A Textbook of

Clinical Pharmacy

for Pharmacy Students

Lesson 4:

Clinical Pharmacy in Renal and Hepatic Impairment

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Lesson 4: Clinical Pharmacy in Renal and Hepatic Impairment

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4.1 Renal impairment

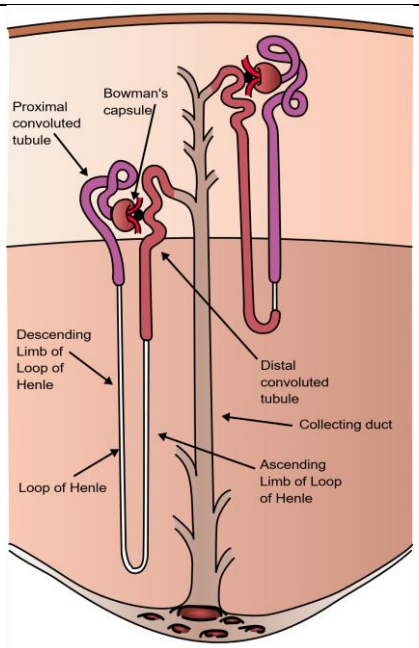
Renal impairment is one of the most frequent and clinically significant determinants of variability in drug exposure and response, making it a central concern for clinical pharmacy and pharmacotherapy optimization. Even modest reductions in kidney function can lead to accumulation of renally eliminated drugs or their active metabolites, altered pharmacodynamics, and increased susceptibility to adverse effects, particularly in older adults and patients with multimorbidity. Because many commonly used therapeutic classes suffer from renal excretion and because kidney function often fluctuates during acute illness, systematic assessment of renal function and proactive adjustment of dosing, interval and monitoring are essential tasks for clinical pharmacists to ensure safe, effective and individualized pharmacotherapy.

4.1.1 Recap of Physiology of Renal Excretion

Renal excretion is the result of coordinated processes that occur along the nephron, the functional unit of the kidney, and together they determine how efficiently substances (including drugs) are removed from the body. The nephron consists of the glomerulus, proximal tubule, loop of Henle, distal convoluted tubule and collecting duct, each contributing in a distinct way to filtration, secretion and reabsorption, and thereby shaping the renal clearance of solutes and water.

At the glomerulus, plasma is filtered across the capillary wall into Bowman's space, driven by hydrostatic pressure and modulated by oncotic and intraglomerular pressures, producing an ultrafiltrate that is essentially protein free and contains freely filtered, low-molecular-weight solutes, including many drugs. The effective glomerular filtration rate is therefore a major determinant of the initial delivery of a medicine or its metabolites into the tubular system, provided they are not extensively protein bound or too large to cross the filtration barrier.

The proximal tubule is responsible for reabsorbing the bulk of filtered sodium, water, bicarbonate, glucose and amino acids, and is also a major site of active tubular secretion of organic anions and cations, including numerous drugs. Specific transporters, such as organic anion transporters (OATs) and organic cation transporters (OCTs), mediate the uptake of compounds from blood into tubular cells and their subsequent secretion into the tubular lumen, allowing active clearance that can greatly exceed glomerular filtration alone. This segment therefore plays a central role in the elimination of drugs like many beta-lactam antibiotics or some antivirals, and competition at these transporters underlies clinically important interactions that modify renal clearance.



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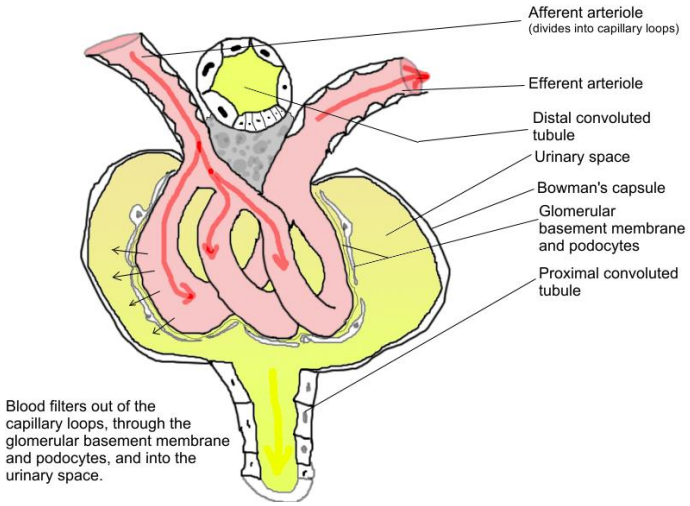

By Tieum (CC BY-SA 4.0)

The loop of Henle, with its descending and ascending limbs, is crucial for urine concentration through the countercurrent multiplier mechanism, reabsorbing large fractions of sodium, chloride and water and generating the corticomedullary osmotic gradient. Although relatively fewer drugs are handled specifically in this segment, changes in tubular flow and medullary tonicity here influence the concentration of solutes in tubular fluid and can modify passive reabsorption of non-ionized drug molecules.

The distal convoluted tubule and the collecting duct make the final, precise adjustments to how much sodium, potassium, acid (hydrogen ions) and water are kept or excreted, under the control of aldosterone and antidiuretic hormone, so that the fluid leaving the kidney becomes the final urine. These segments are less prominent sites of active secretion for most drugs, but they are critical for creating the electrochemical gradients and urinary pH that govern passive back-diffusion of weak acids and bases. Changes in distal tubular function or in urinary pH, whether due to disease, diet or co-medications, can therefore significantly alter the fraction of a medicine that is reabsorbed versus excreted, particularly for drugs with pH-dependent ionization.

Overall, renal excretion of drugs reflects the balance of three processes along the nephron: **glomerular filtration** bringing unbound drug into the filtrate, **active tubular secretion** adding drug to the tubular lumen, and **tubular reabsorption** removing drug back into the circulation. For

a given drug, the relative importance of each process depends on its physicochemical properties, protein binding, affinity for transporters and susceptibility to pH-dependent ionization.

4.1.2 Pathophysiological Basis of Impaired Renal Excretion

Kidney disease alters pharmacokinetics through a combination of reduced renal clearance and more systemic pathophysiological changes that affect absorption, distribution, metabolism and excretion, so that standard drug dosage regimens often produce either excessive exposure or subtherapeutic concentrations in these patients. Even before advanced stages are reached, structural and functional changes in the nephron, together with the metabolic and inflammatory milieu of chronic kidney disease, begin to modify how drugs are handled, which is why clinical pharmacy practice increasingly treats **impaired renal function as a continuum rather than a binary present/absent variable**.[1]

From the perspective of **absorption**, uremia and associated gastrointestinal disturbances can slow gastric emptying, alter intestinal motility and change gastric pH, while common co-medications such as phosphate binders or proton pump inhibitors can chelate or otherwise interfere with oral medicines. These factors may reduce the bioavailability of some drugs or occasionally increase it when first-pass metabolism is impaired, making the timing of doses relative to food or binders and the choice of formulation clinically relevant issues for the pharmacist.

