A Textbook of

Clinical Pharmacy

for Pharmacy Students

Lesson 8:

Clinical Pharmacy in Patients under Renal Replacement Therapy

ISBN-13: 979-13-992562-9-1

Porto, Portugal.

Published by CIPF, S.L.

Suggested citation: Fernandez-Llimos F. Lesson 8: Clinical Pharmacy in Patients under Renal Replacement Therapy. In: A Textbook of Clinical Pharmacy for Pharmacy Students. Porto: CIPF; 2026.

Available at http://www.cipf-es.org

Lesson 8: Clinical Pharmacy in Patients under Renal Replacement Therapy

Contents

8.1 Dosing in renal impairment 1
8.2 Kidney Failure and Progression to RRT 2
8.3 Renal replacement 3
8.3.1 Overview of renal replacement modalities 4
8.3.2 Convective and diffusive RRT techniques 6
8.3.3 Pharmacokinetic determinants under RRT 7
8.3.4 Assessing "renal function" and extracorporeal clearance during RRT 9
8.4 General dosing principles during RRT 10
8.4.1 Dosing in Intermittent Hemodialysis 10
8.4.2 Dosing in Peritoneal Dialysis 11
8.4.3 Dosing in Continuous RRT and SLED 12
8.4.4 When to maintain, reduce, or supplement dosing 12

8.1 Dosing in renal impairment

Dose adjustment in renal impairment starts with a quantitative estimate of kidney function and proceeds by relating the patient's drug clearance to that of a reference individual with normal renal function. The key pharmacokinetic principle is that maintenance dose and dosing interval should be proportional to total body clearance when the therapeutic target concentration remains unchanged.[1]

The **first step is to estimate glomerular filtration rate or creatinine clearance**, because most renal dose recommendations are expressed as bands of GFR or creatinine clearance (see Lesson 4: Clinical Pharmacy in Renal and Hepatic Impairment). Once renal function is quantified, the next step is to **consider how much of the drug's total clearance is renal**. For drugs in which 50% or more of systemic clearance is via the kidney as unchanged drug, even moderate reductions in GFR can substantially prolong the elimination half-life and promote accumulation with repeated dosing. Conceptually, total clearance can be decomposed into a non-renal component, which is usually unaffected by kidney disease, and a renal component that is roughly proportional to GFR. If the fraction of total clearance accounted for by the kidney is denoted as the renal fraction, then the maintenance dose for a patient with reduced GFR can be obtained by multiplying the usual dose by a factor that scales the renal component in proportion to the patient's estimated clearance.

$$Drug\ clearance = Renal\ clearance + nonRenal\ clearance$$

This idea can be written explicitly by defining relative renal function (RRF), also called factor Q, as the ratio of the patient's renal clearance to that of a typical adult.

[1] Jones GR. Estimating renal function for drug dosing decisions. Clin Biochem Rev. 2011;32(2):81-88.

$$RRF\ or\ Factor\ Q = \frac{CrCl_{patient}}{CrCl_{standard}} \approx \frac{eGFR_{patient}}{eGFR_{standard}}$$

Standard normal creatinine clearance ranges between 90 and 120 mL/min. For the sake of simplicity, standard normal clearance is accepted as 100 mL/min.

Then, calculations consider that the non-renal clearance is left unchanged, while the renal component is reduced in direct proportion to the fall in renal function.

$$Adjusted\ Dose = Normal\ Dose\ [(RRF * proportion_{Renal}) + proportion_{nonRenal}]$$

Instead of lowering the dose, one can also extend the dosing interval while keeping the individual dose size unchanged. Because average steady-state concentration for a linear drug is proportional to dose per unit time divided by clearance, reducing clearance can be compensated either by reducing dose or by giving the same dose less frequently. To calculate the adjusted interval, the proportion method (rule of three) is the simplistic form.

$$Adjusted\ Interval = \frac{Normal\ Dose}{RFF}$$

In practice, this mathematical adjustment is rounded to clinically convenient intervals, such as moving from every 8 hours to every 12 or 24 hours based on creatinine clearance categories, as seen in many renal dosing tables.

Loading doses are usually not reduced solely because of renal impairment, since they depend primarily on the apparent volume of distribution rather than clearance.

