers. It occurs due to repeated cannulation in the same location.
- Pseudoaneurysm (false aneurysm):
 - It is localized bulging or dilatation of the vessel, which is bounded only by the tunica adventitia, the outermost layer of the arterial wall.
 - It usually occurs secondary to an organized extravascular hematoma communicating with the access lumen, which may occur due to:
 - Repeated puncturing of the vein at the same site.
 - Inadequate hemostasis post-dialysis.

Which is more common?

- **In AVF:** Pseudoaneurysm is much more common than a true aneurysm.
- **In AVG:** There is no true expansion of the vessel lumen; it is really a pseudoaneurysm.

Stable versus unstable aneurysm/pseudoaneurysm

The following criteria were mentioned before in Chapter 9:

- **Criteria of stable aneurysm/pseudoaneurysm:**
 - Overlying skin is intact without any change in pigmentation.
 - The fistula has no evidence of outflow obstruction on physical examination by arm elevation test (see arm elevation test in chapter 9).
 - Stationary aneurysm size.
- **Criteria of unstable aneurysm “impending rupture”:**
 - Thin and shiny overlying skin.
 - Depigmentation of overlying skin.
 - Ulceration of overlying skin.
 - Rapid enlargement in size.
 - Prolonged leaking after needle removal.

Complications of aneurysm/pseudoaneurysm

- **In both stable and unstable aneurysm/pseudoaneurysm:**
 - Improper insertion of needles and limited potential puncture sites.
 - Infection.
 - Thrombosis.
 - Cosmetic bad effect.
- **Unstable aneurysm/pseudoaneurysm:** They would rupture, which leads to fatal hemorrhage.

Imaging to diagnose aneurysm/pseudoaneurysm

KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to use **duplex ultrasound** to confirm the physical examination findings suggesting an AV access aneurysm/pseudoaneurysm and to obtain information on the size, presence of stenosis/thrombus, and impact on the access flow.

Management of aneurysm/pseudoaneurysm: KDOQI Vascular Access Guideline (2019 Update) recommendations:

- **Stable aneurysm/pseudoaneurysm:**
 - Puncture the fistula in a site away from the aneurysm.
 - If there are absolutely no suitable alternative cannulation sites, the sides (base) of the aneurysm/pseudoaneurysm should be cannulated (i.e., avoid the top).
- **Indications for open surgical intervention:**
 - Symptomatic (such as pain and throbbing) aneurysm/pseudoaneurysm.
 - Unstable “impending rupture” aneurysm/pseudoaneurysm (surgical emergency).
 - Anastomotic aneurysms/pseudoaneurysms.
- **Intraluminal stents (stent grafts) as an alternative to open surgical repair:**
 - This option could be considered whenever surgery is contraindicated.
 - Use of stent grafts to manage aneurysms/pseudoaneurysms is not FDA-approved.
 - Cannulation over the stent graft segment should be avoided when possible.
 - Complications:
 - Stent-graft damage: This occurs as a result of repeated cannulation. Broken stent struts can sometimes protrude through the skin, posing a threat of injury to staff who place the patient on dialysis
 - Stent-graft infection.
 - Pseudoaneurysm recurrence.

AV access infection

Onset of AV access infection

AV access infection could occur at one of two onsets:

- Immediately after surgery.
- Later at needle insertion sites.

Common sites of AV access infection

- AVF infection is rare.
- AVG infection occurs eventually in 5%–20% of grafts placed.
- The infection rate is higher in thigh AVF or AVG than in upper extremities AV access.

Manifestations of AV access infection

- Erythema.
- Pain.
- Purulent exudate from needle sites.
- Skin breakdown.
- Presence of exposed graft.
- Fever with no other obvious source.

Diagnosis of AV access infection

- Cultures (of blood and any wound if present) should be taken, and empiric broad-spectrum antibiotic therapy should be initiated.
- KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to use Duplex ultrasound (or others such as CT scan, PET, or nuclear medicine scans such as indium scan) to help confirm the diagnosis of AV access infection. However, physical examination remains the hallmark for assessing for infection.

Treatment of AV access infection

- **Infected access rest:** An alternative access must be used while the infection is being treated.
- **AVF infection:**
 - **Causative organism:** Infections usually caused by staphylococci.
 - **Antibiotic therapy:** AVF infection should be treated with antibiotics for six weeks, as in the case of subacute endocarditis.
 - **Fistula removal/excision:** This is indicated if a septic embolus develops.
- **AVG infection:**
 - **Causative organisms:**
 - Staphylococcal infection is the most common.
 - Gram-negative organisms such as *Escherichia coli* may be cultured, especially from thigh grafts.
 - **Local AVG infection treatment:**
 - Antibiotics (against gram-negative and gram-positive organisms as well as against *Enterococcus*).
 - Surgical removal or incision of the infected part.
 - **Extensive infection** requires total removal of AVG.
- **Search for other sources of infection:** The possibility of endocarditis or other sources of infection should be investigated, depending on the pathogen found, especially if cultures fail to turn negative after antibiotic treatment and in patients using buttonhole cannulation.

Prevention of AV access infection

- Use complete aseptic techniques when dealing with vascular access.
- In the case of AVG, it is advisable to administer prophylactic antimicrobials to patients undergoing procedures that can potentially induce bacteremia, such as dental extraction or genitourinary manipulation.

AVG seroma

- A seroma refers to the accumulation of clear fluid under the skin, typically near the site of a surgical incision.
- KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to carefully monitor for complications of AVG seroma and manage based on the patient's individual circumstances and the clinician's best judgment.

Congestive heart failure in patients with AV access

Drawbacks of AV access to the cardiovascular system

- AV access causes hyperdynamic circulation that may precipitate high-output heart failure.
- Increased pulmonary arterial flow (which could be associated with high-flow access) can aggravate pulmonary hypertension.

Risk factors for development of congestive heart failure

The following are the risk factors, particularly if there is coexistent heart disease:

- Upper arm or femoral fistulas, unusual with forearm access.
- If access flow exceeds 20% of the cardiac output.
- Access flow >2,000 mL/min.

Management

- At first correct risk factors:
 - Volume overload.
 - Anemia.
- Consider surgical narrowing or banding of access to reduce access flow should be considered.

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Chapter 11

Venous Catheter: Basics, Insertion, Use and Care

Venous catheters are used in all types of blood-based dialysis, whether intermittent, prolonged intermittent, or continuous kidney replacement therapy.

In this chapter, the terminology “venous catheters” and “central venous catheters (CVC)” are interchangeable according to how they are mentioned in the original reference.

Indications for venous catheter insertion and use

The following are the common indications for venous catheter insertion for hemodialysis:

- Patients with acute kidney injury (AKI) requiring dialysis.
- Patients with intoxication or overdose requiring dialysis.
- Patients requiring plasmapheresis.
- End-stage kidney disease (ESKD) patients with one of the following:
 1. ESKD patients needing urgent hemodialysis but without available mature access.
 2. ESKD patients with limited life expectancy.
 3. ESKD patients with AV access-related issues, examples:
 - AV access major infiltration injury or cellulitis that results in temporary nonuse until the problem is resolved.
 - Multiple prior failed AV accesses with no available options.
 - Absence of AV access creation options due to a combination of inflow artery and outflow vein problems (e.g., severe arterial occlusive disease or non-correctable central venous outflow occlusion).
 - Clinical conditions that would worsen with AV access, e.g.:
 - Heart failure with ejection fraction (EF) <15%.
 - Non-treatable skin lesions where cannulation/scratching significantly increases infection or rupture risk.
 - Valid patient preference as the AV access would severely limit his QOL or achievement of life goals. In this case, the patient has been properly informed of patient-specific risks and benefits of other potential and reasonable access options for that patient.
 - Patient choice after proper informed consent.
 - Needle phobia.
 4. Peritoneal dialysis patients with complications that require time-limited peritoneal rest or resolution of complication (e.g., severe peritonitis or pleural leak)
 5. Transplant recipients needing temporary hemodialysis due to acute transplant rejection or other complications.

Venous catheters versus AVF and AVG in ESKD

KDOQI Vascular Access Guideline (2019 Update) suggestions:

- KDOQI suggests arteriovenous access (AVF or AVG) in preference to central venous catheter (CVC) in most incident and prevalent ESKD patients due to the association with lower vascular access–related events (e.g., infection, thrombotic, and non-thrombotic complications).
- KDOQI suggests that most incident ESKD patients starting dialysis with a CVC should convert to either an AVF or AVG, if possible, to reduce their risk of infection/bacteremia, infection-related hospitalizations, and adverse consequences.

Venous Catheter types:

Tunneled (cuffed) versus non-tunneled (uncuffed) catheters

- **Tunneled catheters (cuffed, long-term, semipermanent vascular access, permcath):** The Dacron “cuff” provokes a local inflammatory response that progresses to form fibrous and granulation tissue. This fibrous tissue serves to:
 - Fix the catheter cuff in position in the tunnel.
 - Prevent bacterial migration from the skin surface into the subcutaneous tunnel.
- **Non-tunneled catheters (uncuffed, short-term, temporary vascular access):** The risk of infection of uncuffed catheters increases markedly after the first week.
- **KDOQI Vascular Access Guideline (2019 Update) considerations for end-stage kidney disease (ESKD) patients:**
 - Tunneled CVC is preferred over non-tunneled CVC due to the lower infection risk.
 - Use non-tunneled internal jugular CVC only temporarily for a limited period (<2 weeks or per individual facility policy) to limit infection risk.
- **KDIGO Acute Kidney Injury Guideline (2012) considerations for patients with acute kidney injury (AKI):** KDIGO suggests initiating dialysis in patients with AKI via an uncuffed non-tunneled dialysis catheter rather than a tunneled catheter.