Changes in **distribution** are driven largely by altered body composition and plasma protein binding in kidney disease. Fluid overload and expansion of the extracellular compartment increase the apparent volume of distribution of hydrophilic medicines, potentially lowering peak concentrations, whereas hypoalbuminemia and the accumulation of endogenous organic acids can displace highly protein-bound drugs such as phenytoin or warfarin, increasing the free (pharmacologically active) fraction. At the same time, binding to α1-acid glycoprotein may increase for some basic drugs, partially offsetting these effects, so that interpreting total plasma concentrations without considering protein binding can be misleading in advanced kidney disease.

The most obvious pharmacokinetic consequence of renal impairment is reduced renal clearance of drugs and active metabolites that are normally **eliminated** by glomerular filtration or active tubular secretion. A fall in glomerular filtration rate proportionally reduces filtration of unbound drug, while tubular secretion via transporters such as organic anion and cation transporters is also diminished, leading to decreased overall clearance and prolongation of elimination half-life. For medicines where 30% or more of the dose is excreted unchanged in urine, or where toxic or active metabolites depend on renal excretion, this can cause marked accumulation unless the maintenance dose or dosing interval is adapted to the patient's level of kidney function.

Less intuitively, chronic kidney disease can also affect non-renal clearance through down-regulation of hepatic cytochrome P450 enzymes and transporters, changes in hepatic blood flow, and alterations in intestinal metabolism, probably mediated by uremic toxins and chronic inflammation. Consequently, even drugs that are hepatically cleared may require dose

[1] Lea-Henry TN, Carland JE, Stocker SL, et al. Clinical Pharmacokinetics in Kidney Disease: Fundamental Principles. Clin J Am Soc Nephrol. 2018;13(7):1085-1095.

adjustment or closer monitoring in advanced renal impairment, particularly when they have a narrow therapeutic index or when active metabolites are renally eliminated.

Altogether, the pathophysiological disturbances of kidney disease mean that the standard relationship between dose and exposure (and subsequently, effects) no longer apply and inter-individual variability becomes pronounced. Clinical pharmacists therefore need to integrate knowledge of nephron physiology, the extent of renal impairment and the specific pharmacokinetic profile of each medicine to design and continuously adapt dosing regimens that maintain exposure within the desired therapeutic window, while also recognizing when therapeutic drug monitoring or intensified clinical surveillance is warranted.

Chronic kidney disease and Acute kidney injury

Chronic kidney disease (CKD) and acute kidney injury (AKI) differ in definitions, time course, pathophysiology, implications, and should be presented as distinct but interconnected entities.

CKD is defined as abnormalities of kidney structure or function persisting for at least 3 months, with consequences for health, most operationalized as a sustained decrease in glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2 or persistent markers of kidney damage such as albuminuria or structural abnormalities. CKD usually results from long-standing conditions such as diabetes, hypertension or chronic glomerulonephritis, leading to progressive nephron loss, maladaptive hyperfiltration, and chronic structural remodeling of the kidney. Clinically, CKD follows a slowly progressive course and is staged according to GFR and albuminuria categories, with strong associations with cardiovascular morbidity, mortality and complications such as anemia and mineral-bone disorder. CKD produces relatively stable but chronically altered pharmacokinetics, with reduced renal clearance, altered distribution (e.g. fluid overload, hypoalbuminemia) and sometimes reduced non-renal clearance, allowing the use of stage-specific dose-adjustment nomograms based on estimated GFR or creatinine clearance for many drugs and drug classes.

AKI is characterized by an abrupt decline in kidney function occurring over hours to days, diagnosed using dynamic changes in serum creatinine and urine output according to KDIGO criteria (for example, an increase in serum creatinine by at least 0.3 mg/dL within 48 hours, or a 1.5-fold increase from baseline, or oliguria). AKI reflects an acute insult, classically categorized as prerenal, intrinsic, or postrenal, and is primarily a functional disturbance that may be reversible if the underlying cause is promptly identified and corrected. The clinical course is much more rapid and variable than in CKD, ranging from transient creatinine rises to severe oliguric AKI requiring renal replacement therapy. An episode of AKI markedly increases the risk of incident CKD, progression of pre-existing CKD, and mortality. AKI poses specific challenges because kidney function is non-steady-state and can change within hours, making creatinine-based GFR estimates unreliable for dosing and requiring frequent reassessment of renal function, careful avoidance of nephrotoxins and dynamic adaptation of doses, particularly for narrow-therapeutic-index drugs and renally eliminated antimicrobials, including during and after renal replacement therapies.

- Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179-c184.
- CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4S):S117-S314.

4.1.3 Renal Biomarkers

Direct measurement of renal function refers to the quantification of true **glomerular filtration rate** (GFR) using an exogenous filtration marker that is freely **filtered at the glomerulus, not secreted or reabsorbed by the tubules, and not metabolized**, such as inulin, radiolabeled iothalamate, iohexol, or chromium-EDTA. These procedures require intravenous administration of the marker followed by multiple timed blood or urine samples with precise analytical assays, often under standardized hydration and hemodynamic conditions. GFR is then calculated from the clearance of the marker from plasma or urine. Although these methods provide the most accurate assessment of kidney function and are used as reference standards in nephrology research and in specific clinical situations, they are invasive, time-consuming, technically demanding, costly, and depend on specialized laboratory facilities that are not available in most clinical settings. For these reasons, **direct GFR** measurements are impractical for routine care and for everyday pharmacotherapy decisions, leading to widespread reliance on endogenous markers such as serum creatinine and cystatin C, together with estimating equations or creatinine clearance, as pragmatic surrogates of renal function at the bedside.[2]

Serum creatinine and **cystatin C** are the two main endogenous markers used to estimate glomerular filtration rate (**eGFR**) and thus to assess renal function in clinical practice. Their utility and limitations differ significantly, which has important implications for pharmacotherapy and for interpreting kidney function in specific patient populations.

Serum creatinine

Serum creatinine is a breakdown product of creatine and creatine phosphate in skeletal muscle, **produced at a relatively steady rate** within a given individual and **eliminated almost entirely by the kidneys through glomerular filtration with a contribution from tubular secretion**. As GFR falls, serum creatinine rises in a hyperbolic fashion, which makes it a sensitive marker for advanced renal impairment but relatively insensitive for detecting mild reductions in GFR, particularly in individuals with low creatinine generation.[3]

In routine practice, serum creatinine is attractive because it is **inexpensive, widely available, and standardized assays** (traceable to isotope-dilution mass spectrometry) have improved comparability across laboratories and over time. However, its concentration is strongly influenced by non-renal factors such as muscle mass, age, sex, ethnicity, diet (especially meat intake), and certain drugs that interfere with tubular secretion or analytical measurement, leading to substantial misclassification of kidney function if creatinine is interpreted in isolation. In older adults, malnourished or cachectic patients, and those with reduced muscle mass (for example, chronic illness, paralysis, limb amputation), creatinine generation is low, so serum creatinine may remain “normal” despite a markedly reduced GFR, potentially delaying recognition of renal impairment and resulting in inappropriate maintenance doses of renally cleared drugs. Conversely, in very muscular individuals or with high protein intake, serum creatinine may overestimate the degree of renal impairment and prompt unnecessary dose reductions.