8.2 Kidney Failure and Progression to RRT

Kidney failure represents the extreme end of the spectrum of renal impairment, where intrinsic kidney function is no longer sufficient to maintain fluid, electrolyte, acid–base and metabolic homeostasis compatible with life or acceptable quality of life despite optimized conservative measures. In chronic kidney disease (CKD), this stage often corresponds to a sustained glomerular filtration rate (GFR) in the range of approximately 5–10 ml/min/1.73 m^2, but the decision to initiate kidney replacement therapy is largely driven by symptoms and complications rather than any fixed creatinine or GFR threshold. In acute settings, similar derangements can develop over hours to days, so that acute kidney injury (AKI) may rapidly progress to a state in which supportive measures alone are insufficient. In both CKD and AKI, renal replacement therapies (RRT) are therefore best conceptualized as life-sustaining interventions that partially substitute for lost kidney function rather than as treatments that correct the underlying disease.

In CKD, indications for starting RRT arise from a composite assessment of uremic symptoms, clinical signs and biochemical abnormalities. Patients typically present with progressive fatigue, anorexia, nausea, pruritus, cognitive changes or sleep disturbance, alongside more objective features such as refractory volume overload, poorly controlled hypertension, pericarditis or worsening nutritional status. Persistent hyperkaliemia, metabolic acidosis or hyperphosphatemia that cannot be controlled with dietary measures, pharmacotherapy and diuretics are additional warning signs that kidney function has fallen below the threshold at which conservative management can safely maintain homeostasis. Practical guidance therefore recommends advance planning for RRT (including access creation and patient education) when GFR declines below roughly 15–20 ml/min/1.73 m^2 or when progression risk is high, with actual

initiation when this constellation of uremic manifestations and complications becomes evident rather than at a predetermined filtration rate.

In AKI, the timing of RRT initiation is often more urgent and is driven by specific life-threatening indications. Classic triggers include severe or rapidly worsening fluid overload with pulmonary oedema, refractory hyperkalemia despite maximal medical treatment, severe metabolic acidosis compromising hemodynamic or respiratory function, and overt uremic complications such as encephalopathy, pericarditis or bleeding. Outside these emergency situations, decisions are guided by the broader clinical context, including the trajectory of kidney function, the degree of catabolism, comorbid organ failure and anticipated reversibility of the insult. For clinical pharmacists, it is crucial to recognize that many of the precipitating factors for AKI and its complications are drug-related, such as nephrotoxins, inappropriate diuretic use, ACE inhibitors or ARBs in susceptible patients, and agents that raise serum potassium, and that timely dose adjustment or withdrawal may prevent or delay the need for RRT.

From the perspective of a clinical pharmacist, patients requiring renal replacement therapy represent one of the most fragile and therapeutically complex populations, in whom inappropriate prescribing can rapidly translate into toxicity, therapeutic failure or destabilization of dialysis. **During RRT, total drug clearance becomes the sum of residual renal elimination, extracorporeal elimination, and non-renal elimination**, and the extracorporeal component is highly variable across modalities and over time, so that fixed 'renal impairment' dosing tables are often misleading. Small, hydrophilic, low–protein-binding drugs such as many beta-lactams, aminoglycosides, fluoroquinolones or low-molecular-weight antivirals may be removed very efficiently, particularly by high-efficiency hemodialysis or high-dose continuous techniques, whereas large, lipophilic or highly protein-bound agents are scarcely affected, creating a sharp divergence in exposure between drug classes that can only be managed with modality-specific dosing, careful scheduling around sessions and, whenever feasible, therapeutic drug monitoring. At the same time, dialysis patients live with extreme polypharmacy, high symptom burden and frequent intercurrent illness, which makes medication review, avoidance of nephrotoxins, rational deprescribing, adjustment of doses to the actual delivered RRT dose rather than the theoretical prescription, and close monitoring of clinical and laboratory endpoints essential components of high-quality care.

8.3 Renal replacement

Renal replacement therapy refers to extracorporeal or peritoneal techniques that partially substitute for lost kidney function by removing solutes, correcting electrolyte and acid–base disturbances and managing fluid balance in acute kidney injury and chronic kidney failure. Clinical pharmacists most often encounter renal replacement therapy in three broad contexts: chronic intermittent **hemodialysis** in outpatient dialysis centers, **peritoneal dialysis** delivered either as continuous ambulatory or automated regimens, and **continuous renal replacement** therapies prescribed for hemodynamically unstable critically ill patients in intensive care.