Venous catheter tip design

- **Tunneled cuffed catheters are available with several tip shapes:**
 - Split tip with performed curved tips.
 - Split tip standard.
 - Stepped tip.
 - Symmetric tip with side slots.
 - Symmetric tip with side holes (Figure 11.1).
 - Dual catheter (Tesio twin catheter).
- **Non-tunneled catheter tip** is available as a symmetric tip with side holes (Figure 11.1).

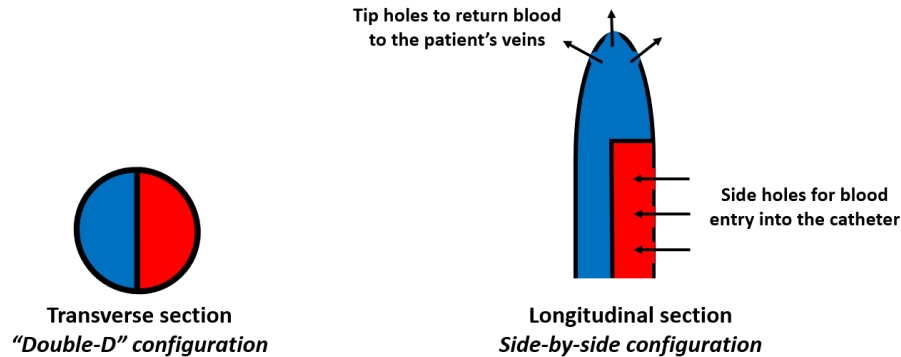


Figure 11.1. Symmetric tip venous catheters with side holes

Insertion location

I. Tunneled cuffed venous catheters for ESKD patients

KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to choose the site (location) of the tunneled cuffed CVC for ESKD patients as follows:

- **Upper extremity before lower extremity**, only if choices are equivalent.
- **Right versus left upper extremity:**
 - In the absence of contraindications such as prior pathology (e.g., central stenosis) or intervention (e.g., pacemaker), CVC insertion on the right side is preferable to the left side due to more direct anatomy.
 - If one side has pathology that limits AV access creation but allows for CVC insertion, this side should be used for the CVC to preserve the other side for AV access creation.
- **If the duration of use is expected to be <3 months, use upper extremity tunneled CVC:**
 - AV access is likely to be ready for use in the near future: Use tunneled cuffed CVC in the opposite extremity to anticipated AV access.
 - Transplant is anticipated in the near future: Use tunneled cuffed right IJ catheter. The main aim is to preserve iliac vessels.
- **Some experts support if the duration of use is expected to be <1 month and transplant is not an option, use femoral tunneled cuffed CVC:**
 - The use of a tunneled, cuffed femoral CVC is acceptable until the AV access or PD catheter can be quickly created and used.
 - The use of the femoral vein preserves the upper extremity vessels for future AV access creation.
 - Contraindications to femoral vein CVC include:
 - Femoral or iliac vessel pathology or prior surgery/reconstruction.
 - Hygienic reasons (e.g., chronic unresolved diarrhea).
 - Morbid obesity (BMI > 35 kg/m²).
 - Difficult vein access.

- If the duration of use is expected to be >3 months, without anticipated use of AV access, tunneled cuffed CVC may be placed in the following locations in order of preference:
 - Internal jugular.
 - External jugular.
 - Femoral.
 - Subclavian.
 - Lumbar.

II. Non-tunneled uncuffed venous catheters for AKI patients

KDIGO Acute Kidney Injury Guideline (2012) considers it reasonable to choose the site (location) of the non-tunneled uncuffed venous catheters for AKI patients in the following locations in order of preference:

- **Right internal jugular:** It is the first preferred site because the venous pathway to the right atrium is relatively short and straight.
- **Femoral.**
- **Left internal jugular:** It has a relatively long and twisty pathway to the right atrium.
- **Subclavian (right side insertion location to be used preferentially):**
 - It has a high incidence of insertion-related complications.
 - It has a high incidence (up to 40%) of central venous stenosis.

Catheter length

Catheter length differs according to catheter type and location of insertion. Tables 11.1 and 11.2 show examples of tunneled and non-tunneled catheter lengths, respectively. It is essential to mention that there are wide variations worldwide according to catheter availability.

Table 11.1. Different examples of tunneled catheter lengths

Location of tunneled catheter	Worldwide length range	Common in Egypt	Size
Right internal jugular	19-31 cm	24, 28 cm	Fr ≥ 14
Left internal jugular	23-36 cm	28, 32 cm	Fr ≥ 15.5
Right femoral	36-55 cm	36, 42, 55 cm	Fr ≥ 15.5
Left femoral	55 cm	55 cm	Fr ≥ 15.5

Table 11.2. Different examples of non-tunneled catheter lengths

Location of non-tunneled catheter	Length
Right internal jugular	12-15 cm
Left internal jugular	20-24 cm
Right femoral	20 cm
Left femoral	20 cm

Insertion technique

I. Initial steps for both non-tunneled (uncuffed) and tunneled (cuffed) catheters:

1. Antiseptic measures and local anesthesia:

- The procedure can be performed at the bedside.
- The procedure is done under a sterile technique, with sterile gowns, gloves, masks, and drapes.
- The skin is cleaned and prepared with an antiseptic solution.
- Local anesthetic is applied to the area.

2. Localization and cannulation of the vein:

- **Localization by imaging:**
 - Vein localization by only palpation without any imaging aids is better avoided as it carries the risk of unsuccessful cannulation with the development of complications.
 - Ultrasonic visualization of the vein before placement of catheters has made the technique much safer and has become standard practice. This is because veins may exhibit anatomic variability.
 - KDOQI Vascular Access Guideline (2019 Update) recommends using image-guided CVC insertions to improve the success of insertions.

- **Internal jugular vein localization and cannulation (Figures 11.2 and 11.3):**

Place the patient in a supine position with the head lowered at 15–20° and turned away to the other side. Three approaches to the internal jugular vein are recognized (Figure 11.3):

- **Central approach:**
 - It is the most commonly used approach.
 - The apex of the triangle formed by the heads of the sternocleidomastoid is approximately 5 cm superior to the clavicle and marks the preferred needle insertion site.
 - Introduce the needle (see needle insertion below) lateral to the carotid pulsation at a 30–45° angle to the skin.
 - Direct the needle lateral to the sagittal plane toward the ipsilateral nipple.
 - If the first needle pass fails, promptly withdraw the needle to the skin surface and redirect the needle 10 degrees medially.
- **Posterior approach:**
 - Insert the needle (see needle insertion below) along the posterior edge of the sternocleidomastoid at the junction of the middle and lower third of the muscle. This point is approximately 5 cm above the clavicle and is commonly marked by the presence of the external jugular vein.
 - After needle introduction beneath the posterior sternocleidomastoid, advance anteromedially toward the sternal notch.

- **Anterior approach:**
 - Introduce the needle (see needle insertion below) 5 cm above the sternum, at the midpoint of the anterior border of the sternocleidomastoid.
 - Direct the needle lateral to the carotid pulsation along a plane aimed at the ipsilateral nipple.
- **Subclavian vein localization and cannulation (Figure 11.2):**
 - The patient lies supine with their head down and turned away from the operator.
 - Approaches to subclavian vein:
 - **Infraclavicular approach (the most commonly used):** The needle is inserted (see needle insertion below) into the area under the clavicle (where its medial third joins the lateral two-thirds at the lateral aspect of the deltopectoral groove). The needle first touches the inferior margin of the clavicle and then advances deeper into the subclavian vein.
 - **Supraclavicular approach:** If the infraclavicular approach is difficult, an experienced operator can use the supraclavicular approach.
- **Femoral vein localization and cannulation:**
 - The patient should be positioned supine.
 - The target leg is abducted and externally rotated 15 degrees with a slight flexion of the knee to open the femoral triangle.
 - Elevation of the buttock with rolled sheets or a firm pillow facilitates exposure in some patients.
 - Palpate the common femoral artery pulsation.
 - Insert the needle (see needle insertion below) 1 to 2 cm inferior to the inguinal ligament and just medial to the femoral artery.
 - In general, the needle should be introduced at a 20° to 30° angle to the skin.
 - The vessel is usually reached within 2 to 4 cm but may be deeper in patients with edema or obesity

