UNDERSTANDING PROCESS OF DIALYSIS

Introduction:
- **End-stage renal disease (ESRD)**, the final stage of **chronic kidney disease (CKD)**, occurs when the kidneys have deteriorated to the point that they are no longer capable of sustaining life.
- There are several mechanisms by which a patient can develop ESRD. For many patients, ESRD is the final chapter in a long battle with CKD as a direct consequence of poorly managed hypertension and diabetes.
- ESRD may result from an episode of acute renal failure that is not reversed, such as a severe adverse drug reaction or exposure to a nephrotoxin that irreversibly shuts down kidney function.
- A patient who develops ESRD has two choices: **renal replacement therapy (RRT)** or kidney transplantation.
- The inability of the kidneys to function results in the accumulation of toxins, electrolytes, and fluid in the body, which can be managed with RRT. There are different types of RRT, including **hemodialysis (HD)** and **peritoneal dialysis (PD)**. RRTs are further classified as intermittent or continuous based on their modality.
- Pharmacists play a key role in the management of patients receiving dialysis. In this review, the concept of dialysis is explored, along with the staging and presentation of patients leading up to ESRD and dialysis. Drug-dosing considerations for HD patients will be provided, as well as a discussion covering new concepts and research initiatives.

Socioeconomic Factors:
- As of December 31, 2012, an estimated 401,600 U.S. patients received HD and 30,517 patients received PD. Among dialysis modalities, HD and PD constitute the two largest groups, with HD the most commonly prescribed.
- Dialysis represents a significant cost in the U.S. Total costs for ESRD in 2012, as measured by Medicare spending, reached $27.8 billion.
- Significantly more was spent on HD ($19.4 billion) compared with PD ($1.04 billion) and renal transplants ($2.08 billion). The annual per-person cost of HD in 2012 was $87,506.

Kidney Deterioration and Progression to ESRD:
- The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) set forth guidelines for staging CKD in 2002. In these guidelines, the patient’s **glomerular filtration rate (GFR)** is estimated using the Modification of Diet in Renal Disease Study equation and measured in mL/min/1.73 m². There are **five stages of CKD**, with stages 1 and 2 reserved for patients exhibiting normal or slightly decreased GFR and the presence of some form of kidney damage.
- Stage 3 is when GFR falls below 60 mL/min/1.73 m², stage 4 is GFR below 30 mL/min/1.73 m², and stage 5 is GFR below 15 mL/min/m². A patient who reaches stage 5 is considered to have ESRD.
- Current terminology for categorizing CKD patients indicates whether a patient is receiving HD; e.g., a non–HD dependent CKD patient has not yet reached stage 5, whereas an HD-dependent CKD patient is in stage.
- Patients typically do not present with clinical symptoms until stage 4, although exceptions exist. **As kidney function declines, serum creatinine and blood urea nitrogen (BUN) begin to rise. Serum phosphorus increases**, as this element is primarily **eliminated renally**.
- **Toxic waste molecules** such as **urea** and **uric acid** start to accumulate in the blood, causing the patient to become symptomatic. Patients often experience **nausea** and **vomiting**, **weight loss**, **poor appetite**, and **fatigue** as they approach kidney failure.
- Uric acid may accumulate and crystallize on the skin, a condition termed **uremic frost**.
As a consequence of uremic encephalopathy, patients may become disoriented and confused and have difficulty concentrating. Anemia develops as the kidney becomes unable to produce enough erythropoietin to maintain adequate hemoglobin concentrations. Alterations in vitamin D, calcium, and parathyroid hormone concentrations also develop in conjunction with the rise in serum phosphorus. Many of these conditions require medications for correction. For example, erythropoiesis-stimulating agents are used to treat anemia, phosphate binders correct hyperphosphatemia, and vitamin D analogues treat secondary hyperparathyroidism. Mental-status changes, uremic frost, and volume overload, as well as nausea and vomiting, can be improved through adequate dialysis therapy.