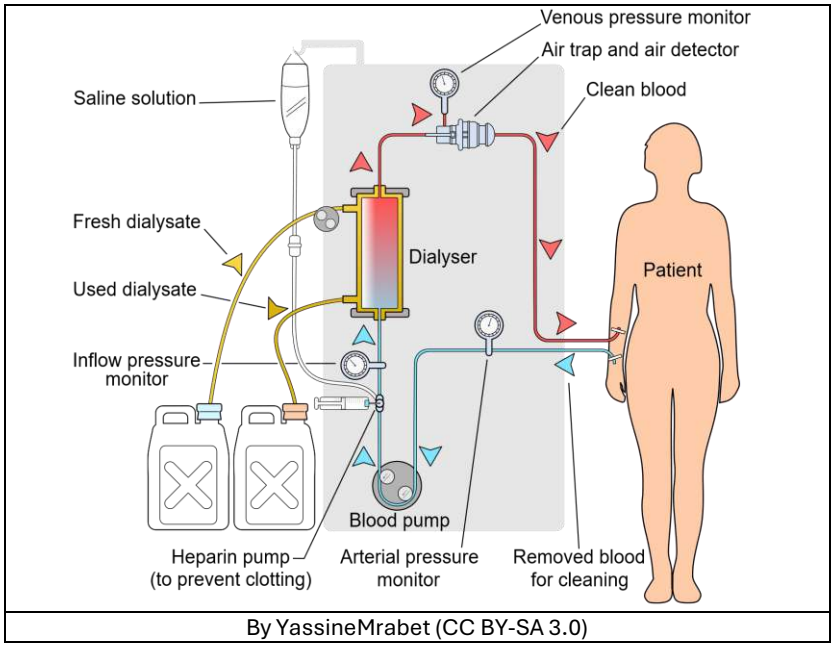
Epidemiological data show that hemodialysis remains the predominant modality worldwide, accounting for the majority of kidney replacement therapy, while peritoneal dialysis and continuous techniques contribute to important but smaller proportions that are nonetheless highly relevant to pharmacotherapy because of their distinct solute-clearance profiles and treatment schedules.

8.3.1 Overview of renal replacement modalities

Renal replacement techniques differ substantially in how they remove solutes and water, and these mechanistic differences largely govern their impact on drug clearance and exposure. For clinical pharmacy it is essential not only to recognize the names and schedules of the various modalities, but also to understand whether **solute removal is predominantly diffusive or convective**, how **continuous or intermittent** the treatment is, and how modifiable prescription parameters such as blood flow, dialysate or effluent flow and session duration translate into **variability in drug elimination**.[2]

Intermittent hemodialysis

Intermittent hemodialysis typically consists of three to five sessions per week, each lasting about three to five hours, during which blood is circulated at relatively high flow through a dialyzer while dialysate runs counter-current on the other side of a semi-permeable membrane, providing predominantly diffusive clearance of small solutes down their concentration gradients. High-flux membranes, with larger pore size and greater hydraulic permeability, support more efficient removal of middle molecules and allow higher ultrafiltration rates than low-flux membranes, but both types rely on the combination of blood flow, dialysate flow and membrane surface area to determine the overall mass transfer of dialysable drugs during a session. Because solute removal is intensive but time-limited, many small, hydrophilic and poorly protein-bound drugs exhibit substantial intradialytic clearance with post-dialysis "rebound" in plasma concentrations as drug redistributes from peripheral compartments back into the intravascular space, a phenomenon that has direct implications for the timing of dosing and the need for supplemental post-dialysis doses.

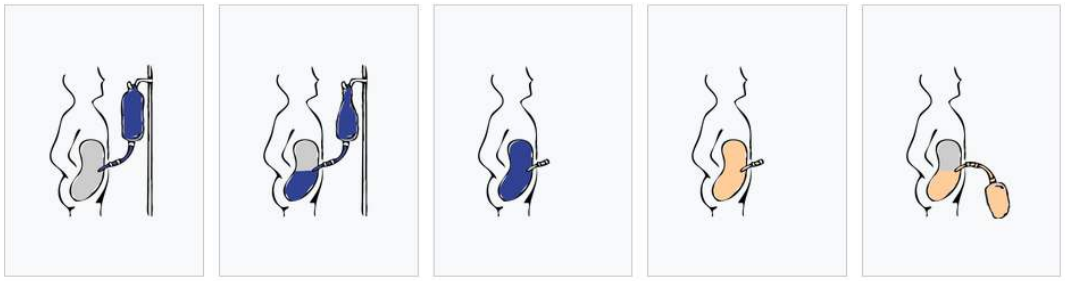


By YassineMrabet (CC BY-SA 3.0)

[2] Jang SM, Infante S, Abdi Pour A. Drug Dosing Considerations in Critically Ill Patients Receiving Continuous Renal Replacement Therapy. Pharmacy (Basel). 2020;8(1):18.

