

Renal Dose Adjustment Under Dynamic Kidney Function: Reconciling Estimated Filtration, Acute Kidney Injury, Dialysis, Drug Exposure, and Clinical Response When Conventional Dosing Signals Disagree

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ABSTRACT

Renal dose adjustment is commonly operationalized by assigning a patient to a kidney-function category and applying a corresponding dosing recommendation. This approach is practical when renal function is relatively stable, but it becomes increasingly fragile when estimated filtration, acute kidney injury trajectories, extracorporeal clearance, measured drug exposure, and clinical response evolve on different timescales or point toward different dosing decisions. This Current Opinion argues that renal dosing under dynamic kidney function should be treated as a recurrent reconciliation problem rather than a one-time classification task. Estimated glomerular filtration rate and creatinine clearance remain important inputs, but neither directly represents total drug clearance, and both may become misleading when creatinine is non-steady, biomarker determinants are altered, augmented renal clearance emerges, or dialysis contributes variable extracorporeal removal. Drug concentrations can provide a more proximal exposure signal for selected therapies, yet their interpretation depends on sampling, pharmacokinetic targets, assay availability, model assumptions, and clinical context. Likewise, efficacy and toxicity should trigger reassessment without being mistaken for direct measures of renal elimination. We therefore propose a dynamic renal-dose reconciliation approach in which kidney estimates, trajectory, dialysis conditions, drug exposure, and observed response are repeatedly interpreted according to their temporal relevance, drug specificity, directness to exposure, and reliability. The model is conceptual rather than validated, and important boundaries include drugs without informative therapeutic drug monitoring, rapidly changing physiology, heterogeneous dialysis prescriptions, nonrenal clearance, uncertain pharmacodynamic targets, and settings with limited measurement infrastructure.

Keywords: Renal dose adjustment, Acute kidney injury, Kidney function, Dialysis, Therapeutic drug monitoring, Drug exposure

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Introduction

Renal dose adjustment is often presented as a numerical exercise: estimate kidney function, identify the corresponding renal category, and modify dose or interval. That sequence is useful, but it compresses several distinct pharmacokinetic processes into one variable. Kidney disease can influence renal elimination while also altering distribution, protein binding, metabolite handling, and other determinants of drug disposition [1]. In acute kidney injury (AKI), the problem becomes explicitly temporal because kidney function, fluid status, extracorporeal support, and medication exposure can change during the same treatment course; consequently, dose appropriateness may require repeated reassessment rather than a single baseline decision [2].

Drug-development approaches to renal impairment already illustrate that dosing recommendations need not rest on one isolated renal estimate, because pharmacokinetic and other drug-specific evidence can be integrated when determining an appropriate regimen [3]. At the bedside, however, the inputs themselves may conflict. In hospitalized patients receiving renally eliminated medications, creatinine- and cystatin C-based estimated glomerular filtration rates (eGFRs) can differ substantially [4]. Such disagreement matters because the calculated kidney-function category can alter the apparent need for dose reduction, intensification, or further measurement. The central problem is therefore not simply which equation is “best.” Rather, clinicians must decide what each signal represents, whether it is current, whether it is relevant to the drug, and whether a competing signal is closer to the exposure or clinical state that dosing is intended to control. Certain populations already demonstrate the need for confirmatory or multimarker assessment when standard estimates are unreliable; contemporary onco-nephrology guidance, for example, emphasizes that patient phenotype and treatment context can materially affect GFR assessment [5]. This Current Opinion extends that principle to dynamic renal dosing. We argue that estimated filtration, AKI trajectory, dialysis-dependent clearance, measured or inferred exposure, and clinical response should be treated as analytically distinct signals that may converge, conflict, or become obsolete at different times.

Why static renal-dosing categories fail under dynamic kidney function

Static renal categories imply that the measured marker, the equation applied to it, the patient's physiological state, and the drug's clearance pathway are sufficiently aligned for a categorical dosing recommendation to remain meaningful. Contemporary discussion of renal dose-adjustment methods shows that the choice and interpretation of kidney-function equations are themselves unsettled across clinical contexts [6]. More importantly, the serum creatinine concentration can move for reasons other than a genuine fall in filtration. Several drugs inhibit renal creatinine transport and can produce an apparent deterioration in creatinine-based kidney function without a corresponding loss of filtration, creating the possibility of inappropriate dose reduction if the laboratory change is accepted uncritically [7].