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[2] Pottel H, Delanaye P, Cavalier E. Exploring Renal Function Assessment: Creatinine, Cystatin C, and Estimated Glomerular Filtration Rate Focused on the European Kidney Function Consortium Equation. Ann Lab Med. 2024;44(2):135-143.
[3] Doogue MP, Polasek TM. Drug dosing in renal disease. Clin Biochem Rev. 2011;32(2):69-73.

Beyond these non-renal determinants, serum creatinine is also an imperfect reflection of glomerular filtration because a variable fraction of creatinine is handled by the tubules. In healthy individuals, **10 - 20% of creatinine clearance arises from active tubular secretion via organic cation and anion transporters**, so measured creatinine clearance tends to overestimate true GFR, especially in the clinically relevant range of moderate renal impairment. Tubular secretion becomes proportionally greater as GFR declines and may increase by up to 60% in severe renal insufficiency, further exaggerating this overestimation and blunting the rise in serum creatinine for a given fall in true GFR. Conversely, experimental and clinical data indicate that creatinine can also undergo **modest tubular reabsorption under some conditions**, for example at low urine flow, introducing additional variability in the relationship between creatinine and GFR. Moreover, several commonly used drugs, including cimetidine, trimethoprim and other proximal-tubule transporter inhibitors, acutely reduce tubular secretion of creatinine without affecting GFR, causing a reversible rise in serum creatinine that mimics a deterioration in renal function but actually reflects altered tubular handling. Taken together, this complex balance of secretion, occasional reabsorption and drug-transporter interactions means that serum creatinine and creatinine clearance systematically overestimate true GFR to a variable extent and can change independently of real alterations in filtration, limitations that clinical pharmacists must keep in mind when using creatinine-based estimates for drug dosing.

Because of these limitations, serum creatinine is rarely used alone; instead, it is incorporated into estimating equations such as Cockcroft-Gault, MDRD or CKD-EPI, which adjust for age, sex and sometimes other factors to provide an estimated GFR or creatinine clearance. Even then, clinicians and pharmacists must remain aware that creatinine-based estimates assume stable creatinine production and steady-state conditions and can be unreliable in acute kidney injury, during rapid changes in volume status, or when muscle mass deviates substantially from the populations in which the equations were derived.

Cystatin C

Cystatin C is a low molecular weight polypeptide (approximately 13 kDa, 120 amino acids) that serves as cysteine protease inhibitor. Cystatin C is produced at a constant rate by all nucleated cells, **freely filtered by the glomerulus and then almost completely reabsorbed and catabolized in the proximal tubule, with virtually no tubular secretion**. Because its production is much less dependent on muscle mass and diet than creatinine, cystatin C concentrations correlate more linearly with GFR across a wide range of kidney function statuses and are particularly useful for detecting mild to moderate decreases in GFR and for assessing renal function in patients with abnormal muscle mass.[4]

Cystatin C-based eGFR equations, and combined creatinine-cystatin C equations, have repeatedly shown better accuracy and less bias than creatinine-only equations in diverse populations, including older adults, transplant recipients and patients with advanced chronic kidney disease. In scenarios where creatinine is expected to be misleading (e.g., sarcopenia, chronic liver disease, spinal cord injury, or in individuals with extremes of body habitus measuring cystatin C and using a cystatin C-based or combined equation can substantially improve classification of CKD stage and estimation of drug-relevant renal clearance. For high-risk medicines with a narrow therapeutic index, guidelines increasingly recommend

[4] Benoit SW, Ciccia EA, Devarajan P. Cystatin C as a biomarker of chronic kidney disease: latest developments. Expert Rev Mol Diagn. 2020;20(10):1019-1026.

confirmatory cystatin C-based eGFR when creatinine-based estimates are borderline or discordant with the clinical picture.[5]

Nevertheless, cystatin C is not completely free from non-renal influences: inflammation, thyroid dysfunction, corticosteroid therapy and some neoplastic diseases can affect its concentration, and assays are more costly and less widely available than creatinine. As a result, c**ystatin C is not yet universally measured for all patients but is used selectively when a more accurate GFR estimate is needed or when creatinine is clearly unreliable**, with combined creatinine-cystatin C equations offering the best overall performance in many studies and increasingly being incorporated into contemporary CKD-EPI formulations.

Creatinine clearance and eGFR equations

Creatinine clearance can be measured directly using timed urine collections, but this is cumbersome and prone to collection errors, so it is rarely used outside specific situations such as drug development studies or selected clinical scenarios. In routine practice, CrCl is usually estimated by the **Cockcroft-Gault equation**[6], which incorporates age, body weight, sex and serum creatinine, and historically underpins many regulatory product-information dosing recommendations.

The **MDRD** (Modification of Diet in Renal Disease) and **CKD-EPI** (Chronic Kidney Disease Epidemiology Collaboration)[7] equations estimate GFR standardized to a body surface area of 1.73m^2, using serum creatinine (with or without cystatin C), age and sex, and are now preferred for diagnosing and staging CKD. CKD-EPI is generally more accurate than MDRD, especially at higher GFR values, and updated 2021 formulations (creatinine-only and creatinine-cystatin C) have been endorsed by major societies to improve accuracy and reduce race-related bias.

4.1.4. Assessing Renal Function

Direct quantification of glomerular filtration rate (GFR) using exogenous filtration markers such as inulin, radioisotopic iothalamate or iohexol provides the closest approximation to “true” GFR. However, these reference methods require intravenous administration, multiple timed blood or urine samples, specialized analytical techniques and tightly controlled conditions, and are therefore logistically burdensome and costly. As a result, clinical nephrology and clinical pharmacy have converged on **the use of endogenous filtration markers (i.e., primarily serum creatinine and cystatin C) embedded in equations that model the nonlinear relationship** between marker concentration and measured GFR across large, diverse cohorts, incorporating age, sex and sometimes race and body size as surrogates for generation and distribution of the biomarker. These **estimating equations operationalize renal function as a continuous quantitative variable** that can be automatically reported by laboratories and directly integrated into population pharmacokinetic models, therapeutic windows and regulatory dose-band definitions.