Peritoneal dialysis

Peritoneal dialysis uses the patient's peritoneal membrane as the dialyzer, instilling hyperosmolar dialysate into the peritoneal cavity and allowing solute and water exchange with the peritoneal capillary circulation before the fluid is drained, which produces predominantly diffusive clearance of small solutes with an element of convection through ultrafiltration. In continuous ambulatory peritoneal dialysis, several manual exchanges are performed during the day with relatively long dwell times, whereas automated peritoneal dialysis uses a cycler to perform multiple exchanges overnight. In both cases the combination of dwell time, peritoneal transport characteristics and dialysate composition determines the modest but continuous solute-clearance profile that distinguishes peritoneal dialysis from the more intense, intermittent clearance of hemodialysis. From a pharmacokinetic perspective, **peritoneal dialysis generally removes drugs less efficiently than high-efficiency hemodialysis**, but the near-continuous nature of therapy and the possibility of intraperitoneal administration, particularly of antimicrobials for peritonitis, create a distinct pattern of drug disposition that must be considered when individualizing dosing regimens.[3]



By Nanoxyde (BY-SA 3.0)

Continuous renal replacement therapies

Continuous renal replacement therapies (CRRT) are typically used in hemodynamically unstable critically ill patients and **operate over 24 hours** or most of the day, providing slow, continuous solute and fluid removal that is better tolerated than conventional intermittent dialysis in this population. **Continuous veno-venous hemofiltration** removes solutes mainly by convection through ultrafiltration of plasma water and replacement-fluid infusion, **continuous veno-venous hemodialysis** relies primarily on diffusion between blood and dialysate, and **continuous veno-venous hemodiafiltration** combines convective and diffusive mechanisms. In all these modalities the effluent flow rate (dialysate plus ultrafiltrate) is a key determinant of extracorporeal clearance for small, non–protein-bound drugs. Filter membrane characteristics, including surface area and material, and practical issues such as circuit downtime, filter clotting and frequent changes in prescription in the ICU introduce considerable day-to-day variability in

[3] Ansari N. Peritoneal dialysis in renal replacement therapy for patients with acute kidney injury. Int J Nephrol. 2011;2011:739794.

drug removal, so that nominal effluent flow may overestimate actual clearance if interruptions are common.[4]

Hybrid and extended modalities

Hybrid techniques such as **sustained low-efficiency dialysis (SLED)** and related prolonged intermittent renal replacement therapies aim to combine the hemodynamic tolerability of continuous therapies with the logistical advantages of intermittent hemodialysis by using lower blood and dialysate flows over extended sessions, often six to twelve hours in duration. Compared with conventional intermittent hemodialysis, these modalities provide slower but more prolonged solute clearance, leading to different time–concentration profiles for dialysable drugs, while still generating a clear on–off pattern of extracorporeal clearance that contrasts with the truly continuous nature of CRRT. From a pharmacokinetic standpoint, SLED and similar treatments are often positioned between intermittent and continuous therapies in terms of intensity and cumulative daily clearance, and dose-adjustment commonly requires extrapolation from both hemodialysis and CRRT data, with particular attention to session timing, duration and the specific prescription used in the local ICU.[5]

8.3.2 Convective and diffusive RRT techniques

Convective techniques and diffusive techniques differ fundamentally in the physical mechanism of solute transport, the range of molecules removed, and how prescription parameters influence clearance.

In **diffusive techniques** such as conventional **intermittent hemodialysis or continuous veno-venous hemodialysis (CVVHD)**, solutes move across the membrane down a concentration gradient between blood and dialysate, analogous to gas exchange across the alveolar membrane. Small solutes with rapid diffusivity, such as urea, creatinine and many low–molecular weight electrolytes, are therefore cleared very efficiently, especially when high blood and dialysate flow rates and large membrane surface areas are used. Because diffusion depends on the gradient between plasma and dialysate, dialysate composition and flow rate are key determinants of clearance, and these treatments typically deliver high-intensity but time-limited solute removal during discrete sessions. **Drug removal in purely diffusive modalities thus favors small, hydrophilic, poorly protein-bound compounds with a relatively small volume of distribution**.