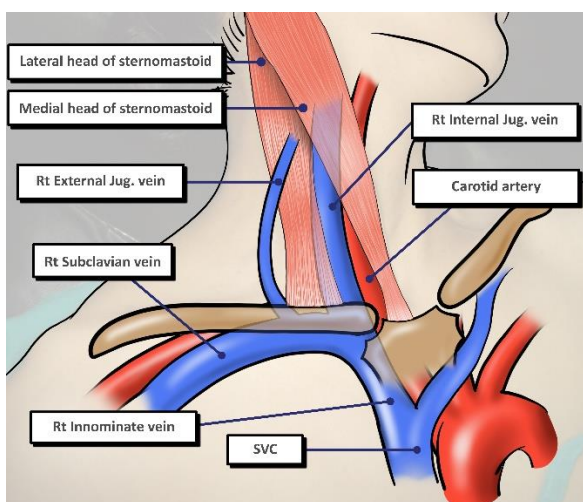


Figure 11.2. Localization of veins

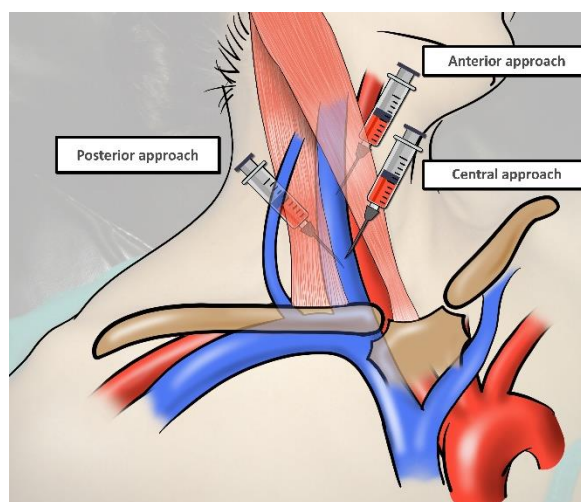


Figure 11.3. Internal jugular vein cannulation

3. Needle insertion:

- The needle attached to a syringe is advanced toward the vein with gentle suction.
- Some experts prefer to introduce a small (20- to 21-gauge) needle (called a seeker needle) at first, especially when cannulating internal jugular or subclavian veins. The use of a small needle limits potential complications if the carotid artery is accidentally punctured.
- As soon as venous blood is seen in the seeker needle syringe, a larger (18-gauge) needle is inserted into the vein in the same direction and depth as the thin needle to access the vein and remove the small needle.

4. Guide wire insertion:

- Once the vein is accessed, a guide wire is advanced through the needle (Seldinger method) to a distance of 10–15 cm.
- If the wire does not advance freely, it should not be forced but must be withdrawn and a fresh attempt made.
- If the inserted catheter is tunneled, use fluoroscopy to check the guidewire site. KDOQI Vascular Access Guideline (2019 Update) suggests that if fluoroscopy is not used, alternative imaging must be used to ensure the tip has been correctly placed.
- Once the guide wire is in place, the large needle is withdrawn. Care must always be taken to maintain control of the guidewire to be held in place to prevent its withdrawal.
- The entry site is enlarged with a blade.

5. The continuing steps differ according to the type of catheter inserted, whether it is a non-tunneled or tunneled catheter (see next).

II. Continuing steps for non-tunneled (uncuffed) catheters

After going through the above-mentioned initial steps (1 to 5), continue as follows:

1. In stepwise fashion, two dilators of increasing size are passed over the guidewire to progressively dilate the soft tissue and venous tract, and then the dilator is withdrawn:
 - The dilator should move freely on the guidewire.
 - The dilator should not be forcefully advanced, as it is possible for the dilator to get off-axis, impinge on the guidewire, and perforate the vein and/or the mediastinum.
2. The catheter is then passed gently over the guide wire into the vein.
3. The catheters are aspirated and flushed with saline (or heparinized saline) to confirm good inflow and outflow.
4. Fill the catheter with a locking solution (e.g., heparin lock – see later) to prevent clotting.
5. The catheter is secured with two interrupted non-absorbable stitches.
6. Apply antibiotic or povidone-iodine ointment at the catheter exit site (see catheter exit site care later).
7. Do a chest x-ray after internal jugular or subclavian insertion to check for any insertion-related complications (see below) and confirm the correct positioning of the catheter tip (see catheter tip position below).

III. Continuing steps for tunneled (cuffed) internal jugular catheters

After going through the above-mentioned initial steps (1 to 5), continue as follows:

1. In a stepwise fashion, two dilators of increasing size are passed over the guidewire under fluoroscopy; the second dilator contains a peel-away sheath, which is left in place after the dilator is removed.
2. A marking pen is used to mark the catheter exit site (or subcutaneous port site), which is then incised with a scalpel.
3. The catheter length is then measured to ensure that the tip of the catheter will reside in the right atrium.
4. Using a tunneler with a tapered tip at one end and the catheter attached at the other end, the catheter is tunneled along the subcutaneous tissue from the chest wall over the clavicle and toward the neck.
5. The catheter is then detached from the tunneler and fed through the sheath. Care must be taken not to twist the catheter when placed through the sheath, as this can cause kinking and flipping of the catheter.
6. Afterwards, the sheath is peeled away from the catheter with care taken not to dislodge the catheter.
7. The location of the catheter tip is then confirmed with fluoroscopy.
8. The catheters are aspirated and flushed with saline (or heparinized saline) to confirm good inflow and outflow.
9. Fill the catheter with a locking solution (e.g., heparin lock – see later) to prevent clotting.
10. The neck incision is closed with a stitch.
11. The catheter is secured with two interrupted non-absorbable stitches.
12. Apply antibiotic or povidone-iodine ointment at the catheter exit site (see catheter exit site care later).

N.B. The steps for tunneled subclavian and femoral vein catheters are the same except for the position of the catheter exit site.

Catheter tip position after placement

- **The tip of non-tunneled internal jugular or subclavian hemodialysis catheters (Figure 11.4):**
 - It should be positioned at the cavoatrial junction.
 - Because of the stiffness of short-term non-tunneled catheters and the risk for complications, atrial placement should be avoided.
- **The tip of tunneled internal jugular or subclavian hemodialysis catheters (Figure 11.5):**
 - It should be positioned within the right atrium when the patient is supine.
 - As the patient transitions to the upright position, the catheter will tend to retract 2 to 4 cm.
- **The tip of femoral hemodialysis catheters (non-tunneled or tunneled) should be placed in the inferior vena cava.**

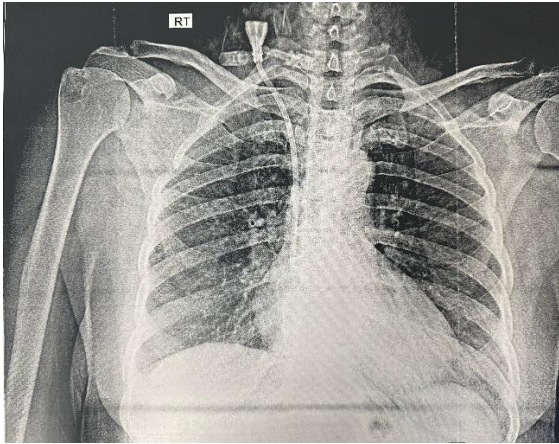


Figure 11.4. Right non-tunneled internal jugular hemodialysis catheters

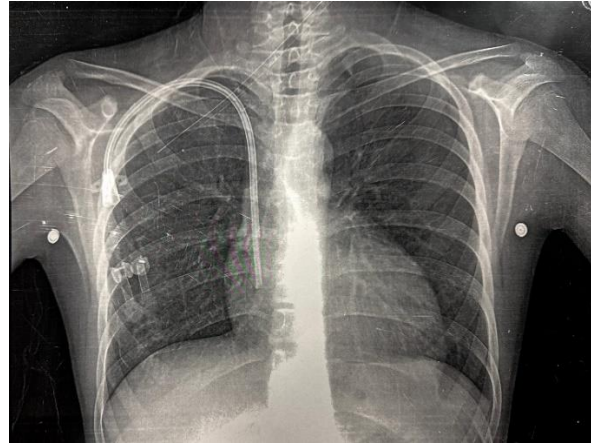


Figure 11.5. Right tunneled internal jugular hemodialysis catheters

Insertion related complications

I. Complications related to all catheters (internal jugular, subclavian, and femoral):

- **Arterial puncture:** Arterial puncture by the initial small-gauge probing needle should be treated by uninterrupted local pressure for 15–20 minutes.
- **Accidental arterial insertion of a dialysis catheter:**
 - Dialysis should be postponed, and surgical opinion should be sought to avoid major hematoma and tracheal compression.
 - If urgent dialysis is necessary, this should be done on the opposite side and without anticoagulation.
- **Air embolism:** More common with internal jugular and subclavian catheters than femoral catheters.

II. Complications related to internal jugular and subclavian catheter insertion:

- **Pneumothorax, hemothorax, arrhythmias, pericardial tamponade.**
- **Perforation of superior vena cava or cardiac chamber:**
 - It is a life-threatening condition.
 - Diagnosis is suggested by unexplained chest pain, shortness of breath, or hypotension soon after commencing dialysis.
 - Surgical intervention is usually needed for correction.
- **Injury to adjacent structures, such as:** Brachial plexus or recurrent laryngeal nerve.