The HD Process:
- The basic concept of modern HD involves running a patient’s blood through an external circuit, where it is funneled through a semipermeable membrane filter and exposed to a dialysate (dialysis fluid). Here the blood is cleansed of uremic toxins and excess fluid while, simultaneously, beneficial solutes are transported from the dialysate to the blood.
- For example, bicarbonate serum concentrations, often low in ESRD patients, can be corrected by dialyzing the blood against a rich bicarbonate solution. In the U.S., an HD session typically lasts 3 to 4 hours and occurs 3 to 4 days per week, usually in a free-standing center or clinic.
- HD requires a vascular-access site, a dialyzer, and a dialysate. The dialysate consists of a concentrated electrolyte solution dissolved in water. Different types of dialysate solutions are available commercially.
- A typical dialysate contains 130 to 145 mEq/L sodium, 2 to 3 mEq/L potassium, 2.5 to 3.5 mEq/L calcium, and 100 to 200 mg/dL glucose, along with magnesium and alkaline buffers.
- The bicarbonate, which comes as a dry powder, is added later, as it is too unstable to be mixed with the dialysate. The water must initially be passed through a reverse osmosis system each week to remove the aluminum and biomaterials such as bacteria and endotoxins.
- The dialyzer, also referred to as a filter or artificial kidney, is a semipermeable membrane responsible for diffusion and ultrafiltration. Diffusion is the movement of solutes from high to low concentration through a semipermeable membrane. This mechanism removes waste products from the blood during HD. Ultrafiltration, the movement of fluid across a semipermeable membrane that is caused by differences in pressure, removes excess fluids from the body and is used primarily to treat edema.
- Many different types of dialyzers are available. The most common form is the hollow-fiber or capillary dialyzer, which contains thousands of hollow fibers surrounded by a rigid polyurethane shell.
- Two ports are located on each end of the dialyzer to allow the blood and dialysate to flow in and out. The blood flows through the fibers and the dialysate surrounds the fibers.
- The two fluids flow in opposite directions, allowing a concentration gradient to form and resulting in diffusion and ultrafiltration. Low-molecular-weight (LMW) molecules (<5 kDa) move freely across the membrane, while large molecules are restricted. The LMW molecules that are cleared include urea, creatinine, vitamin B12, phosphate, and inulin, among others.
- One of the best-known dialyzer–drug interactions occurs between ACE inhibitors and certain dialyzers. Several studies in the early 1990s reported on anaphylactic reactions observed when AN69 dialyzer membranes were used in conjunction with ACE inhibitors. AN69 dialyzers were composed of polyacrylonitrile membranes that could increase bradykinin generation. When this effect was magnified by the ability of ACE inhibitors to decrease bradykinin breakdown, patients experienced severe and sometimes life-threatening anaphylactic reactions.
- Because dialysis requires access to the patient’s blood supply on a regular basis, one of the challenges in delivering successful treatment is finding a reliable mode of ongoing IV access.
- Dialysis needles are large in diameter (generally 14-17 gauge) to allow for maximal blood flow in a relatively short period of time; it would take too long to dialyze a patient using a needle with a very small bore.
- The three types of access commonly employed in ESRD patients are the arteriovenous fistula (AVF), polytetrafluoroethylene (PTFE) graft, and central venous catheter.
• An AVF is created surgically by joining an artery to a vein, thereby increasing pressure in the vein so that it swells and creates a site for cannulation. The forearm is the most common site, but the upper arm or leg may also be used. In some cases, different methods have been used to locate acceptable vasculature for fistula creation, including regional anesthesia.

• Once the procedure is completed, the AVF may take up to 2 months to fully mature before it can be used. AVF is the preferred choice in many cases and is recommended by the NKF-KDOQI clinical practice guidelines for vascular access and the Fistula First Breakthrough Initiative because it carries the lowest risk of infection.

• PTFE grafts use a synthetic tube to connect the artery to the vein and provide a point of access for cannulation. The PTFE graft takes less time to fully mature, but it carries a higher infection rate.

• Central venous catheters may be used immediately, which is their greatest advantage over AVF and PTFE grafts. They may also have some use in bridge therapy for ESRD patients who are waiting either for a kidney transplant or for their fistula or graft to fully mature. In some instances, a central venous catheter may be the only option if the patient has unusable or unsuitable vasculature.