Cockcroft-Gault estimates creatinine clearance (CrCl) from age, body weight, sex and serum creatinine, and historically underpins many pharmacokinetic studies and regulatory

[5] Levin A, Ahmed SB, Carrero JJ, et al. Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease: known knowns and known unknowns. Kidney Int. 2024;105(4):684-701.
[6] https://www.kidney.org/professionals/gfr_calculatorCoc
[7] https://www.kidney.org/professionals/gfr_calculator

product-information dosing recommendations. Cockcroft-Gault main strength is this continuity with the evidence base: dose-response and safety data for many older drugs are explicitly stratified by Cockcroft-Gault CrCl categories, which is why several drug labels and some regulatory guidances still recommend Cockcroft-Gault for dosing, especially for narrow-therapeutic-index medicines. However, Cockcroft-Gault assumes that body weight is a reasonable surrogate for muscle mass and creatinine generation, so it tends to **overestimate renal function** when actual body weight is used in obese or edematous patients and may underestimate function in very thin individuals if ideal or adjusted body weight is not applied. Cockcroft-Gault performance is particularly problematic in older adults and at extremes of body size, and, like all creatinine-based equations, it presupposes steady-state creatinine, making it unreliable in acute kidney injury or rapidly changing renal function.

$$CG = \frac{(140 - age) * weight_{in_{Kg}}}{72 * SCr} * A$$

$$\text{A} = 0.85 \text{ if female}$$

The **MDRD** equation estimates eGFR indexed to 1.73m^2 using serum creatinine, age and sex (with race in original formulations), and was a major advance over Cockcroft-Gault for patients with moderate to severe CKD. MDRD is reasonably accurate at lower GFR values and formed the basis for earlier CKD staging and risk stratification schemes, which explains why it is still encountered in older literature and some laboratory reports. Nonetheless, MDRD systematically underestimates true GFR at higher levels (> 60 mL/min/1.73m^2), reducing its ability to detect early CKD and misclassifying kidney function in general populations. Because MDRD reports a Body Surface Area-indexed eGFR, it may also misrepresent drug-relevant clearance in very small or very large individuals unless eGFR is de-indexed to the patient's actual body surface area before translating it into dosing categories.

$$MDRD = 175 * SCr^{-1.154} * age^{-0.203} * A * B$$

$$\text{A} = 1.212 \text{ if black; B} = 0.742 \text{ if female}$$

The **CKD-EPI creatinine** equation was developed to improve upon MDRD, particularly at higher GFR, and **has become the preferred method for CKD diagnosis** and staging in many guidelines and laboratories. CKD-EPI demonstrates less bias and better precision than MDRD across a broad GFR range, reducing underestimation at near-normal GFR and improving risk prediction for outcomes such as end-stage kidney disease and cardiovascular events. Recent race-free CKD-EPI formulations, aligned with standardized creatinine assays, have further improved generalizability and are being actively implemented in clinical systems. The advantages are the widespread reporting of CKD-EPI eGFR and its alignment with contemporary CKD staging, which facilitates the use of guideline-based eGFR cut-offs for many drugs. However, CKD-EPI shares the fundamental limitations of all creatinine-based equations: dependence on muscle mass and other non-renal determinants of creatinine, requirement for steady-state conditions, and potential inaccuracy in populations with markedly abnormal body composition or rapidly changing renal function.

$$CKDEPI = 141 * \min\left(\frac{SCr}{K}, 1\right)^{\alpha} * \max\left(\frac{SCr}{K}, 1\right)^{-1.209} * 0.933^{age} * A$$

If female: K = 0.7; α = -0.329; A = 0.018.
If male: K = 0.9; α = -0.411; A = 1.159

Cystatin C-based CKD-EPI equations, and especially **combined creatinine-cystatin C CKD-EPI** equations, offer important advantages in these problematic settings. Multiple studies show that cystatin C-based or combined equations provide more accurate and less biased GFR estimates than creatinine-only equations in older adults, patients with reduced muscle mass, transplant recipients and those with advanced CKD, and they improve risk prediction for mortality and cardiovascular outcomes. For drug dosing, combined creatinine-cystatin C CKD-EPI often yields the closest approximation to measured GFR and can meaningfully change dosing categories in patients where creatinine alone underestimates impairment, such as sarcopenic[8] elderly individuals. The main drawbacks are **higher cost, more limited assay availability, and susceptibility of cystatin C to non-renal influences** (e.g. inflammation, thyroid disease, corticosteroids), which require clinical judgement when interpreting discrepant results. Despite the insistence of consensus statements on using cystatin C or combined CKD-EPI equations[9], these limitations made the CKD-EPI creatinine the preferred estimate equation in clinical practice, and clinical pharmacists should monitor the timely assessment of serum creatinine in routine practice.[10]

In non-steady-state conditions such as acute kidney injury, all creatinine-based equations assume stable creatinine production and excretion and therefore become unreliable: estimated GFR lags behind true changes in kidney function, and single-time-point eGFR or CrCl should not be used to make fine dosing decisions. In these situations of AKI, other equations like Kinetic eGFR (KeGFR) were created, although their use in clinical practice is still controversial.[11]

$$KeGFR = \frac{SSP_{Cr} \times CrCl}{MeanP_{Cr}} \times \left(1 - \frac{24 \times \Delta P_{Cr}}{\Delta Time(h) \times Max\Delta P_{Cr}/Day}\right)$$

In practice, this means that no single eGFR equation is best for all purposes. Cockcroft-Gault remains important when dose recommendations and regulatory documents are explicitly expressed in creatinine clearance bands, particularly for narrow-therapeutic-index drugs. CKD-EPI creatinine is preferred for general CKD detection, staging and long-term risk stratification, and is increasingly accepted for dosing most drugs, provided its limitations in

[8] Sarcopenic: a person who has a pathological loss of skeletal muscle mass accompanied by reduced muscle strength and physical performance.
[9] Gunning S, Alexander J. Classification and Risk Assessment of Chronic Kidney Disease. JAMA. 2026;335(1):84-85.
[10] Oliveira CL, Duarte-Ramos F, Alves da Costa F, Fernandez-Llimos F. Effects of inpatient creatinine testing frequency on acute kidney injury identification and staging: a historical cohort study. Int J Clin Pharm. 2024;46(3):623-630.
[11] Chen S. Retooling the creatinine clearance equation to estimate kinetic GFR when the plasma creatinine is changing acutely. J Am Soc Nephrol. 2013;24(6):877-888.

atypical body composition and non-steady-state conditions are recognized. Cystatin C-based and combined CKD-EPI equations are best reserved for situations where creatinine is clearly unreliable and where a more accurate GFR estimate could materially change therapeutic decisions, such as dosing of high-risk medicines in frail older adults or in patients with complex comorbidities.

4.1.5 Creatinine Clearance vs. eGFR in Dosing Decisions

Clinical pharmacists are often confronted with **two different estimates of renal function**: **creatinine clearance** (usually derived from the Cockcroft-Gault equation) and **estimated glomerular filtration rate** (eGFR, usually reported by using CKD-EPI). Although both are derived from serum creatinine and correlate with true GFR, **they are not interchangeable and are used for different purposes**: most contemporary nephrology guidelines and CKD staging schemes are based on eGFR, whereas many drug labels and dosing studies were developed using Cockcroft-Gault creatinine clearance.[12]

Creatinine clearance estimates the volume of plasma from which creatinine is cleared per unit time and historically served as a surrogate for GFR in pharmacokinetic trials. The Cockcroft-Gault equation incorporates age, sex and body weight, and most older product information expresses renal dosing recommendations in terms of creatinine clearance bands (for example, 'CrCl 30 to 59 mL/min'). In contrast, eGFR (CKD-EPI) is normalized to a body surface area of 1.73m^2 and was designed primarily for diagnosis and staging of chronic kidney disease, and risk stratification, not originally for drug dosing. This difference in derivation means that, in a given patient, especially one who is very underweight or obese, Cockcroft-Gault CrCl and CKD-EPI eGFR can diverge by 20 - 30% or more, sometimes crossing dosing cut-offs.