III. Complications related to femoral catheter insertion:

- **Retroperitoneal hemorrhage:**
 - Femoral artery puncture or an accidental puncture of the back wall of the femoral vein may cause severe and life-threatening retroperitoneal bleeding.
 - Retroperitoneal hemorrhage is suspected if there is abdominal pain and rapidly decreasing hemoglobin. Diagnosis is by CT abdomen.

Central venous catheter (CVC) connection and disconnection procedures

The KDOQI Vascular Access Guideline (2019 Update) suggests the following steps for connecting and disconnecting central venous catheters (CVC).

Suggested steps for the connection procedure of CVC:

- **Step 1:** Explain the procedure to the patient. Ask him/her to minimize talking and turn the head in the opposite direction of the CVC. KDOQI considers it reasonable to use masks for patients and staff performing catheter connection procedures.
- **Step 2:** Perform hand hygiene. Remove any gauze or tape covering the CVC limbs.
- **Step 3:** Ensure that both limbs of the CVC are clamped. Place a clean or sterile pad/towel under the CVC so that the limbs are on top of the pad/towel.
- **Step 4:** Perform hand hygiene and prepare supplies, maintaining sterility. Put on gloves.
- **Step 5:**
 - Ensure the clamp on CVC is closed. Remove the Luer lock cap and clean (scrub) the hub with a chlorhexidine-based solution. If chlorhexidine is contraindicated (e.g., sensitivity, allergy), povidone-iodine solution (preferably with alcohol) is a reasonable substitute and should be used. Ensure that the disinfected hub does not touch nonsterile surfaces.
 - If a closed system, high-flow, needleless-style caps are used, follow the manufacturer's recommendations and CVC care for cleaning and changing the caps.
 - Repeat with the second port.
- **Optional for Step 5:** Before removing the Luer lock cap, disinfect the caps and part of the hub with an antiseptic pad, using a separate antiseptic pad for each hub or catheter limb.
- **Step 6:** Attach a syringe, unclamp CVC, and aspirate 2 to 5 mL of blood and CVC locking solution from the lumen. Reclamp CVC. Detach the syringe and attach the catheter port to the dialysis circuit. Repeat with the second port.
- **Optional for Step 6:** If no resistance is felt with blood aspiration and locking solution, attach a 5-10 mL syringe of 0.9% normal saline and flush the lumen using a turbulent flushing technique.
- **If step 6 failed:** If limbs do not aspirate or flush freely, ensure clamps are open and rule out external causes of resistance (kink in CVC limb or patient position). If problems persist, the CVC may indicate fibrin or thrombus formation or CVC tip malposition. A gentle back-and-forth motion (irrigate) may promote CVC patency. After irrigation, flush the lumen (e.g., with 10 mL of normal saline) using a turbulent flushing technique to ensure that blood is cleared from the CVC lumen (optimize line patency). Observe for bleeding if the anticoagulant locking solution cannot be removed (aspirated).
- **If step 6 succeeded:** Initiate dialysis.
- **Step 7:** Discard the syringe and used materials.

Suggested steps for the disconnection procedure of CVC

- **Step 1:**
 - Explain the procedure to the patient, re-transfuse the patient's blood as per unit protocol, perform hand hygiene, and prepare supplies for CVC locking.
 - KDOQI considers it reasonable to use masks for patients and staff performing catheter disconnection procedures.
- **Step 2:** Close the clamp on the CVC lumens and bloodlines. Disconnect one bloodline from one CVC lumen and clean the CVC hub.
- **Step 3:** Attach a 5- to 10-mL syringe with 0.9% normal saline to the CVC lumen, unclamp the CVC, and flush the lumen.
- **Step 4:**
 - Remove the saline syringe from the lumen, attach a syringe with CVC locking solution to the lumen, and instill locking solution volume as per unit CVC care protocols.
 - If closed-system, high-flow needleless caps are used, follow unit protocols and manufacturer's recommendations.
- **Step 5:** Close the clamp on the lumen, remove the syringe, clean the hub, and apply a sterile Luer lock cap.
- **Step 6:** Repeat steps with the second lumen.
- **Step 7:** Discard used supplies.

Catheter Lock

Importance

- The main goal of catheter lock is to prevent intraluminal clot formation, catheter colonization, and biofilm formation.
- Biofilm development on a catheter surface begins with microbial attachment, extracellular polymeric substance production, maturation of the biofilm, and final detachment of microbes from the biofilm surface.

Catheter lock manipulation:

I. After each hemodialysis session:

- The dead space of each lumen is filled with the lock solution through the catheter injection ports. The dead space of each catheter lumen is usually labeled on the catheter hub.
- Injection of a volume of lock solution larger than necessary should be avoided as it results in systemic anticoagulation that may be hazardous to patients at risk for bleeding.

II. Before each dialysis:

The lock solution in each lumen is aspirated, the catheter is flushed with heparinized saline (100 units/mL) or pure saline, and hemodialysis is initiated.

Types of catheter lock solutions:

I. Heparin and citrate lock:

- **Heparin lock:** The dead space of each lumen is filled with heparin through the catheter injection ports using 1,000–5,000 units/mL.
- **Citrate lock:** KDOQI Vascular Access Guideline (2019 Update) suggests the use of low-concentration citrate (<5%) CVC locking solution.
- **Heparin versus citrate lock:** KDOQI Vascular Access Guideline (2019 Update) considers it reasonable that the choice to use citrate or heparin as a CVC locking solution be based on the clinician's discretion and best clinical judgment, as there is inadequate evidence to demonstrate a difference in CVC survival or complications between these locking solutions.

II. Tissue plasminogen activator (TPA) lock:

KDOQI Vascular Access Guideline (2019 Update) suggests that TPA may be prophylactically used as a CVC locking solution in the following cases:

- In general, once per week to help reduce CVC dysfunction.
- Once weekly in patients in need of long-term CVC who are at high risk of CRSBI (prior multiple CRSBI or staph aureus nasal carriers), especially in facilities with high rates of CRBSI (>3.5/1,000 days).

III. Antibiotic or antimicrobial-containing lock:

- **Indications:**
 - KDOQI Vascular Access Guideline (2019 Update) suggested that **prophylactic** antibiotic or antimicrobial-containing locks can be considered in patients in need of long-term CVC who are at high risk of CRSBI (e.g., multiple prior CRSBI or staph aureus nasal carriers), especially in facilities with high rates of CRBSI (e.g., >3.5/1,000 days).
 - Antibiotic lock is used as a part of the **management of** catheter-related bloodstream infection (CRBSI). This will be discussed in chapter 12.
- **Which antibiotic or antimicrobial-containing lock should be used for prophylaxis?**
 - **KDOQI Vascular Access Guideline (2019 Update) recommendations:**
 - KDOQI supports the use of:
 - Specific antibiotics: cefotaxime, gentamicin, or cotrimoxazole (TMP-SMX).
 - Antimicrobial: methylene blue.
 - KDOQI cannot support the routine prophylactic use of antibiotic or antimicrobial locks with very low supporting evidence.
 - **A recently published randomized, double-blind, active-control, phase 3 study (Agarwal et al. 2023)** showed that:
 - Taurolidine/heparin reduced the risk of developing CRBSI in 800 patients receiving hemodialysis via tunneled CVC compared with heparin.
 - Taurolidine/heparin had a comparable safety profile over a mean of 200 days compared with heparin.

Instructions for venous catheter dressing

I- Catheter exit site care

1. Skin cleansing:

KDOQI Vascular Access Guideline (2019 Update) considers it reasonable at the time of catheter dressing change to cleanse the skin surrounding the catheter exit site with a chlorhexidine-based solution. If chlorhexidine is contraindicated (e.g., sensitivity, allergy), povidone-iodine solution (preferably with alcohol) is a reasonable substitute and should be used.

2. Skin ointment for exit site:

- **Apply antibiotic ointment or povidone-iodine ointment to catheter exit sites during dressing at each hemodialysis session:**
 - Examples:
 - CDC recommends bacitracin/gramicidin/polymyxin B ointment or povidone-iodine ointment.
 - Triple antibiotic ointment (bacitracin/neomycin/polymyxin B) might have a similar benefit, but studies have not thoroughly evaluated its effect on preventing bloodstream and exit-site infections.
 - Single antibiotic ointments (e.g., mupirocin). However, concerns exist about the development of antimicrobial resistance and their ability to cover the spectrum of potential pathogens (e.g., gram-negative and gram-positive bacteria) that can cause bloodstream infections in dialysis patients.
 - KDOQI Vascular Access Guideline (2019 Update) mentioned that there is inadequate evidence to demonstrate a difference in catheter-related infections between the use of various antiseptic or antibiotic topical exit site barriers, and the choice of topical exit site barrier should be based on the clinician's discretion and best clinical judgment.
- **There is a high concern about the emergence of resistant organisms with the continuous use of antibiotic ointment. The following are other suggested strategies:**
 - KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to use a topical antiseptic or antibiotic barrier at the catheter exit site in addition to cleansing until the exit site is healed to reduce the risk of catheter-related infection.
 - Also, the European Renal Best Practices group, in a 2010 commentary, recommends using exit-site antibiotic ointment only until the insertion site has healed.
 - As an intermediate strategy, exit-site ointment use can be limited to patients with repeated episodes of infection.
- **Interaction with the catheter:** Ingredients in antibiotic and povidone-iodine ointments may interact with the material of the catheters. Therefore, before any product is applied to the catheter, first check with the catheter manufacturer to ensure that the selected ointment will not interact with the catheter material.