• For example, a diabetic patient with poor blood flow to the extremities may not have veins suitable for fistula creation or graft insertion. The greatest drawback of central venous catheters is their high infection rate compared with PTFE grafts and AVF. For this reason, central venous catheters are utilized much less for HD access. In 2008, 18% of U.S. HD patients used catheters for HD access, 27% used PTFE grafts, and 55% used AVF.

The PD Process:

• There are two types of PD: continuous ambulatory PD (CAPD) and continuous cyclic PD (CCPD).

• Unlike HD, which is administered intermittently, PD is performed continuously. PD also allows for ambulation during dialysis and can be administered by the patient at home or work.

• In PD, a plastic catheter is permanently placed in the peritoneal cavity. The catheter allows approximately 1.5 to 3 L of an electrolyte solution (dialysate) to flow into the peritoneal cavity.

• The solution remains in the peritoneal cavity for roughly 2 to 4 hours (maximum 6 hours), after which it is removed via the catheter. This process is repeated multiple times per day to allow for proper removal of toxins, salt, and water.

• Toxins are removed from the peritoneal cavity by diffusion; salt and water are removed by osmosis due to the high concentration of glucose in the dialysate. The rate of diffusion slows and eventually stops once equilibrium between plasma and dialysate is reached.

• Solutes and water are absorbed from the peritoneal cavity by crossing the peritoneal membrane and entering the peritoneal capillary circulation; they also are absorbed by crossing from the peritoneal lymphatics to the lymphatic circulation.

• The rate of solute transportation is individualized, and factors such as infection (peritonitis), drugs, and physical makeup affect the rate. During CAPD, the dialysate is manually infused into the peritoneal cavity via the catheter and exchanged three to five times daily.

• Another dialysate may be instilled at bedtime and left overnight. The removal of dialysate from the peritoneal cavity is performed manually and with the help of gravity.

• CCPD, the second type of PD, differs from CAPD in that it is performed during the night by an automated cycler that conducts exchange cycles while the patient sleeps. The number of exchange cycles required for adequate peritoneal solute clearance is patient specific and requires close monitoring.

• The dialysate used in PD may consist of lactate (preferred buffer), heparin (to prevent catheter obstruction), and antibiotics during an episode of acute peritonitis.

• Insulin may be added if the patient has diabetes. Major complications of PD include peritonitis, catheter-associated nonperitonitis infections, weight gain, metabolic disturbances, and residual uremia.

Measuring the Efficacy of the HD Session:

• For HD to be maximally effective, certain parameters must be maintained. Two values that the clinician assesses when determining dialysis efficacy are the $Kt/V$ ($K_{urea}$ = clearance of urea, $t$ = time spent on dialysis, $V$ = volume of distribution of urea) and the urea reduction ratio (URR).

• Urea, a solute that is removed during dialysis, is a marker representing solute clearance. The target $Kt/V$ for HD patients is 1.4.
Since Kurea is measured in millimeters per minute, $T$ is measured in minutes, and $V$ is measured in millimeters, the calculated $Kt/V$ is a unitless parameter. Often, $Kt/V$ is reported as an “adjusted” or “total” value.

If the patient has any residual kidney function, that value may be calculated into the $Kt/V$ to give a more accurate figure; if this has been done, the $Kt/V$ is reported as an adjusted value.

The URR, a simpler calculation, is essentially the difference between predialysis BUN and postdialysis BUN divided by predialysis BUN and expressed as a percentage (e.g., if predialysis BUN = 110 and postdialysis BUN = 38, then URR = 65%).

According to NKF-KDOQI guidelines, the recommended URR goal for ESRD patients is 70%. If target goals ($Kt/V = 1.4, \text{ URR} > 70\%$) are not achieved, the patient may receive additional HD sessions or be prescribed additional time for each session (e.g., 4 hours three times/week vs. 3.5 hours).

Maintaining adequate HD will help manage conditions associated with ESRD, including edema, uremia, and acid or base disorders. Clinicians can then focus on maximizing drug therapy for complications not corrected by HD (e.g., hyperphosphatemia, anemia, secondary hyperparathyroidism).