In a thin, sarcopenic older adult, for example, CKD-EPI eGFR might report 55 mL/min/1.73m^2, suggesting only mildly reduced kidney function, whereas Cockcroft-Gault (using a low body weight) might yield a creatinine clearance of 35-40 mL/min. If the drug's Summary of Product Characteristics specifies dose reduction below 'CrCl 50 mL/min' and the medicine has a narrow therapeutic index (e.g., low-molecular-weight heparin, some direct oral anticoagulants), using the Cockcroft-Gault estimate is more conservative and better aligned with the evidence base of the pivotal studies. By contrast, in a very obese patient, Cockcroft-Gault using actual body weight may overestimate renal function (for example, a calculated CrCl of 80 mL/min versus an eGFR of 55 mL/min/1.73 m^2), so de-indexing eGFR to actual body surface area or re-calculating Cockcroft-Gault with adjusted body weight may provide a safer basis for dosing renally cleared nephrotoxic drugs such as aminoglycosides.

A pragmatic approach is to match the renal function estimate to the context. For drug dosing, Cockcroft-Gault creatinine clearance remains the default when: (a) the product label or dosing guideline explicitly uses CrCl bands; (b) exposure-response data are known to be CrCl-based; or (c) the drug has a narrow therapeutic index and small differences in exposure are clinically important. CKD-EPI eGFR can be used for dosing most other drugs, especially when integrated into local dosing protocols, but values should be interpreted cautiously in very low or high body weight, in sarcopenic patients, and in non-steady-state conditions such as acute kidney injury.

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[12] Castel-Branco MM, Lavrador M, Cabral AC, et al. Discrepancies among equations to estimate the glomerular filtration rate for drug dosing decision making in aged patients: a cross sectional study. Int J Clin Pharm. 2024;46(2):411-420.

Finally, when creatinine-based estimates are clearly discordant with the clinical picture—such as a very frail patient with 'normal' creatinine and eGFR, or conflicting Cockcroft-Gault and CKD-EPI values around a critical dosing threshold—measurement of cystatin C and calculation of a cystatin C-based or combined CKD-EPI eGFR can refine the assessment, particularly for high-risk drugs. In selected cases where a major therapeutic decision hinges on renal function (e.g. dosing of a highly toxic agent, or eligibility for a clinical trial), direct measurement of GFR with an exogenous marker may be justified, but this remains the exception rather than the rule in routine clinical pharmacy practice.

4.1.6 General Dosing Principles in Renal Impairment

In theory, extending therapeutic drug monitoring (TDM) to all medicines in patients with renal impairment would offer an attractive way to individualize dosing by directly measuring drug exposure rather than relying on imperfect estimates of glomerular filtration rate and population-based dose tables. In practice, universal TDM is unfeasible for several reasons: for most drugs, validated assays and exposure-response targets are lacking; analytical methods are costly, technically demanding and not available around the clock; and the logistics of frequent sampling and result turnaround are incompatible with routine ward workflows, particularly when many drugs are administered concomitantly. So, extrapolating the TDM paradigm to all renally cleared drugs would risk false reassurance, misinterpretation and inefficient use of resources without clear benefit.[13] TDM is in depth explored in Biopharmacy and Pharmacokinetics course (4th year).

General dosing in renal impairment relies on aligning the intensity of drug exposure with the patient's reduced and often unstable renal clearance, while minimizing both toxicity and therapeutic failure. Therapeutic strategies can be conceptualized around four main decisions: to avoid a drug, to reduce the dose, to prolong the dosing interval, or to maintain standard dosing with intensified monitoring, applied according to the drug's pharmacokinetics, therapeutic index and nephrotoxic potential.[14]

When to avoid a drug

Avoidance is appropriate when a drug is predominantly renally cleared or has renally cleared active metabolites, and accumulation leads to serious or irreversible toxicity that cannot be safely mitigated by dose reduction, especially in advanced CKD. Classic examples include metformin in severe CKD due to risk of lactic acidosis, certain sulfonylureas with long-acting active metabolites (e.g., glyburide) because of prolonged hypoglycemia, and morphine or codeine whose renally eliminated metabolites can accumulate and precipitate neurotoxicity and respiratory depression. Nephrotoxic agents without compelling indications, such as non-steroidal anti-inflammatory drugs, iodinated contrasts (outside life-saving indications), or high-dose aminoglycosides are also best avoided in patients with pre-existing severe CKD or replaced by safer alternatives whenever possible.

[13] Lea-Henry TN, Carland JE, Stocker SL, Sevastos J, Roberts DM. Clinical Pharmacokinetics in Kidney Disease: Fundamental Principles. Clin J Am Soc Nephrol. 2018;13(7):1085-1095.
[14] Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011;80(11):1122-1137.

When to reduce the dose

Dose reduction while maintaining the usual dosing interval is often preferred for drugs with a relatively wide therapeutic index, where maintaining more stable peak-trough fluctuations around a lower average concentration is acceptable. This approach is appropriate for many beta-lactam antibiotics, several oral antidiabetics, and low-molecular-weight heparins, where proportional reduction of the maintenance dose according to estimated decline in clearance can maintain target exposure while limiting accumulation. For example, standard dosing of renally cleared beta-lactams such as piperacillin/tazobactam is gradually reduced across CKD stages, while preserving dosing frequency to sustain time above minimum inhibitory concentration (MIC); similarly, dose de-escalation of enoxaparin is recommended in CKD to mitigate bleeding risk.

When to prolong the dosing interval

Prolonging the dosing interval without changing the unit dose is useful when peak concentrations are important for efficacy or post-antibiotic effect, and when the main concern is avoiding excessive accumulation with repeated dosing. Aminoglycosides exemplify this principle: they exhibit concentration-dependent killing and significant post-antibiotic effect, so extended-interval dosing (once daily or less, with interval lengthened as renal function declines) preserves high peaks for bactericidal activity while allowing trough levels to fall sufficiently to reduce nephrotoxicity and ototoxicity. Interval extension can also be used for other renally cleared drugs when monitoring is available (for example, some antiepileptics or glycopeptides), but it often produces larger peak-trough variability and may be less suitable for drugs where stable concentrations are critical to effect or safety.

When to maintain dose but intensify monitoring

Standard dosing with intensified clinical and laboratory monitoring is appropriate when renal impairment has limited impact on drug exposure, when the therapeutic index is narrow but reliable biomarkers exist, or when the drug confers major prognostic benefit and underdosing would be harmful. This approach is common with cardiovascular agents such as beta-blockers, some renin-angiotensin-aldosterone system inhibitors, and SGLT2 inhibitors, where careful monitoring of blood pressure, potassium, volume status and renal function is more appropriate than a priori large dose reductions. For narrow-therapeutic-index drugs (e.g. digoxin, certain anticonvulsants, LMWHs, some antibiotics and many opioids in advanced CKD), standard or modestly adjusted doses may be used initially, but therapeutic drug monitoring, anti-Xa measurement, or close assessment of sedation, respiratory status and analgesia is essential to guide subsequent titration.