The opposite problem also occurs: alternative kidney markers may place the same critically ill patient into substantially different dosing categories. A retrospective intensive-care study found clinically relevant discordance between creatinine-based and cystatin C-informed renal estimates when applied to renally dosed medications [8]. Even when creatinine clearance is estimated using the familiar Cockcroft–Gault equation, performance can vary with the body weight selected and with the presence of augmented renal clearance [9]. These are not merely competing formulas; they are manifestations of different assumptions about body composition, creatinine generation, and the relationship between filtration and observed clearance.

Recent kidney guidance interpreted for pharmacy practice increasingly emphasizes context-aware use of GFR estimates rather than unquestioned reliance on historical dosing conventions [10]. Static categories therefore remain useful reference points, but they should not function as irreversible dose states. Under dynamic physiology, a renal category is better understood as a provisional description whose dosing relevance depends on the validity, timing, and drug-specific meaning of the signal that produced it.

Estimated filtration and the problem of non-steady-state renal function

Modern creatinine- and cystatin C-based equations have improved GFR estimation and reduced reliance on older demographic adjustments, but their purpose remains estimation of filtration rather than direct measurement of drug clearance. Creatinine- and combined creatinine–cystatin C equations have been developed and validated against measured GFR across large populations [11]. Cystatin C-based approaches provide an additional filtration signal with different biological determinants, yet they remain estimators with their own assumptions rather than a universally unbiased reference [12].

The distinction becomes more consequential in critical illness. Direct comparisons with measured kidney function show that creatinine and cystatin C can perform differently in critically ill patients because acute illness changes the determinants of both biomarkers [13]. Non-steady-state creatinine adds another problem: when serum creatinine is rising or falling, the value observed at one moment reflects both current filtration and the lag created by creatinine distribution and accumulation. Kinetic GFR approaches attempt to incorporate the direction and rate of creatinine change, and retrospective AKI analyses show that using kinetic estimates can reclassify medication-dosing categories relative to conventional approaches [14]. This supports their relevance to dosing interpretation,

but it does not establish that kinetic estimates improve clinical outcomes or should replace conventional measures in every patient.

Patient phenotype further modifies measurement reliability. In cancer, for example, altered muscle mass, treatment effects, and other non-GFR determinants can make routine filtration estimation especially difficult [15]. The broader dosing implication is that an eGFR value should be interpreted as a time-stamped estimate generated under specific physiological assumptions. When those assumptions are unstable, renal dosing should incorporate trajectory and corroborating information rather than treating the latest laboratory-derived category as a definitive clearance state.

Acute kidney injury and rapidly changing clearance

AKI creates a mismatch between the speed at which renal physiology changes and the speed at which conventional markers reflect that change. During rapidly rising or falling creatinine, the clinically relevant question is not only whether kidney function is impaired, but whether renal drug clearance is currently decreasing, stabilizing, or recovering. In a retrospective vancomycin cohort evaluated through simulation, kinetic GFR-based dosing estimates aligned more closely with observed trough behavior in selected patients with acutely changing renal function than conventional estimates [16]. This finding supports temporal updating as a dosing principle, but it is not prospective evidence that kinetic-GFR dosing is universally superior.

Interpretive uncertainty also exists at the clinician level. Scenario-based international data indicate that clinicians can reach different judgments from the same changing creatinine trajectories, illustrating that dynamic renal function is not converted into dosing action uniformly [17]. Furthermore, AKI should not be assumed to imply persistently reduced clearance. Critically ill patients can develop augmented renal clearance, producing renal elimination that exceeds conventional expectations and potentially causing antimicrobial underexposure [18]. Thus, a conservative dose chosen during deteriorating function may become inadequate as clearance recovers or becomes augmented.

Drug-specific pharmacokinetics remain essential even when renal biomarkers are available. Population pharmacokinetic work in children with sepsis demonstrated substantial variability in meropenem distribution and clearance despite incorporation of renal biomarkers [19]. Although that study cannot be generalized directly to adult dosing, it illustrates the broader limitation of treating a kidney marker as a complete pharmacokinetic model. In dynamic AKI, the clinically relevant renal signal is therefore not a single creatinine value but a trajectory interpreted alongside the drug's clearance characteristics, recent dosing, physiological change, and—when available—evidence of actual exposure.

Dialysis modality, timing, and extracorporeal drug removal

Dialysis adds a second clearance system whose contribution can change even when the drug and patient's intrinsic characteristics appear unchanged. Continuous renal replacement therapy (CRRT) pharmacokinetic research identifies multiple interacting determinants of antimicrobial clearance, including treatment modality and intensity, residual kidney function, protein binding, drug properties, and circuit-related variables [20]. Consequently, “receiving dialysis” is not a sufficiently specific dosing state.