### Dosing Calculations in HD

#### Factors That Affect Drug Clearance:

- In order to appreciate alterations in drug dosing during dialysis, it is important to understand the process of drug removal. Drug removal resembles the mechanism utilized to remove solutes in conventional HD.
- Drugs primarily undergo diffusion across the dialysis membrane by moving from a high concentration to a low concentration via the concentration gradient that forms between the plasma and the dialysate.
- HD is much more efficient than PD at removing drugs. PD does not remove drugs rapidly, but instead allows them to be adequately absorbed when placed in the peritoneal dialysate.
- This explains why many antibiotics require intraperitoneal placement to reach concentrations needed to appropriately treat peritonitis. Other factors favoring absorption of drugs during peritonitis treatment include inflamed membranes and high-concentration gradients. Many drugs reach inconsistent concentrations in the peritoneal fluid if administered IV or orally.
- Specific drug properties can render an agent more likely to be removed by HD. Drugs that are less than 500 Da and less than 90% protein bound are most effectively removed by HD.
- High-molecular weight drugs with low protein binding are more easily removed by PD than by HD because of secretion into peritoneal lymphatic fluid. A drug with a small volume of distribution—indicating that less of the drug distributes into adipose tissue—is also more effectively removed by dialysis.
- Larger molecules require more porous membranes to allow for increased removal by HD. The type of membrane also plays a role in drug removal during dialysis; this is due to the clearance characteristics of the dialyzer as well as to the membrane charge that is present.
- The drug’s charge and its ability to bind to charged proteins will affect removal. It is also important to consider whether the dialyzer has been reused, as the functional ability to remove drugs decreases with increasing use.

#### Appropriate Dosing:

- Appropriate dosing of drugs in patients undergoing dialysis requires the clinician to conduct a thorough medication history to obtain drug-related allergy or toxicity information and identify concurrent medications.
- The patient’s weight and height, physical examination, and laboratory data assessing renal function are also pertinent to determining appropriate dosing. On average, **patients undergoing dialysis receive approximately 11 different medications** and are three times more likely than patients with normal renal function to experience an adverse drug event.
- This exemplifies the importance of individualizing the medication therapy for each patient and appropriately dosing each medication.
- Recommendations are available for drug dosing in dialysis patients. These recommendations are merely guidelines; adjustments may be required for individual patients.
- Drugs with a long half-life may be initiated with a loading dose that is equal to the usual dose in patients with normal renal function. Once the patient has initiated a drug, the clinician may adjust the dose by decreasing the individual doses or increasing the dose interval.
Anti-hypertensives and Cardiovascular Agents:

- The most commonly prescribed drugs in patients with renal disease are antihypertensives and cardiovascular agents. This is because of the close relationship between the renal and cardiovascular systems with regard to blood pressure control.
- Many of the medications in these two classes are administered by dose titration based upon the patient’s clinical response. Long-acting drugs are more desirable because of improved compliance and should be considered when the patient’s medication regimen is being selected.
- Because these drug classes are often used in patients with renal disease, it is important for the clinician to understand the pharmacokinetic and pharmacodynamic alterations that occur when these drugs are administered to a patient with CKD. Cardiovascular agents and their metabolites can accumulate when renal insufficiency is present.
- There is also a risk of protein and drug-binding abnormalities, which cause an increase in free drug at the site of action and result in enhanced drug efficacy and toxicity. Antihypertensives have toxicity risks as well, and in general their adverse-event profiles are related to their pharmacologic effects.
- Medications that alter the normal pressor response and compensatory cardiac output in dialysis are undesirable to initiate. CKD patients started on antiarrhythmic agents require close monitoring, as the medication may cause the arrhythmia it was intended to treat.
- Diuretics are another drug class often used in patients with renal disease. These agents may be used to treat fluid overload and are a common part of an antihypertensive regimen.
- Proteinuria and renal impairment are two complications that can alter the pharmacokinetics and pharmacodynamics of diuretic agents. Protein binding in the tubule fluid decreases the efficacy of thiazide and loop diuretics.
- If kidney function continues to decline, there is a risk of hypovolemia with diuretic use; this can result in a further decline in renal function. If hypertension is being managed with diuretics, it is important to control blood pressure with little volume contraction.
- Hyperkalemia is an adverse event that is possible with potassium-sparing diuretics, so these agents should not be used in patients with a creatinine clearance (CrCl) below 30 mL/min. The risk of hyperkalemia increases if potassium-sparing diuretics are administered with potassium supplements, ACE inhibitors, angiotensin receptor antagonists (ARBs), or nonsteroidal antiinflammatory drugs (NSAIDs).
- When used alone to reduce fluid volume, potassium-sparing diuretics are less effective than thiazide diuretics and loop diuretics, but they may be used to prevent and treat diuretic-induced hypokalemia and edema when administered concurrently with thiazide or loop diuretics. Organic-acid diuretics must compete with endogenous organic acids to reach the tubule lumen and become active.
- As kidney function declines, larger doses are required. Thiazides become ineffective once the GFR falls below approximately 30 mL/min, but large doses of loop diuretics still may produce a diuretic effect. The combination of a loop diuretic and a thiazide diuretic may be required to achieve an adequate effect.
- ACE inhibitors and ARBs are two common antihypertensives with renal-protective effects in patients with diabetes. These agents must be used with caution in patients who have decreased renal function or are on dialysis.
- Patients with renal artery occlusion or microvascular renal disease may have a sudden decline in renal function because of the hemodynamic effects resulting from decreased angiotensin II in the body. If an ACE inhibitor or ARB is used, the initial dose should be low, the dose should be titrated slowly, and renal function should be monitored closely. Renal function may decrease modestly while these agents are being used, which may be acceptable. If renal function progressively declines, these agents should be discontinued.

Antimicrobials:

- Patients undergoing dialysis respond differently to antimicrobial therapy than patients with normal renal function do. Most antimicrobials are excreted renally and thus require dosing alterations.
- The most important goal of antimicrobial therapy in patients with renal insufficiency is to initiate appropriate and effective therapy early and at doses that can achieve therapeutic concentrations quickly. It would be inappropriate to maintain drug concentrations below therapeutic range; this could be dangerous to the patient.
Drug selection hinges on which pathogen is present. Therapy could initially start with empirical drugs and then be narrowed to focus on a specific pathogen once results of microbial-sensitivity tests are available.

Signs and symptoms of infection may be absent in patients with renal insufficiency, and it is common for uremic symptoms and dialysis to mask symptoms such as fever.

A single loading dose equivalent to the typical maintenance dose in patients with normal renal function should be initiated in patients with renal insufficiency. From there, the dose can be adjusted appropriately based on therapeutic drug-concentration monitoring and microbial sensitivities.

Adverse reactions and drug toxicities are a high risk in patients with impaired renal function. These may be caused by the accumulation of a drug and/or its metabolites after repeated doses.

Adverse reactions can affect any organ system, and **neurotoxicity, nephrotoxicity, hematologic toxicity, and coagulopathy** are common reactions. If new symptoms arise after therapy is initiated, drug toxicity should be considered and evaluated.

Side effects that are uncommon in patients with normal renal function may occur more frequently in patients with kidney failure. For example, accumulation of beta lactam rarely causes seizures in normal patients, but when large doses are given to CKD patients and the drug accumulates, seizures are more likely.

Two ways antimicrobial drugs can induce nephrotoxicity are direct cellular toxicity and allergic interstitial nephritis. **Aminoglycosides** are a specific class of antimicrobials that are **nephrotoxic**.

Patients with normal renal function who are receiving aminoglycoside therapy may have a reduction in renal function that goes unnoticed. However, a CKD patient with a CrCl of 20 mL/min who experiences the same reduction might require dialysis. This underscores the need for careful drug-concentration monitoring in CKD patients receiving antimicrobials.