Convective techniques, exemplified by **hemofiltration and continuous veno-venous hemofiltration (CVVH)**, remove solutes by **solvent drag**: plasma water is forced across the membrane by transmembrane pressure, and solutes are carried with the convective flow in proportion to their **sieving coefficient**.[6] In this setting, the driving force is ultrafiltration rate

[4] Jang SM, Awdishu L. Drug dosing considerations in continuous renal replacement therapy. Semin Dial. 2021;34(6):480-488.
[5] Brown P, Battistella M. Principles of Drug Dosing in Sustained Low Efficiency Dialysis (SLED) and Review of Antimicrobial Dosing Literature. Pharmacy (Basel). 2020;8(1):33.
[6] The **sieving coefficient** is a quantitative measure of how easily a solute crosses the hemofilter membrane during convective therapies such as hemofiltration. In RRT, it is defined as the ratio of the solute concentration in the ultrafiltrate (effluent) to the mean solute concentration in plasma water within the filter, often written conceptually as: **sieving coefficient = ultrafiltrate concentration / plasma concentration**. A sieving coefficient of 1 indicates that the solute is freely permeable and fully filterable (e.g. urea, creatinine), whereas a value close to 0 indicates that the solute does not effectively cross the membrane (e.g. albumin).

rather than a concentration gradient with dialysate, and replacement fluid is infused to maintain fluid balance while achieving a prescribed convective "dose". Convection is particularly **effective for clearing middle-molecular-weight solutes that diffuse more slowly**, such as many inflammatory mediators, so high-volume hemofiltration can achieve better removal of these solutes than purely diffusive hemodialysis, provided membrane pore size and surface area are adequate.

A further practical difference is that diffusive regimens (e.g. conventional intermittent hemodialysis) are usually delivered intermittently with high instantaneous clearance, producing marked on–off patterns and post-dialysis rebound of drug and toxin concentrations, while convective therapies in critical care are often continuous or prolonged, providing slower but more stable clearance over 24 hours. Continuous convective or mixed convective–diffusive CRRT thus adds an extracorporeal clearance component that may approach or exceed residual renal clearance, whereas intermittent diffusive therapies overlay brief episodes of very high extracorporeal clearance on periods without treatment. These mechanistic distinctions support the different impacts of convective versus diffusive modalities on drug pharmacokinetics and dosing, especially for compounds with significant tissue distribution or non-renal elimination.

8.3.3 Pharmacokinetic determinants under RRT

Pharmacokinetic determinants under renal replacement therapy (RRT) are best conceptualized as the interaction of drug-related, system-related and patient-related factors that together define the magnitude and variability of extracorporeal drug clearance on top of any residual kidney function.

Drug-related factors

For drugs, the key properties that determine dialyzability across modalities are molecular weight, protein binding, volume of distribution, water–lipid solubility balance and their translation into sieving and saturation coefficients in each circuit. Small, hydrophilic drugs with low protein binding and a low to moderate volume of distribution (e.g., many beta-lactams and aminoglycosides) are efficiently removed by both intermittent hemodialysis and high-dose CRRT, whereas large molecules and highly protein-bound drugs (e.g., many lipophilic psychotropics like amitriptyline, imipramine, or olanzapine) show negligible extracorporeal clearance even when native GFR is minimal. In convective techniques, the **sieving coefficient** approximates the unbound fraction for small solutes and predicts how closely extracorporeal clearance will follow effluent flow, while in diffusive techniques a saturation coefficient (ratio of dialysate to plasma concentration) plays an analogous predictive role for dialyzer clearance. These coefficients are not fixed constants but depend on membrane characteristics, blood flow, protein binding in critically ill plasma and saturation phenomena at high solute fluxes, so that extrapolation between modalities requires caution even for the same drug.

Sieving Coefficient and Saturation Coefficient

In clinical pharmacokinetics of RRT, the **sieving coefficient** (Sc) is used for convective therapies (e.g. CVVH, hemofiltration, HDF) and is defined as the ratio of the solute concentration in ultrafiltrate (or effluent generated by convection) to its concentration in plasma (usually plasma water) entering the filter: $Sc=C_{UF}/C_{plasmaSc}=C_{UF}/C_{plasma}$. A value of 1 indicates that the solute is freely filtered with the same concentration in ultrafiltrate and plasma water, whereas values approaching 0 indicate that the solute is effectively retained (e.g. large, protein-bound molecules such as albumin).

By contrast, the **saturation coefficient** (Sa) is used for diffusive therapies (e.g. intermittent hemodialysis, CVVHD) and is defined as the ratio of solute concentration in dialysate (or diffusive effluent) to its concentration in plasma entering the dialyzer: $Sa=C_{dialysate}/C_{plasmaSa}=C_{dialysate}/C_{plasma}$. When Sa is near 1, the solute equilibrates almost completely between blood and dialysate; lower values indicate limited diffusive transfer, typically because of larger molecular size, high protein binding or lower membrane permeability.