II- Dressing type

- The catheter should be covered with a **sterile dry dressing**.
- **Nonbreathable or nonporous dressings should be avoided** as they pose a greater threat of exit-site colonization.
- **Transparent versus nontransparent dressing:** KDOQI Vascular Access Guideline (2019 Update) mentioned that there is inadequate evidence to demonstrate a difference in catheter-related infections with the use of transparent film dressing compared with nontransparent dressing; thus, the choice of catheter dressing material should be based on the clinician's discretion that considers the patient's circumstances and uses best clinical judgment.

III- Dressing frequency

KDOQI Vascular Access Guideline (2019 Update) considers it reasonable that the frequency of catheter dressing change should be based on the clinician's discretion and best clinical judgment, with a **minimum of once weekly**.

IV- Dressing and wet environment

- KDOQI Vascular Access Guideline (2019 Update) considers it reasonable that catheter dressings should be **protected against wet and dirty environments**, particularly when the exit site is not yet fully healed (e.g., avoid swimming and showering).
- If the patient insists on showering, some experts suggest that:
 - Showering should be done only after the exit-site sinus tract has become established
 - Showering should be done before coming to the dialysis unit, where a new dressing and antibacterial ointment will be promptly applied.

Duration of venous catheter use

Tunneled cuffed catheter duration of use

- **KDOQI Vascular Access Guideline (2019 Update)** considers it reasonable that in hemodialysis patients for whom a tunneled cuffed CVC is the most appropriate permanent dialysis access, there is no maximum time limit to CVC use, but a regular evaluation is required to determine if the CVC remains the most appropriate dialysis access.
- **The overall survival of tunneled catheters is highly variable according to the available studies:**
 - One study reported six-month patency ranging from 77 to 87 percent and 12-month patency ranging from 72 to 76 percent.
 - In one report, tunneled hemodialysis catheters successfully survived in some patients for 343 days.
 - In another report, the mean survival time was beyond 2 years.

Non-tunneled catheter duration of use

- **KDOQI Vascular Access Guideline (2019 Update)** considers it reasonable to limit the use of temporary, non-tunneled uncuffed dialysis catheters to a maximum of 2 weeks due to increased risk of infection, and this should be considered only in patients in need of emergent access.
- **KDOQI Vascular Access Work Group (2006):**
 - Non-tunneled venous catheters should be used only in the inpatient setting for the patient's safety. This is because of the associated risk of infection, accidental removal, hemorrhage, and other complications with the use of non-tunneled venous catheters.
 - Duration:
 - Non-tunneled internal jugular catheters: According to the infection rate for non-tunneled internal jugular catheters, they should be used for no more than 1 week.
 - Non-tunneled femoral catheters: They could be left in place for no more than 5 days and only in bed-bound patients with good exit-site care. This is because of the infection and dislodgment rates for femoral catheters.

Risk of air embolism on removal of dialysis catheters from the neck

- A lethal air embolism has been reported after the removal of a jugular venous catheter.
- Because of this risk, specific protocols should be in place for removing venous catheters from the neck. The recommended protocol is as follows:
 - No heparin on the day of planned removal.
 - Put the patient in a head-down position during catheter removal.
 - Patient instructed not to cough or inhale deeply during removal.
 - Air-occlusive dressing with a generous amount of inert ointment to provide an instantaneous air seal.
 - Observe the patient for 30 minutes before leaving the dialysis facility.
 - Air-occlusive dressing left in place for at least 24 hours.

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Chapter 12

Venous Catheter: Complications (Diagnosis and Management)

KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to physically examine the venous catheter and surrounding area before every connection for potential complications.

In this chapter, the terminology “venous catheters” and “central venous catheters (CVC)” are interchangeable according to how they are mentioned in the original reference.

Venous catheter infections

Infection is the leading cause of catheter loss and increases morbidity and mortality.

I. Exit-site infection

Manifestations:

- **Local signs:**
 - Hyperemia, induration, and/ or tenderness ≤ 2 cm from catheter exit site.
 - It may be associated with drainage from the exit site.
- **Systemic manifestations:** Exit-site infection may or may not be associated with bacteremia.

Diagnosis: If there is exit site drainage, it should be collected and sent for Gram staining, culture, and sensitivities.

Treatment:

- **Antibiotic therapy (topical antibiotic cream and oral antibiotics):**
 - Oral antibiotics should cover gram-positive organisms:
 - Modify the antibiotic regimen once culture and sensitivity results are available.
 - Duration of therapy: Exit-site infections are typically treated for 7 to 14 days, depending on the microorganism isolated and local practice.
- **The patient should be investigated for nasal carriage of *Staphylococcus*** and, if present, treat with intranasal mupirocin cream (half tube twice a day to each nostril for 5 days) to prevent future infections.
- **Catheter removal if exit-site infection is associated with:**
 - Systemic signs of infection (leukocytosis or temperature $>38^{\circ}\text{C}$).
 - Pus expressed from the track of the catheter.
 - Blood cultures are positive.
 - Infection persists or recurs after an initial course of antibiotics.

Prevention: This is achieved by good exit-site care and the use of skin antimicrobial ointment, as described before in Chapter 11.

II. Tunnel infection

Manifestations:

- **Local signs:** Tenderness, hyperemia, and/or induration that extends >2 cm from the exit site and along the subcutaneous tunnel.
- **Systemic manifestations:** Tunnel infection may or may not be associated with bacteremia.

Diagnosis: Collect any drainage and send it for Gram staining, culture, and sensitivities.

Treatment:

- **Catheter removal:** The catheter should always be removed. A new catheter should be inserted at another site.
- **Antibiotic therapy:**
 - Start broad-spectrum antibiotics to cover both gram-positive and gram-negative organisms. Modify antibiotics after culture and sensitivity results are obtained.
 - Duration of therapy:
 - In the absence of a concurrent catheter-related bloodstream infection (CRBSI), tunnel infection is typically treated for 10 to 14 days, depending on the microorganism isolated and local practice.
 - If CRBSI is present, then the duration of therapy will be determined by the management of the CRBSI (see next).

III. Catheter-related bloodstream infection (CRBSI)

Manifestations:

- **Milder cases** present with fever or chills, while **severe cases** exhibit hemodynamic instability.
- **Patients may develop septic symptoms after initiation of dialysis**, which suggests systemic release of bacteria and/or endotoxin from the catheter.
- **Patients may develop metastatic infections:**
 - Example: endocarditis, osteomyelitis, epidural abscess, and septic arthritis.
 - It is important to note that metastatic infections may not be immediately apparent, as they can first manifest clinically weeks or months after the initial bacteremia event.

Causative organisms: Gram-positive organisms are the causative organisms in most cases, but gram-negative infections occur in minor cases.

Diagnosis

1. Blood and catheter tip cultures:

- Peripheral blood culture: From a vein or as an alternative from the dialysis circuit.
- Catheter culture:
 - Blood culture from catheter hub (i.e., catheter lumen).
 - If the catheter has been removed, culture the distal 5 cm of its tip.

2. Culture results: Different possibilities for the culture's result are shown in Table 12.1.

Table 12.1. Different possibilities for the culture result to diagnose or to exclude CRBSI

CRBSI confirmed if	CRBSI unlikely	Contamination or colonization
CRBSI confirmed if: <ul style="list-style-type: none"> • Absence of other apparent source of infection and isolated same organism (species and antibiogram) from: <ul style="list-style-type: none"> ○ Peripheral source and catheter hub blood cultures if the catheter is not removed. ○ Peripheral source blood culture and the catheter tip culture if the catheter is removed. • If available, the following would be supportive: <ul style="list-style-type: none"> ○ Simultaneous quantitative cultures with a ratio of $\geq 3:1$ (catheter tip/hub blood culture versus peripheral source blood culture). ○ Differential time to positivity (DTTP) of catheter tip/hub blood culture versus peripheral source blood culture is 2 hrs. 	CRBSI is unlikely if both peripheral blood and catheter cultures are negative	Contamination or colonization is suggested if there is a negative peripheral blood culture and a positive catheter hub or tip culture. <ol style="list-style-type: none"> 1. Contamination: When taking cultures from a catheter hub, the IDSA recommends cleaning and sterilizing the area with alcoholic chlorhexidine rather than povidone-iodine and allowing the antiseptic to dry before sampling; this avoids contamination of the cultured material. 2. Catheter colonization (check its treatment below).

Management of catheter colonization

- **Remove the catheter if feasible.**
- **If the catheter is left in place:**
 - There may be an increased risk for subsequent development of CRBSI. Follow the patient closely for clinical manifestations of CRBSI.
 - For patients with multiple positive catheter-drawn blood cultures that grow coagulase-negative staphylococci or gram-negative bacilli and concurrent negative peripheral blood cultures, antibiotic lock therapy can be given without systemic therapy for 10–14 days.