4.1.7 Classification of Drugs by Renal Dependence

From a clinical pharmacy perspective, medicines can be pragmatically classified by their dependence on renal elimination and nephrotoxic potential to guide dosing strategy.

- **Predominantly renally cleared parent drug**: Examples include many beta-lactams, aminoglycosides, certain direct oral anticoagulants, and low-molecular-weight heparins. In these cases, clearance falls roughly in proportion to GFR, so **dose reduction or interval extension is mandatory**, with choice between the two driven by pharmacodynamics (e.g. time-dependent vs concentration-dependent killing for antibiotics).

- **Active metabolites renally cleared**: Several opioids (morphine, codeine, meperidine), some antidiabetics (e.g. glyburide) and various cardiovascular drugs have pharmacologically active or neurotoxic metabolites that accumulate in CKD. Here, the preferred strategy is often **to avoid the drug and choose an alternative** with inactive or hepatically cleared metabolites (e.g. using fentanyl or carefully titrated hydromorphone instead of morphine; or glipizide/repaglinide instead of glyburide), or to use substantial dose reductions with close monitoring when alternatives are unavailable.
- **Nephrotoxic potential**: Aminoglycosides, amphotericin B, calcineurin inhibitors, radiocontrast media and NSAIDs are prototypical nephrotoxic drugs, and existing renal impairment magnifies their toxicity. In these cases, the primary principle is **to avoid or minimize exposure**, use the lowest effective dose for the shortest duration, correct additional risk factors (hypovolemia, concomitant nephrotoxins), and apply intensive monitoring of creatinine, urine output and drug levels where available.
- **Narrow therapeutic index**: Drugs for which small changes in concentration produce toxicity or loss of efficacy, such as digoxin, certain antiarrhythmics, lithium, LMWHs and some antimicrobials, require particularly cautious adjustment in renal impairment. **Dosing decisions in this group should not rely solely on crude eGFR bands**. Instead, individualization based on drug levels, anti-Xa activity, electrocardiographic monitoring, and clinical endpoints is recommended, with lower initial doses and slower titration where kidney function is reduced or unstable.

Incorporating these broad principles into dosing tables and decision tools allows clinical pharmacists to move beyond simple “percent dose reductions” and towards structured, mechanism-informed drug optimization across the spectrum of renal impairment.[15]

4.2 Hepatic impairment

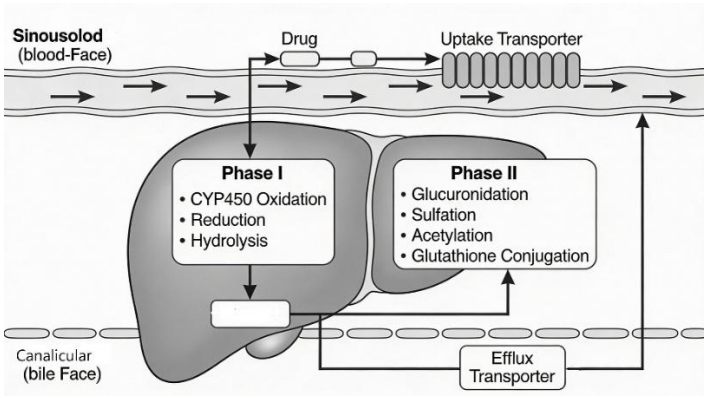
4.2.1 Recap of Hepatic Metabolism

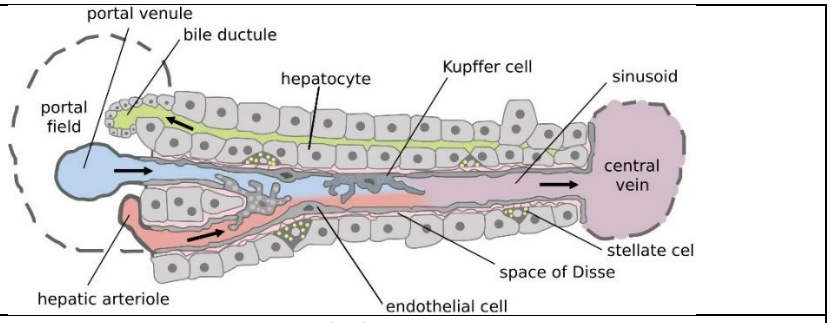
Hepatic metabolism is a central determinant of systemic drug exposure, particularly for lipophilic compounds that require biotransformation before renal or biliary excretion is possible. In contrast to the kidney, where glomerular filtration is relatively homogeneous, hepatic drug handling reflects the architecture of the hepatic lobule, the dual blood supply (portal vein and hepatic artery) and the coordinated activity of uptake and efflux transporters together with phase I and phase II enzymes within hepatocytes.

The sinusoidal surface of the hepatocyte is equipped with a range of uptake transporters (e.g., organic anion transporting polypeptides, organic cation transporters and sodium-taurocholate co-transporting polypeptide) that move drugs and endogenous substrates from portal blood into the cell, particularly large or polar molecules that cannot freely diffuse across membranes. Once inside the hepatocyte, many drugs undergo **phase I metabolism**, primarily oxidation, reduction or hydrolysis reactions catalyzed by cytochrome P450 enzymes (notably CYP3A4/5, CYP2D6, CYP2C9, CYP2C19 and CYP1A2), which introduce or unmask polar functional groups and can either inactivate the parent drug or generate active or toxic metabolites. **Phase II metabolism**

[15] Eppenga WL, Kramers C, Derijks HJ, et al. Drug therapy management in patients with renal impairment: how to use creatinine-based formulas in clinical practice. Eur J Clin Pharmacol. 2016;72(12):1433-1439.

then conjugates drugs or their phase I metabolites with endogenous hydrophilic moieties such as glucuronic acid, sulfate, glutathione, acetate or methyl groups via transferase enzymes (e.g., UDP-glucuronosyltransferases, sulfotransferases, N-acetyltransferases and glutathione S-transferases), markedly increasing polarity and molecular weight. A further **phase III** layer consists of efflux transporters on the canalicular and basolateral membranes (such as P-glycoprotein/ABCB1, BCRP/ABCG2, MRP2/ABCC2 and BSEP/ABCB11), which pump parent drugs and especially conjugated metabolites into bile or back into sinusoidal blood, thereby completing the hepatic clearance process and contributing to enterohepatic cycling for some compounds. [16]





by Frevert U, Engelmann S, Zougbédé S, Stange J, Ng B, et al. (CC BY 2.5)

The overall hepatic clearance of a drug is therefore governed by the interplay between hepatic blood flow, protein binding, intrinsic metabolic capacity (i.e., sum of phase I and II pathways) and transporter-mediated uptake and efflux, often conceptualized in models such as the well-stirred or parallel-tube model. From a clinical pharmacy perspective, this integrated system explains why liver disease, drug-drug interactions, genetic polymorphisms, and extrahepatic inflammation can simultaneously alter first-pass extraction, systemic clearance and metabolite formation, and why **changes in hepatic function often have complex, pathway-specific effects on pharmacokinetics rather than a uniform "reduction in metabolism"**.