Conceptually, both coefficients range from 0 to 1 and express how "permeable" a solute–membrane combination is, but sieving coefficient quantifies convective passage into ultrafiltrate, whereas saturation coefficient quantifies diffusive equilibration into dialysate.

System-related factors

System-related determinants can be grouped into properties of the membrane and the "dose" of RRT delivered at the bedside. Membrane material and surface area influence drug removal both by defining the effective pore size for diffusive and convective transport and by introducing the possibility of adsorption, which may markedly increase early clearance of some antibiotics and other moderately lipophilic drugs until binding sites are saturated. Blood flow, dialysate flow and ultrafiltration or effluent rate translate these membrane properties into actual extracorporeal clearance. In continuous RRT, extracorporeal clearance of small, freely filtered drugs approximates the effluent flow multiplied by the sieving or saturation coefficient, whereas in intermittent hemodialysis high blood and dialysate flows produce very efficient but time-limited removal with prominent post-dialysis rebound from peripheral compartments. Treatment duration, unplanned interruptions, filter clotting and circuit changes introduce substantial intra- and interpatient variability, so that the prescribed effluent dose may substantially overestimate delivered drug clearance, especially in unstable ICU patients.

Patient-related factors

Patient-related factors modulate how much of the total body drug is accessible to the extracorporeal circuit and how important RRT is relative to intrinsic clearance. Residual kidney function, even at low levels of GFR, can contribute substantially to total clearance of drugs with high renal elimination and must therefore be incorporated into dosing, particularly in continuous RRT where extracorporeal clearance is often in the same order of magnitude as native clearance in advanced chronic kidney disease. Critical illness pathophysiology modifies distribution and binding: capillary leak, fluid resuscitation and hypoalbuminemia expand the apparent volume of

distribution and increase the unbound fraction of many drugs, which may paradoxically enhance extractability by RRT while at the same time lowering peak concentrations and delaying equilibration between compartments. Inflammation and multi-organ dysfunction further alter non-renal clearance pathways, so that for some drugs hepatic or intestinal metabolism becomes the dominant determinant of exposure, whereas for others extracorporeal removal becomes disproportionately important, reinforcing the need to link this section with the broader discussion of altered distribution and non-renal clearance in **Lesson 4 (Clinical Pharmacy in Renal and Hepatic Impairment)** rather than treating RRT in isolation.

8.3.4 Assessing "renal function" and extracorporeal clearance during RRT

Conventional creatinine-based estimates of glomerular filtration lose interpretability once renal replacement therapy starts, so clinical pharmacists must **shift from "kidney function" to a clearance-based view** that explicitly incorporates extracorporeal drug removal alongside any residual renal and non-renal clearance.

During RRT, **serum creatinine and creatinine-based equations no longer provide a reliable measure of drug-relevant clearance** for three main reasons:

- First, acute kidney injury and critical illness are non–steady-state conditions in which creatinine production, distribution volume and elimination fluctuate, so serum creatinine lags behind true changes in GFR and cannot be translated into a stable clearance value.
- Second, creatinine itself is removed by dialysis or hemofiltration, so its plasma concentration reflects both native kidney function and extracorporeal clearance, which breaks the link between a given creatinine level and intrinsic GFR assumed by Cockcroft–Gault or CKD-EPI.
- Third, RRT can provide substantial solute clearance even at low or negligible native GFR, so two patients with the same serum creatinine on different RRT prescriptions may have very different total drug clearance, making creatinine-based CrCl or eGFR largely meaningless for dosing once RRT is established.

Under RRT, pharmacists should conceptualize **drug elimination as the sum of three components: residual renal clearance, extracorporeal clearance, and non-renal clearance**, with extracorporeal clearance largely determined by effluent or dialysate flow and the sieving or saturation coefficient for the drug–membrane combination.

Because extracorporeal clearance is highly variable across modalities, prescriptions and patients, **theoretical clearance estimates based on flows and coefficients are necessary but insufficient for high-risk medicines**, making therapeutic drug monitoring (TDM) a key complementary tool in selected drugs. TDM is particularly valuable for antimicrobials such as vancomycin, aminoglycosides and some β-lactams, certain anticonvulsants and triazole or echinocandin antifungals, where RRT, critical illness and shifting volumes of distribution combine to make standard dosing tables unreliable, and concentration targets or pharmacodynamic indices can be linked to outcomes. TDM is further explored in Biopharmacy and Pharmacokinetics course (4th year).