Management of CRBSI

- From an infectious disease perspective, the catheter is always best removed whenever a CRBSI occurs, regardless of the causal organism.
- The following stepwise approach for CRBSI management (from Figure 12.1 to Figure 12.4 and from Table 12.2 to Table 12.7) is mainly applied for long-term tunneled cuffed catheters.
- Short-term non-tunneled uncuffed catheters with CRBSI should always be removed from patients, and then the approach in Figure 12.4 and Table 12.7 should be followed. However, some units use the same approach used for long-term tunneled cuffed catheters to manage short-term non-tunneled catheters with CRBSI, especially in patients with precious access.

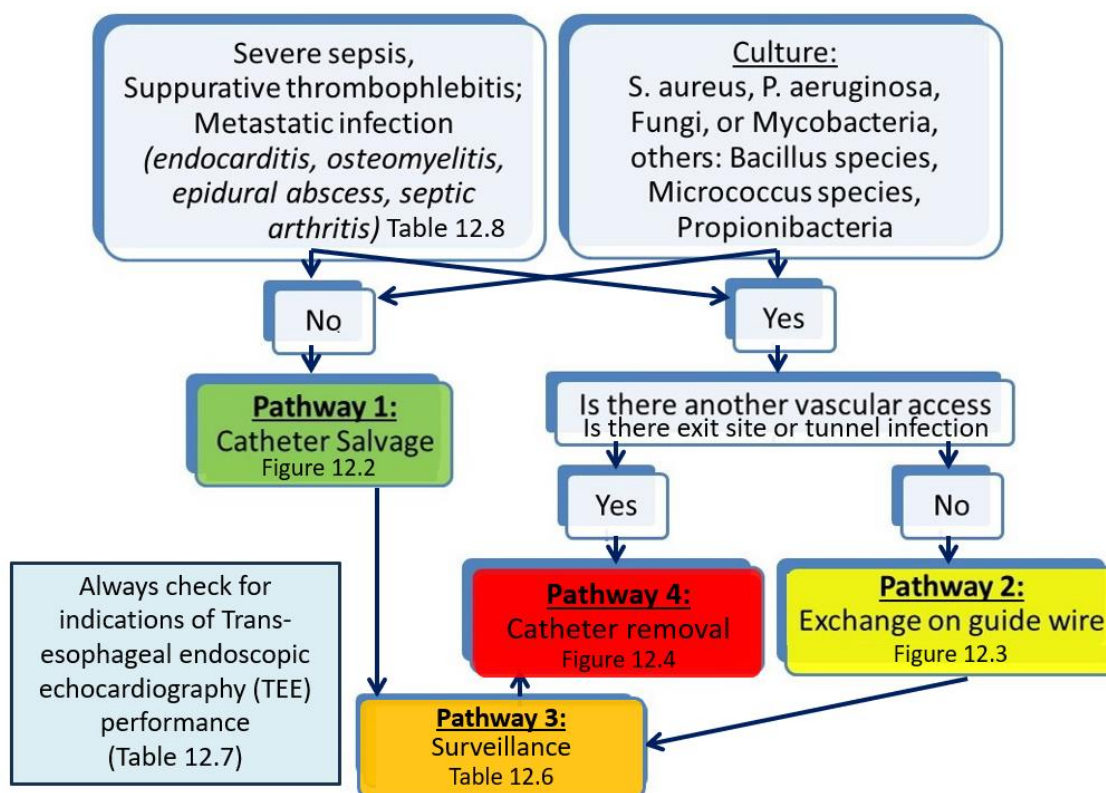


Figure 12.1. Management of CRBSI: Stepwise approach

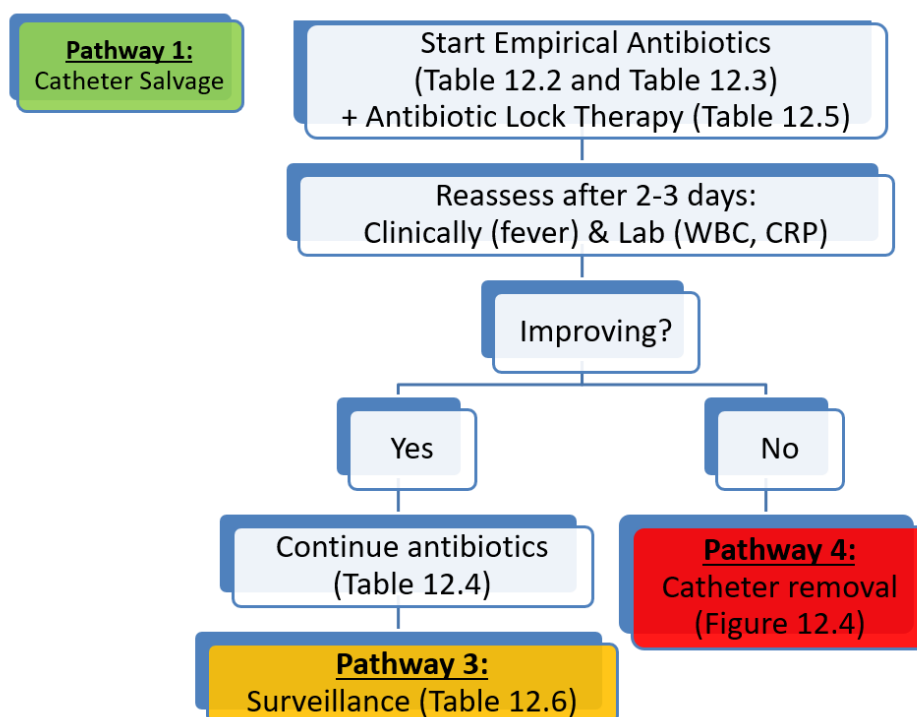


Figure 12.2. Management of CRBSI (Pathway 1): Catheter Salvage

Table 12.2. Empiric therapy different protocols used for the management of CRBSI

Empiric therapy protocol*	Rationale
Protocol 1: Vancomycin[¶] ^Δ to cover gram-positive bacteria, including MRSA plus Empirical gram-negative coverage based on local antibiogram data, examples: <ul style="list-style-type: none"> ○ Ceftazidime ○ Carbapenem (meropenem, imipenem or ertapenem) ○ Piperacillin/Tazobactam 	
Protocol 2: Vancomycin[¶] ^Δ plus Gentamicin or tobramycin	
Special situation protocol to cover MDR: Vancomycin[¶] ^Δ plus Two antimicrobial agents with gram-negative activity (from protocol 1) of different classes	Empirical combination antibiotic coverage for multidrug-resistant (MDR) gram-negative bacilli, such as <i>Pseudomonas aeruginosa</i> , should be used when CRBSI is suspected in neutropenic patients, severely ill patients with sepsis or patients known to be colonized with such pathogens.
Special situation protocol to cover candida: Antifungal (fluconazole or echinocandin)	Add an antifungal drug to broad-spectrum therapy in patients with one or more of the following: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, hematologic malignancy, receipt of bone marrow or a solid-organ transplant, femoral catheterization, or colonization due to <i>Candida</i> species at multiple sites.

*KDOQI Vascular Access Guideline (2019 Update) considers it reasonable and necessary to obtain appropriate cultures before initiating empiric antibiotics for the treatment of suspected CVC-related infection, with a change in antibiotics according to culture sensitivities.

¶ IV daptomycin is used instead of vancomycin for patients with a documented vancomycin allergy or documented history of vancomycin-resistant enterococci.

Δ Cefazolin may be used instead of vancomycin in units with a low prevalence of methicillin-resistant staphylococci (MRSA).

Table 12.3. Dosing of drugs used in empiric therapy for CRBSI in hemodialysis patients

Medication		Dose in hemodialysis patients
Drugs to cover gram-positive bacteria in the management protocols 1 and 2	Vancomycin*	<ul style="list-style-type: none"> • High flux: 20 mg/kg IV loading dose, then 1 g IV in the last hour of each hemodialysis session • Low flux: 20 mg/kg IV loading dose, then 500 mg in the last hour of each hemodialysis session
	Daptomycin	<ul style="list-style-type: none"> • High flux: 9 mg/kg IV in the last hour of each HD session • Low flux: 7 mg/kg in the last hour of each HD session
	Cefazolin	<ul style="list-style-type: none"> • 2 g IV or 20 mg/kg (maximum dose: 2 g) after each hemodialysis session
Drugs to cover gram-negative bacteria in the management protocol 1	Ceftazidime	<ul style="list-style-type: none"> • 1 g IV after each hemodialysis session
	Meropenem	<ul style="list-style-type: none"> • 40 mg/kg/dose IV every 48 hours (maximum dose is 2,000 mg/dose). On dialysis days, administer the dose after the hemodialysis session
	Imipenem	<ul style="list-style-type: none"> • 250 to 500 mg IV every 12 hours. When scheduled dosing falls on dialysis days, one of the doses should be scheduled to be given after the hemodialysis session
	Ertapenem	<ul style="list-style-type: none"> • 500 mg or 1 g (IV or IM) after each hemodialysis session
	Piperacillin/Tazobactam	<ul style="list-style-type: none"> • 4.5 g IV every 12 hours or 2.25 g IV every 8 hours. Administration of scheduled doses after the hemodialysis session on dialysis days is preferred but not required
Aminoglycosides in the management protocol 2	Gentamicin or tobramycin*	<ul style="list-style-type: none"> • 1 to 2 mg/kg IV in the last hour of each hemodialysis session (not to exceed 100 mg per dose)
Antifungal	Fluconazole	<ul style="list-style-type: none"> • 200 mg orally daily
	Echinocandin	<ul style="list-style-type: none"> • Caspofungin 70 mg IV loading dose followed by 50 mg IV daily or • Micafungin 100 mg IV daily or • Anidulafungin 200 mg IV loading dose, followed by 100 mg IV daily