[16] https://www.youtube.com/watch?v=qvucMHUVZA4

4.2.2 Pathophysiological Basis of Impaired Hepatic Excretion

Impaired hepatic excretion alters both the biotransformation of drugs within hepatocytes and the subsequent removal of parent compounds and metabolites into bile or back into the systemic circulation, so that standard dosing regimens may lead to excessive exposure or unexpected toxicity. Structural liver disease, cholestasis, altered hepatic blood flow and changes in transporters and enzymes jointly may disturb the normal relationship between dose, concentration and effect.

First-pass metabolism

First-pass extraction (also called first-pass metabolism or pre-systemic elimination) refers to the fraction of an orally administered drug that is removed by the liver before it ever reaches the systemic circulation. After oral intake, a drug is absorbed from the gastrointestinal tract into the portal vein and passes through the liver before entering the systemic circulation. During this "first pass" through the splanchnic organs, a variable proportion of the dose can be metabolized or excreted into bile, reducing the amount of unchanged drug that becomes systemically available.

Two main processes contribute to first-pass extraction. Intestinal first-pass metabolism occurs in enterocytes, where enzymes such as CYP3A4 and various conjugating enzymes, as well as efflux transporters like P-glycoprotein, can metabolize or pump drug back into the gut lumen, effectively reducing net absorption.

Clinically, first-pass extraction has several important implications. For high-extraction drugs, small changes in hepatic blood flow (for example, due to cirrhosis, portal-systemic shunting, heart failure or anesthesia) can cause large changes in oral bioavailability and systemic exposure at a fixed oral dose, even if intrinsic enzyme activity is relatively unchanged. Conversely, for low-extraction drugs, changes in intrinsic metabolic capacity (enzyme induction or inhibition, or loss of functional hepatocyte mass in chronic liver disease) primarily alter total clearance and half-life rather than first-pass extraction, so effects on oral bioavailability may be modest while maintenance dosing and dosing interval need adjustment.

- Almazroo OA, Miah MK, Venkataramanan R. Drug Metabolism in the Liver. *Clin Liver Dis*. 2017;21(1):1-20.

Cirrhosis and severe hepatitis can **decrease the number of functional hepatocytes** and downregulate phase I enzymes (especially CYP3A, CYP2C and CYP1A families), which lowers intrinsic metabolic capacity and slows the biotransformation of many high- and low-extraction drugs. Portal-systemic shunting and **reduced hepatic blood flow** reduce the effective delivery of drug to hepatocytes and **diminish first-pass extraction** of high-extraction medicines such as some beta-blockers, opioids and calcium-channel blockers, increasing their oral bioavailability and systemic exposure at conventional doses. At the same time, **impaired synthesis of albumin and other binding proteins** increases the unbound fraction of acidic and neutral drugs, so that a given total plasma concentration corresponds to a higher active concentration, compounding the risk of toxicity when hepatic clearance is reduced (e.g., warfarin).

Impaired hepatic excretion also reflects disturbances in biliary formation and flow, particularly in cholestatic liver diseases. Cholestasis may result from reduced formation of bile within

hepatocytes, obstruction of the intrahepatic or extrahepatic bile ducts, or functional inhibition of canalicular transporters responsible for exporting bile acids, conjugated bilirubin and many drug conjugates into bile. Drug-induced cholestasis often arises when medicines or their metabolites inhibit the bile salt export pump (e.g., metabolites of cyclosporine A inhibit BSEP/ABCB11) or canalicular efflux pumps such as MRP2, P-glycoprotein or BCRP, leading to intracellular accumulation of bile acids and conjugated metabolites and, ultimately, hepatocellular injury. When canalicular excretion is impaired, compensatory up-regulation of basolateral efflux transporters (e.g., MRP3, MRP4) shifts drug and bile acid excretion back into the systemic circulation. This may preserve hepatocyte viability but raises circulating levels of potentially toxic metabolites and alters enterohepatic cycling.

From a pharmacokinetic perspective, the **net effect of hepatic dysfunction on drug handling depends on the interplay between hepatic blood flow, extraction ratio and protein binding**. **For high-extraction drugs**, clearance in health is blood-flow limited, so reductions in hepatic blood flow or the presence of porto-systemic shunts in cirrhosis substantially reduce total clearance and amplify the impact of first-pass, while changes in enzyme activity have comparatively less influence. **For low-extraction drugs**, clearance is capacity-limited and driven primarily by intrinsic enzyme and transporter activity and the unbound fraction, so down-regulation of CYPs, UDP-glucuronosyltransferases or uptake transporters in chronic liver disease can markedly prolong half-life and increase steady-state concentrations even if hepatic blood flow is relatively preserved. These relationships mirror the renal continuum described earlier, but with the added complexity that impaired hepatic excretion may simultaneously increase oral bioavailability, reduce systemic clearance and modify protein binding, leading to highly drug-specific and stage-dependent changes in exposure.

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[17] https://www.youtube.com/watch?v=A94FJJt6ack

High- and Low-extraction drugs

High-extraction (flow-limited) drugs: (hepatic extraction ratio ER≳0.7), so clearance and first-pass loss depend mainly on liver blood flow.

- Beta-blockers: propranolol, metoprolol, labetalol.
- Calcium-channel blockers: verapamil, diltiazem, nifedipine.
- Opioids/analgesics: morphine, fentanyl, pethidine (meperidine).
- Other frequently used examples: lidocaine, nitroglycerin, bupropion, many tricyclic antidepressants such as imipramine.

Low-extraction (capacity-limited) drugs: (ER≲0.3) so clearance is driven mainly by intrinsic metabolic capacity and protein binding.

- Antiepileptics: phenytoin, valproic acid, carbamazepine, lamotrigine.
- Anticoagulant: warfarin.
- Benzodiazepines: diazepam, lorazepam, alprazolam, oxazepam.
- NSAIDs and other acidic drugs: ibuprofen, naproxen, indomethacin.
- Others often encountered: theophylline, paracetamol (acetaminophen) at therapeutic doses, many SSRIs such as fluoxetine and paroxetine.

https://www.youtube.com/watch?v=A94FJJt6ack

4.2.3 Assessing Hepatic Function

Assessment and classification of hepatic function for pharmacotherapy are inherently indirect, because **no single test measures the liver's capacity to clear drugs in a way comparable to creatinine-based estimates of renal function**. Instead, clinicians infer "**functional hepatic reserve**" from a combination of biochemical tests, clinical signs and composite scores, each reflecting different pathophysiological dimensions and each with important limitations when used to guide dosing.

Routine liver tests provide complementary but non-specific information. Aminotransferases (AST, ALT) primarily signal hepatocellular injury rather than functional capacity and can be normal in advanced cirrhosis where hepatocyte mass is markedly reduced. Alkaline phosphatase and gamma-glutamyltransferase reflect cholestasis and biliary tract involvement, while serum bilirubin (particularly conjugated bilirubin) integrates hepatocellular conjugation and canalicular excretion and therefore correlates more closely with impaired hepatic clearance of drugs that undergo biliary elimination. Albumin and prothrombin time/INR are synthetic function markers; low albumin and prolonged INR indicate reduced hepatocyte synthetic capacity and are strong prognostic indicators, but they are influenced by nutrition, vitamin K status and concomitant anticoagulation, complicating their interpretation for drug dosing.