Even when TDM is unavailable, pharmacists should treat extracorporeal clearance estimates as a starting point and **refine dosing using close follow-up of clinical endpoints** (infection control, seizure control, hemodynamic status, toxicity markers), recognizing that dynamic changes in RRT settings or patient status may require repeated adjustment of both dose and timing relative to dialysis sessions.

8.4 General dosing principles during RRT

The conceptual framework used for renal impairment in general (i.e., avoid nephrotoxic agents when possible, reduce doses of renally cleared drugs, extend dosing intervals, and monitor clinical and laboratory endpoints) remains valid during renal replacement therapy, but its application changes because an additional extracorporeal clearance pathway is introduced. Extracorporeal clearance may be intermittent and intense (intermittent hemodialysis), slow and continuous (continuous RRT), or intermediate (SLED), and its magnitude depends on membrane characteristics, prescription parameters, session duration, downtime, and residual kidney function. Practical dosing therefore requires estimating how the chosen modality modifies total body clearance, deciding whether to maintain, reduce, extend, or supplement dosing, and recognizing that these decisions often need repeated adjustment as RRT prescriptions and residual function evolve.

8.4.1 Dosing in Intermittent Hemodialysis

Intermittent hemodialysis compresses a large fraction of drug removal into three to five hours, usually three times per week, creating a **pronounced on–off pattern of extracorporeal clearance**. Small, hydrophilic, poorly protein-bound drugs (e.g. many β-lactams, aminoglycosides, some fluoroquinolones) are especially affected and may lose a large proportion of their body burden during each session, followed by **post-dialysis "rebound"** as drug redistributes from tissues back to plasma.

For highly dialysable drugs, administration is usually planned immediately after the dialysis session, so that distribution and elimination during the interdialytic period are more predictable and the post-dialysis rebound contributes to exposure rather than being removed again. Once-weekly or twice-weekly post-dialysis aminoglycoside regimens exemplify this approach, achieving adequate peaks and prolonged post-antibiotic effects while limiting accumulation. By contrast, drugs with negligible dialyzability (highly protein-bound, large molecules, or with extensive tissue distribution) can generally be scheduled independent of the dialysis session and do not require post-dialysis supplementation.

Post-dialysis supplemental doses are appropriate when pharmacokinetic data show that intermittent hemodialysis removes a clinically relevant proportion (often 30–50%) of the drug load per session, as described for several parenteral β-lactams. The supplemental dose aims to restore the pre-dialysis body content, is ideally administered in the last minutes of dialysis or immediately after disconnection and requires coordination with dialysis staff to avoid significant delays that undermine its purpose.

Time-dependent antimicrobials such as β-lactams and linezolid require special attention because their efficacy depends on the time that free concentrations exceed the MIC[7], which is difficult to maintain over long 48–72-hour interdialytic intervals. Strategies to minimize underexposure include extended or prolonged infusions (e.g. 3–4-hour β-lactam infusions after dialysis) and, when feasible, therapeutic drug monitoring to verify that the desired pharmacodynamic targets are achieved despite high intradialytic clearance and large volumes of distribution in critical illness.

[7] MIC: minimum inhibitory concentration.

Drugs and dialyzability	
Drugs with negligible dialyzability	**Drugs with high dialyzability**
• Carvedilol and most other highly lipophilic β-blockers (e.g. propranolol, labetalol). • Most benzodiazepines (e.g. diazepam, midazolam, clonazepam). • Tricyclic antidepressants (e.g. amitriptyline, imipramine, nortriptyline). • Many antipsychotics (e.g. olanzapine, quetiapine, clozapine). • Opioids with high protein binding and large Vd such as fentanyl and methadone. • Phenytoin. • Digoxin. • Most statins (e.g. atorvastatin, simvastatin, rosuvastatin). • Warfarin and other highly protein-bound vitamin K antagonists.	• Many β-lactam antibiotics: ampicillin, amoxicillin, most cephalosporins (e.g. cefazolin, ceftazidime, cefepime), piperacillin–tazobactam. • Many carbapenems (e.g. meropenem, imipenem). • Aminoglycosides: gentamicin, tobramycin, amikacin. • Vancomycin. • Several fluoroquinolones, especially levofloxacin and ofloxacin (less so moxifloxacin). • Water-soluble β-blockers such as atenolol and metoprolol. • Many water-soluble, low–molecular weight antidiabetics such as acarbose. • Low-molecular weight antivirals and antiretrovirals (e.g. acyclovir, ganciclovir). • Low-molecular weight, hydrophilic antiepileptics such as levetiracetam and gabapentin.