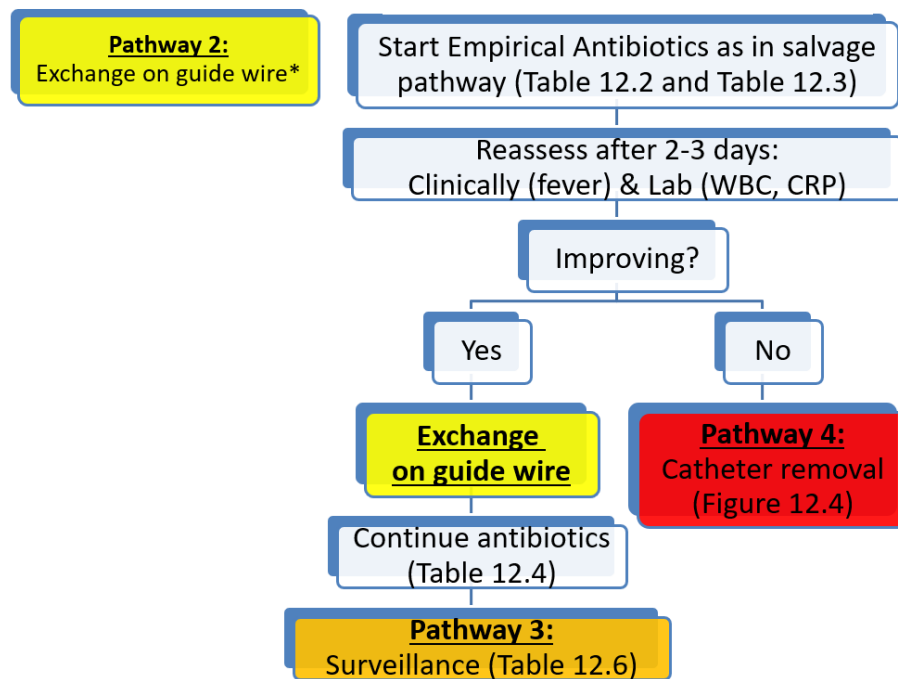
* Predialysis trough drug levels should be monitored whenever possible, but this is usually practical only in the inpatient setting.

Table 12.4. Duration of therapy for different cultured organisms and metastatic complications

Organism	Duration of therapy
<i>Staphylococcus aureus</i>	Antibiotics x 4 weeks.
Coagulase-negative staphylococcus	Antibiotics x 14 days.
Gram-negative bacilli	Antibiotics x 14 days.
<i>Candida</i> species	Antifungal x 14 days after the first negative blood culture.

Table 12.5. Antibiotic lock use for management of CRBSI

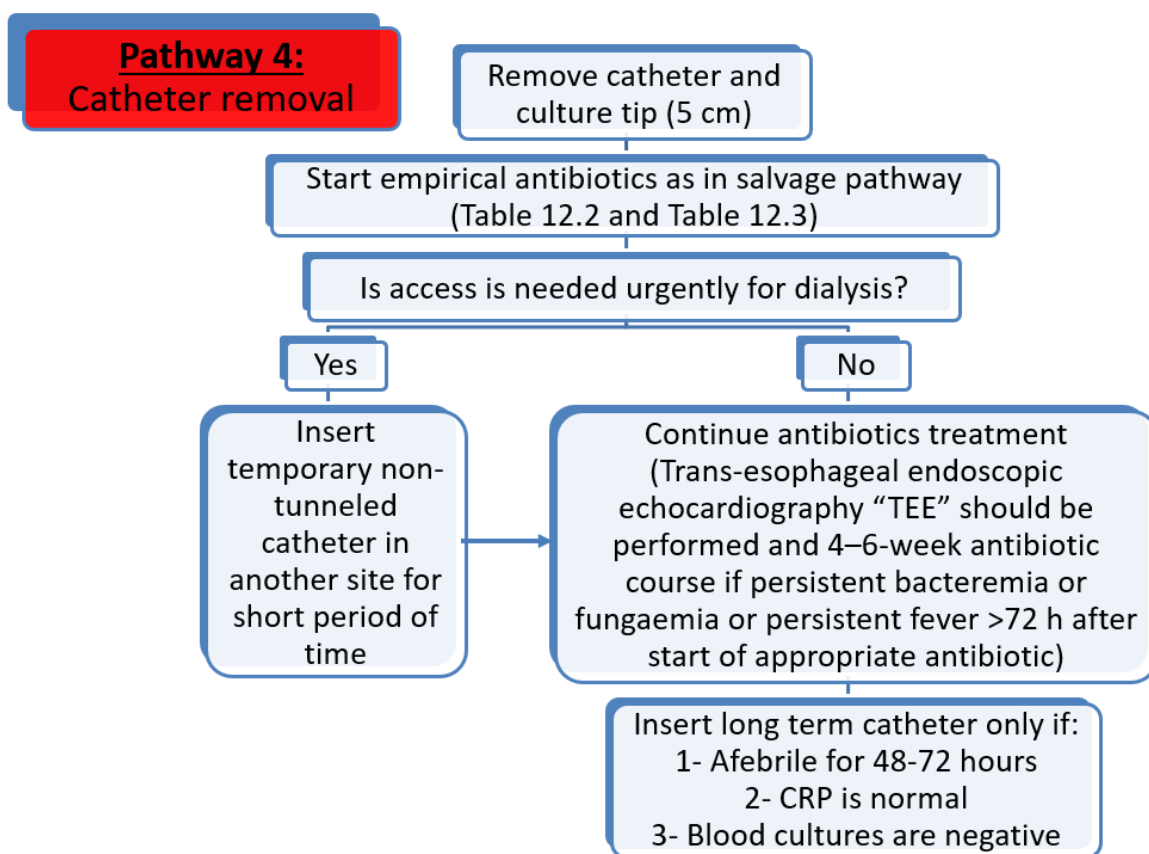
- **Antibiotic lock solutions are designed to kill bacteria present in biofilms.**
 - **Content of antibiotic lock:**
 - Many antibiotic protocols are available. Refer to your local unit protocol for empiric antibiotic lock preparation.
 - The contents of the antibiotic lock are changed to match any changes made to the systemic antibiotic regimen.
 - **Dwell times of antibiotic lock:** It should generally not exceed 48 h before reinstallation of lock solution; preferably, reinstallation should occur every 24 h for ambulatory patients with femoral catheters. However, for patients who are undergoing hemodialysis, the lock solution can be renewed after every dialysis session.
- Duration of antibiotic lock use:** The antibiotic lock is used only for the duration of systemic antibiotics, after which a standard heparin or citrate lock is resumed.

**Figure 12.3. Management of CRBSI (Pathway 2): Exchange on guide wire**

* Exchange on a guide wire should be done only in the case that there is no other access for dialysis and CRBSI is not complicated by an exit site or tunnel infection

Table 12.6. Management of CRBSI (Pathway 3): Surveillance blood cultures

72 h after the initiation of appropriate therapy	1 week after completion of appropriate therapy
If the catheter has been retained, additional blood cultures (e.g., 2 sets of blood cultures obtained on a given day) should be obtained 72 h after the initiation of appropriate therapy, and the catheter should be removed if blood culture results remain positive when blood samples are obtained.	If the catheter has been retained, surveillance blood cultures should be obtained 1 week after the completion of an antibiotic course for CRBSI.

**Figure 12.4. Management of CRBSI (Pathway 4): Catheter removal****Table 12.7. Indications of trans-esophageal endoscopic echocardiography (TEE) in CRBSI**

TEE is indicated in the case of CRBSI is associated with one of the following:
<ul style="list-style-type: none"> • Persistent bacteremia or fungemia or persistent fever >72 h after the start of appropriate antibiotic and catheter removal. • In any case of <i>S. aureus</i> CRBSI as endocarditis is common. • Prosthetic heart valve. • Pacemaker. • Implantable defibrillator.

Table 12.8. Management of CRBSI-associated complications and metastatic infections

Complication	Management
Suppurative thrombophlebitis	Antibiotics for 4-6 weeks.
Endocarditis (new murmur or embolic phenomena)	Antibiotics for 4-6 weeks.
Osteomyelitis	Antibiotics for 6-8 weeks.
Spinal epidural abscess: <ul style="list-style-type: none"> Presenting complaints are fever, backache, local spinal tenderness, leg pain and weakness, sphincter dysfunction, paresis, and/or paralysis. For diagnosis, magnetic resonance imaging appears to be less sensitive than computed tomography–myelography. 	Early (immediate) decompressive surgery is usually advised, although rarely, patients can be successfully treated with antibiotics only.