Composite scores such as the **Child-Pugh classification** and the **Model for End-Stage Liver Disease (MELD)** are widely used to stage chronic liver disease and to stratify prognosis and have been pragmatically adopted as surrogates for hepatic function in drug development and dosing recommendations. The Child-Pugh score combines serum bilirubin, albumin, INR, ascites and encephalopathy into three classes (A-C), and many product labels and regulatory documents

express hepatic dose adjustments in terms of Child-Pugh class.[18] However, **Child-Pugh was not designed to predict pharmacokinetics**, includes subjective components (ascites, encephalopathy), and different combinations of abnormalities can yield the same class despite very different underlying pathophysiology; recent reviews therefore argue that its use as a universal basis for dosing is conceptually crude and may misclassify patients.

Measure		1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)		< 34 (< 2)	34-50 (2-3)	> 50 (> 3)
Serum albumin, g/dL		> 3.5	2.8-3.5	< 2.8
OR	Prothrombin time, prolongation (s)	< 4.0	4.0-6.0	> 6.0
	INR	< 1.7	1.7-2.3	> 2.3
Ascites		None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy		None	Grade I-II	Grade III-IV
Child-Pugh classification: 5-6 points: Class A; 7-9 points: Class B; 10-15 points: Class C				

MELD and MELD-Na, which incorporate bilirubin, creatinine and INR (and sodium), are more objective and strongly predictive of mortality and transplant priority, but they have been less systematically linked to drug disposition, limiting their direct utility for dose individualization.

$$\text{MELD} \overset{\text{def}}{=} 3.78 \times \ln(\text{serum bilirubin (mg/dL)}) + 11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{serum creatinine (mg/dL)}) + 6.43$$

Dynamic liver function tests are more mechanistically appealing but used mainly in specialized settings. Indocyanine green (ICG) clearance, galactose elimination capacity and aminopyrine breath testing quantify specific aspects of hepatic blood flow, uptake and microsomal metabolism, and correlate reasonably with perioperative risk and hepatocellular functional mass. Despite this, they are not routinely available, are more invasive and resource-intensive, and have not been incorporated into standard drug labelling or clinical dosing algorithms, which limits their impact on everyday clinical pharmacy practice.

Altogether, assessment of hepatic function for drug dosing remain semi-quantitative and context-dependent. For most medicines, dose recommendations in hepatic impairment are based on small pharmacokinetic studies in patients grouped by Child-Pugh class, combined with clinical judgement using bilirubin, albumin, INR and signs of portal hypertension. This contrasts sharply with renal dosing, where creatinine-based equations provide a more continuous measure. **This situation reinforces the need for pharmacists to interpret "mild, moderate or severe hepatic impairment" on labels critically, considering the underlying etiology, pattern (hepatocellular versus cholestatic), and the specific clearance mechanisms of the drug when translating these broad categories into individualized dosing decisions.**

4.2.4 General Dosing Principles in Hepatic Impairment

General prescribing in hepatic impairment requires a link between the pattern and severity of liver dysfunction, the drug's extraction characteristics, and drug therapeutic margin. In practice, decisions are framed around whether to avoid a drug, to lower the dose, to modify the dosing interval, or to maintain standard dosing with intensified monitoring, while preferentially selecting agents with mainly renal elimination when appropriate and safe.

[18] https://www.msdmanuals.com/pt/profissional/multimedia/clinical-calculator/classifica%C3%A7%C3%A3o-de-child-pugh-para-gravidade-da-doen%C3%A7a-hep%C3%A1tica

In patients with clinically significant hepatic impairment, especially cirrhosis, medicines should first be screened for intrinsic hepatotoxic potential and for reliance on hepatic clearance. **Drugs with well-established hepatotoxicity** (e.g., paracetamol, high-dose methotrexate, leflunomide, or certain azoles) are preferably avoided when alternative therapies exist or used only at reduced doses and with close monitoring of aminotransferases, bilirubin and clinical signs of decompensation. For **agents with non-negligible hepatotoxic risk** that are nevertheless clinically important (e.g., many psychotropics, antiepileptics or disease-modifying antirheumatic drugs), dose initiation at the lower end of the usual range and slower titration are advisable, with predefined stopping rules if liver tests exceed two to three times the upper limit of normal or if encephalopathy, jaundice or worsening coagulopathy emerge. Where an effective alternative with predominantly renal elimination exists (e.g., levetiracetam instead of carbamazepine), it is generally preferred, provided renal function is preserved.

Pharmacokinetic principles are particularly helpful when classifying medicines in relation to hepatic impairment. For **high-extraction (flow-limited) drugs** (e.g., propranolol, verapamil, morphine or many tricyclic antidepressants), cirrhosis and porto-systemic shunting reduce first-pass metabolism and hepatic clearance, increasing oral bioavailability and systemic exposure. Oral loading and maintenance doses usually need to be reduced, whereas intravenous doses may require more modest adjustment because they bypass first pass. For **low-extraction (capacity-limited) drugs** (e.g., warfarin, phenytoin, many benzodiazepines and non-steroidal anti-inflammatory drugs), intrinsic metabolic capacity and protein binding are the main determinants of clearance. In cirrhosis, downregulation of cytochrome P450 enzymes and reduced albumin synthesis prolong half-life and increase the free fraction, so maintenance doses must generally be reduced and dosing intervals sometimes extended, often guided by therapeutic drug monitoring or pharmacodynamic markers (for example, INR for warfarin, sedation scales for benzodiazepines).

Because **no single numerical index of "hepatic function" is available**, most evidence-based dosing recommendations stratify drugs according to **Child-Pugh class (A-C)** and, less frequently, MELD score. For some agents (e.g., several direct oral anticoagulants or certain biologics), moderate to severe impairment (Child-Pugh B-C) is a formal contraindication or a strong "avoid" recommendation, whereas for others, Child-Pugh B prompts dose reduction and Child-Pugh C justifies avoidance or specialist supervision only. At a pragmatic level, medicines can thus be grouped into:

a. **Contraindicated or to be avoided** in significant hepatic impairment (for example, drugs with high hepatotoxicity or markedly increased exposure and narrow therapeutic index),
b. **To be used with caution and dose adjustment** (most high- or low-extraction hepatically cleared agents, with dosing adapted to Child-Pugh class and clinical status),
c. **Relatively safe medicines**, which show minimal pharmacokinetic change and no signal of excess toxicity in cirrhosis and can usually be prescribed at standard doses with routine monitoring.

These structured lists, such as those developed for cirrhosis-specific prescribing support systems or summarized in national formularies, provide a valuable starting point, but clinical pharmacists must still integrate drug-specific properties, comorbid renal dysfunction and dynamic changes in liver disease when individualizing therapy for each patient.