**Antiplatelet and Anticoagulant Agents:**

- Antiplatelet agents are often used to maintain adequate blood flow to the vascular access site.
- Available classes of antiplatelet therapies are heparin, LMW heparin (LMWH), aspirin, and clopidogrel. Each antiplatelet medication has its own risks and benefits in dialysis patients.
- The **combination of aspirin and clopidogrel in HD patients has been shown to cause hemorrhagic side effects**. Some antiplatelet medications are cleared renally and require dose adjustments.
- Low-dose aspirin does not have a significant effect on renal function in CKD, but LMWH may be risky in patients with significant kidney dysfunction.
- Standard weight-based dose adjustments of LMWH may result in excessive anticoagulation in patients with a GFR less than 50%.
- To reduce the risk of excessive anticoagulation, enoxaparin (an LMWH) in patients with a CrCl of less than 30 mL/min is dosed at half of the normal dose.
- Because of its unpredictable anticoagulation effects and the need for close therapeutic monitoring, **enoxaparin is not recommended in dialysis patients**. The anticoagulant heparin is commonly used to prevent clots from forming in the vascular access site.

**Nonsteroidal Anti-Inflammatory Drugs:**

- The **mechanism of action of NSAIDs is to inhibit prostaglandin synthesis**, which results in anti-inflammatory effects.
- Because prostaglandins are vital in maintaining renal vasodilation and adequate blood flow to the kidneys, **inhibiting this natural process can result in renal arteriolar constriction, decreased renal blood flow, and reduced GFR**.
- Decreased prostaglandin synthesis also may cause salt and water retention by increasing tubule chloride reabsorption in the loop of Henle and increasing the antidiuretic hormone effect on the distal tubule.
- Renin synthesis also may be inhibited, resulting in a reduction in plasma aldosterone production. This can lead to hyperkalemia in patients with renal insufficiency.
- This medication class should generally be avoided in CKD patients, as there is a risk of reducing kidney function even further. Patients with concomitant congestive heart failure, volume contraction, or ascites or edema from liver failure are at greatest risk for developing adverse events owing to their dependence on endogenous renal vasodilator properties.
Cyclo-oxygenase-2 selective NSAIDs demonstrate equivalent effects on the kidneys, and there is no advantage of these agents over nonselective NSAIDs. The nephrotoxicity of NSAIDs is determined by their potency, length of action, and period of administration. The cardiovascular side effects seen with NSAID use have not been determined in patients with CKD.

Emerging Concepts in HD and PRT:
- It has been recommended to begin HD in a CKD patient when the CrCl is below the 10 to 15 mL/min value and is accompanied by signs and symptoms of uremia. However, there remains some controversy regarding the optimal start time for dialysis.
- The Initiating Dialysis Early and Late Study is a prospective, multicenter, randomized, controlled trial investigating whether an early start (CrCl 10-14 mL/min/1.73m2) or late start (CrCl 5-7 mL/min/1.73m2) has any impact on the survival of ESRD patients. Results of the trial are forthcoming.
- Alternative HD regimens that vary the length of dialysis sessions are undergoing increasing evaluation and consideration.
- In the U.S., conventional HD is used for most ESRD patients and requires the patient to dialyze for 3 to 4 hours three times per week. Two types of daily, or quotidian, dialysis—short dialysis and nocturnal dialysis—are alternative HD regimens that may offer some advantages for HD-dependent CKD patients.
- Short daily dialysis requires the patient to dialyze for shorter sessions on more days per week. A typical schedule might be 1.5 to 2 hours for 6 days per week.
- Patients may tolerate this schedule better and experience improved blood pressure control. Although phosphate removal is greater than with conventional HD, it is not of a sufficient degree to negate the use of phosphate binders.
- Daily nocturnal dialysis occurs while the patient sleeps (6-7 nights/week for 6-8 hours). It is well tolerated, reduces phosphorus serum concentrations enough that phosphate binders are often no longer needed, and in some cases controls blood pressure to a greater degree, even to the point of reducing left ventricular hypertrophy.
- In addition, patients may resume a normal diet without regard to salt or phosphate intake. Daily nocturnal dialysis is also the only modality that can help regulate patients with sleep apnea.
- Unfortunately, longer and more frequent dialysis sessions do not necessarily result in better mortality rates. Furthermore, the high cost of short daily dialysis and daily nocturnal dialysis is a barrier for many patients.