8.4.2 Dosing in Peritoneal Dialysis

Peritoneal dialysis (PD) provides lower instantaneous clearance than high-efficiency intermittent hemodialysis but more continuous or pulsatile elimination, depending on whether continuous ambulatory PD (CAPD) or automated PD (APD) is used. Peritoneal drug clearance depends on peritoneal transport type, dwell time, and ultrafiltration, but for many drugs it remains modest compared with residual renal and non-renal clearance, so standard renal-impairment dosing based on residual GFR alone is often sufficient.

In **continuous ambulatory PD**, near-continuous exchanges create gently declining drug concentrations over the day, without the pronounced on–off pattern or large post-treatment rebound characteristic of intermittent hemodialysis. For most systemically administered agents, this pattern favors once-daily or extended-interval maintenance regimens adapted to residual kidney function rather than repeated small doses targeted to brief periods of high clearance. Certain drugs with significant peritoneal clearance, such as vancomycin and aminoglycosides, may require specific PD-adjusted regimens and, when possible, therapeutic drug monitoring to prevent under- or overexposure.

In **automated PD**, most solute and drug removal occur overnight, with limited clearance during the long daytime dwell, resulting in an intermediate pattern between continuous ambulatory PD and intermittent hemodialysis. For most drugs, renal-impairment dosing based on residual kidney function remains appropriate, as overnight cycling usually does not change clearance enough to justify entirely different regimens, though concentrations may vary modestly between day and night.

8.4.3 Dosing in Continuous RRT and SLED

Continuous renal replacement therapy (RRT) and hybrid modalities such as sustained low-efficiency dialysis (SLED) are widely used in hemodynamically unstable critically ill patients and add a continuous or prolonged extracorporeal clearance component that may rival or exceed residual renal clearance. For small, unbound drugs, extracorporeal clearance during continuous RRT approximates effluent flow (dialysate plus ultrafiltrate) multiplied by the sieving or saturation coefficient, normalized to body weight, so that standard prescriptions of 20–25 ml/kg/hour delivered effluent produce substantial drug removal.

In practice, filter clotting, disconnections and other interruptions reduce delivered effluent below the prescribed rate, making theoretical clearance an overestimate and generating variability that is particularly relevant for narrow-therapeutic-index drugs.

SLED, typically delivered for 6–12 hours daily with lower flows than conventional intermittent hemodialysis, produces a clearance profile between intermittent and continuous therapies, often requiring extrapolation from both intermittent hemodialysis and continuous RRT data. For dialysable drugs, SLED can remove more drug per day than conventional intermittent hemodialysis but with less abrupt post-treatment rebound, so dosing regimens are frequently individualized, particularly for antimicrobials and other high-risk medications.

8.4.4 When to maintain, reduce, or supplement dosing

During RRT, total drug clearance reflects the sum of residual renal, extracorporeal, and non-renal pathways, and decisions about dose maintenance, reduction, interval extension, or post-treatment supplementation must integrate this combined clearance rather than focusing on native GFR alone. Residual kidney function, even at very low GFR, can contribute meaningfully to total clearance, especially in continuous RRT, so that applying end-stage renal disease dosing tables designed for anuric patients may lead to underexposure in patients who still have residual filtration and substantial extracorporeal clearance.

Conversely, recovery of renal function after acute kidney injury may progressively increase total clearance under a fixed continuous RRT prescription, so doses that were initially appropriate may become excessive if not adjusted as serum creatinine falls and urine output increases.

Pragmatically, four patterns can be distinguished:

- Unchanged dosing is reasonable when combined clearance during RRT approximates normal renal function;
- Reduced maintenance dosing is used when total clearance is lower but continuous (e.g. in PD or low-dose continuous RRT);
- Interval extension suits drugs where lower troughs are acceptable;
- Post-treatment supplements are reserved for intermittent modalities that remove a predictable fraction of drug during each session, such as intermittent hemodialysis and some SLED prescriptions.

Across all modalities, drugs with narrow therapeutic windows (notably aminoglycosides and vancomycin) should, whenever feasible, be managed with therapeutic drug monitoring, because both underexposure (from high-intensity RRT) and overexposure (from downtime or recovery of renal function) are common and difficult to anticipate from standard nomograms alone.