Prevention of CRBSI:

- Stick to the aseptic technique while inserting, connecting, or disconnecting the catheter, as discussed before in Chapter 11.
- Also as mentioned before in Chapter 11, antibiotic or antimicrobial lock and once-week TPA lock can be used prophylactically in patients in need of long-term CVC who are at high risk of CRBSI (prior multiple CRBSI or staph aureus nasal carriers), especially in facilities with high rates of CRBSI (>3.5/1,000 days).
- KDOQI Vascular Access Guideline (2019 Update) considers it reasonable to use an antimicrobial barrier cap to help reduce CRBSI in high-risk patients or facilities; the choice of connector should be based on the clinician's discretion and best clinical judgment.

Venous catheter thrombosis

I. Intraluminal thrombosis**Management of intraluminal thrombosis:**

- KDOQI Vascular Access Guideline (2019 Update):
 - KDOQI recommends using alteplase or urokinase plus citrate 4% per limb for restoring intraluminal CVC blood flow in an occluded CVC.
 - KDOQI suggests administering alteplase (2 mg in preference to alteplase 1 mg) by the push/pause or dwell method to treat CVC dysfunction (Table 12.9).
- Some references mention that when the dwell technique is unsuccessful, try the alteplase infusion method.
- Mechanical brushing of thrombus is a possible option but is not popular.

Table 12.9. Alteplase push/pause and dwell methods to treat intraluminal thrombosis

Method	Steps
Push/pause method	<ul style="list-style-type: none"> • Instill alteplase* in each CVC lumen, then instill normal saline to fill the internal volume plus 0.2 mL for overfill. If alteplase is instilled into 1 lumen only, lock the other lumen with an anticoagulant lock. • Wait 10 minutes, then gently push normal saline into the lumen(s): 0.3 mL for larger-volume catheters (greater than 1.5 mL) and 0.2 mL for low-volume catheters (less than 1.5 mL). Wait 10 minutes, and then repeat this step x 1. • After waiting another 10 minutes, aspirate clots using a 10 mL syringe and discard. If unable to withdraw, may push remaining alteplase through catheter lumen(s). Lastly, forcefully flush the lumen(s) with normal saline.
Overnight dwell method	<ul style="list-style-type: none"> • Instill alteplase* in each CVC lumen, then instill normal saline to fill the internal volume plus 0.2 mL for overfill. If alteplase is instilled into 1 lumen only, lock the other lumen with an anticoagulant lock. • Leave alteplase in situ until the next hemodialysis run. • Aspirate alteplase immediately before the next hemodialysis run. If unable to withdraw, may push remaining alteplase through the catheter lumen(s). Lastly, forcefully flush the lumen(s) with normal saline.
Short dwell method	<ul style="list-style-type: none"> • Instill alteplase* in each CVC lumen, then instill normal saline to fill the internal volume plus 0.2 mL for overfill. If alteplase is instilled into 1 lumen only, lock the other lumen with an anticoagulant lock. • Leave alteplase in situ for 30 to 60 minutes and withdraw the solution. If unable to withdraw, may push remaining alteplase through the catheter lumen(s). Lastly, forcefully flush the lumen(s) with normal saline. • Longer dwell time is preferred than the short one.

* BC Renal Hemodialysis Committee (2021 Update) suggests using 1 mg of alteplase, while KDOQI Vascular Access Guideline (2019 Update) suggests 2 mg in preference to alteplase 1 mg.

Prevention of intraluminal thrombosis:

- **Clots often occur at the tip of the catheter and may result from poor catheter care:** At the end of the treatment, care must be taken while locking the catheter with an anticoagulant lock to prevent backflow of blood from the vein into the tip of the catheter. This can be done by clamping the catheter while the syringe is still pushing anticoagulant lock-in and with enough pressure on the piston to prevent the entry of blood into the catheter tip.
- **Use of anticoagulants or antiplatelets for prevention of intraluminal thrombosis: KDOQI Vascular Access Guideline (2019 Update) recommendations:**
 - **No role for routine use of prophylactic systemic anticoagulants** as there is inadequate evidence of benefit for CVC patency but suggestion of increased risk of harm.
 - **Low-dose aspirin may be used** to maintain tunneled CVC patency in patients with low bleeding risk.

II. Intracardiac thrombosis

Intra-atrial thrombi need prolonged systemic anticoagulation (6 months or longer) and follow-up for resolution.

III. Embolic complications

Large clots adherent to the end of the catheter or the vessel wall can be clinically silent or can give rise to embolic events.

Venous catheter dysfunction (Poor catheter flow)

Definition of venous catheter dysfunction

- KDOQI Vascular Access Guideline (2019 Update) considers using the following updated definition of CVC dysfunction: Failure to maintain the prescribed extracorporeal blood flow required for adequate hemodialysis without lengthening the prescribed dialysis treatment.
- Another definition for CVC dysfunction is the failure of the catheter to deliver a blood flow rate of at least 300 mL/min at a pre-pump pressure less negative than -250 mm Hg.

Presentation of venous catheter dysfunction

Frequent pressure alarms that are not responsive to patient repositioning or catheter flushing.

Initial (early) dysfunction in recently placed venous catheters

Causes:

- Compression within the catheter tunnel from edema.
- A kink in the catheter or an acute angle in the tunnel (causing collapse of the catheter).
- Improper tip placement.
- Malposition of the catheter (inserted into the azygous or hemiazygos veins).
- Intraluminal thrombosis (discussed before).

Diagnosis: A chest x-ray is valuable in evaluation.

Management:

- Tunnel edema usually subsides within 24 hours.
- Presence of a kink or a malpositioned tip requires replacement of the catheter using a different tunnel or a different length of the catheter:
 - Make the insertion site in the lower part of the neck close to the clavicle as a high insertion site in the neck can cause the catheter to become “positional,” with the position of the neck (the tip moves up with neck movement, leading to poor flow).
 - An exit site close to the breast tissue pulls the tip high into the superior vena cava.
- Treat intraluminal thrombus as mentioned before.

Late dysfunction of venous catheters

Causes:

- Fibrin sheath (sleeve).
- Mural thrombus.

Fibrin sheath (sleeve):

- **Onset:** Almost all catheters inserted into a central vein develop a fibrin sheath within a week or two of insertion.
- **Presentation:**
 - Such fibrin sleeves are initially clinically silent until they obstruct the ports at the distal end of the catheter.
 - Saline infuses easily into the catheter port, but aspiration is difficult, producing a so-called “ball-valve” effect.
- **Risk:** Fibrin sleeves may serve as a nidus for infection.
- **Prevention:** The use of warfarin or other anticoagulants on a chronic basis has not been shown to reduce fibrin sleeve.
- **Diagnosis:** A fibrin sheath is usually determined using radiocontrast material administered through the venous port of the catheter.
- **Management: Balloon catheter:**
 - A balloon catheter is inserted on a guidewire through the catheter tunnel.
 - Then, the balloon catheter is passed into the lumen of the fibrin sheath and is then inflated to disrupt the fibroepithelial sheath.
 - Disruption of the sheath is then confirmed by a repeated radiocontrast injection.

Central venous stenosis

Pathogenesis of central venous stenosis

Central venous stenosis arises from endothelial injury at catheter–endothelial contact sites through the release of various growth factors.

Risk factors of central venous stenosis

The incidence increases with:

- Stiff, non-silicone catheters.
- Subclavian approach (presumably because of higher angular stresses on the catheter in the subclavian position).
- Prolonged duration of the catheter.
- Patients with previous catheter-related infections.
- History of multiple catheter insertions or intravenous pacemaker/cardiovascular implantable electronic device (CIED) implantation.

Presentation of central venous stenosis

- **Stenosis may be asymptomatic until** unmasked by the creation of an AV access.
- **Venous hypertension:**
 - Swelling of the hand, arm, breast, shoulder, neck, and face.
 - Collateral vessels usually develop but may not be adequate to relieve edema.
- **Pain:** Aching and heaviness of an extremity.
- **Skin discoloration:** Red, purple, or blue discoloration or chronic pigmentation changes.
- **Vascular access dysfunction:**
 - High venous pressure on dialysis.
 - Inadequate dialysis.
 - Prolonged bleeding after needle removal post-dialysis.
 - Thrombosis of the AV access may result.
- **Superior vena cava syndrome** may develop due to occlusion of central veins in the chest.

Treatment of central venous stenosis

I. Asymptomatic central venous stenosis should not be treated:

KDOQI Vascular Access Guideline (2019 Update) considers it reasonable that if asymptomatic central venous stenosis without clinical indicators is identified (with a prior or current presence of a CVC), it should not be treated.

II. Symptomatic central venous stenosis with clinical indicators must be treated:

- **Access ligation**, if present, produces the most rapid improvement but sacrifices the access.
- **If thrombosis is present:** Use anticoagulation, in addition to elevation of the upper extremity on the involved side.
- **More definitive therapy usually is required:**
 - Balloon angioplasty has been used for stenosis, but the lesion tends to recur.
 - Stent placement (however, stenosis can reoccur around the stent) combined with angioplasty is indicated in:
 - Elastic (easily distensible) central vein lesions.
 - If dilated stenosis with balloon angioplasty recurs within 3 months.
 - Subclavian vein stenosis can be relieved by an axillary to internal jugular vein bypass.

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