The temporal structure of treatment is equally important. Sustained low-efficiency dialysis can remove clinically relevant amounts of antimicrobial drug, meaning that exposure depends partly on whether a dose is administered before, during, or after the dialysis session [21]. Drug properties modify this effect. Across CRRT studies, fraction unbound and sieving coefficient are related, but their relationship is not precise enough to justify predicting extracorporeal clearance from protein binding alone [22]. Changes in critical illness, protein concentrations, filter performance, and circuit prescription can all alter the fraction of administered drug that remains available for extracorporeal removal.

Observed concentrations reinforce this variability. Multinational sampling of critically ill patients receiving renal replacement therapy demonstrated substantial variation in antibiotic concentrations despite recorded RRT and dose information [23]. Dialysis therefore should be conceptualized as a time-varying clearance contribution layered onto residual renal and nonrenal elimination, not as a binary modifier applied after an eGFR calculation. The timing of dosing and concentration sampling also matters because samples taken during active extracorporeal removal, immediately afterward, or following redistribution may represent different exposure states.

Figure 1 illustrates why apparently unchanged patient and drug characteristics can produce a different renal-dose decision when the dialysis prescription or timing context changes.

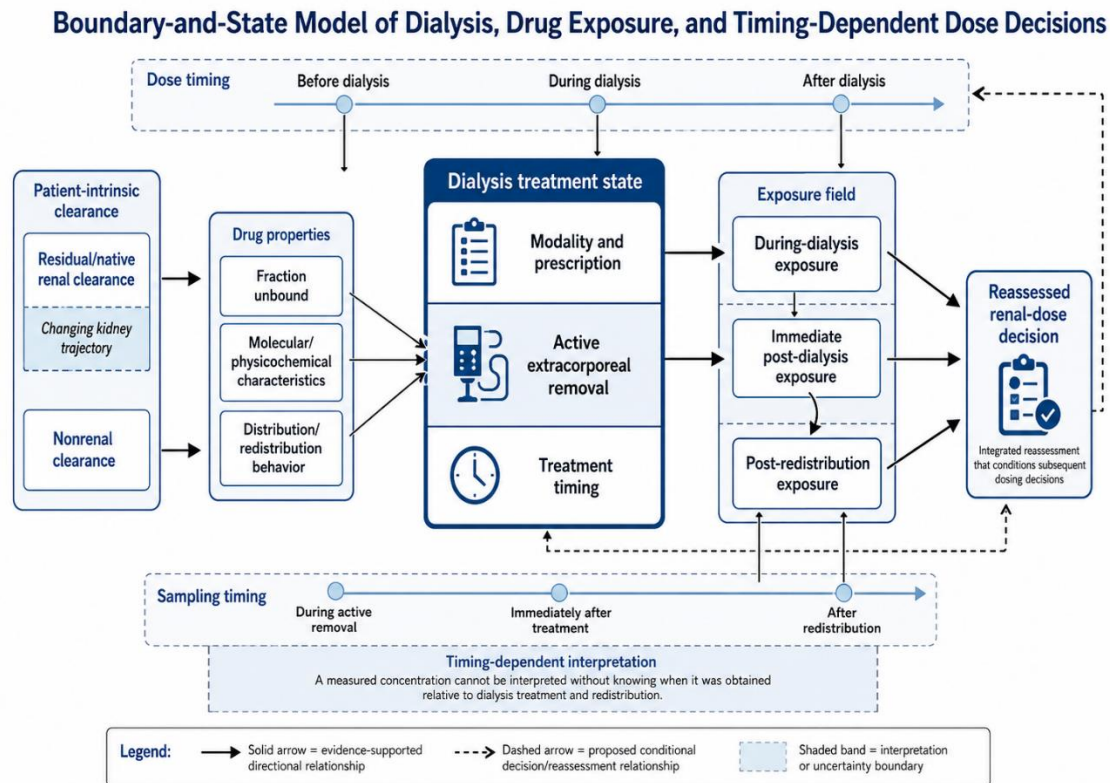


Figure 1. Dialysis Timing Can Reconfigure Drug Exposure Without Changing the Drug or the Patient

Drug exposure and therapeutic drug monitoring

When a renal estimate and expected drug clearance disagree, measured exposure can sometimes provide a more proximal signal than another filtration calculation. This is particularly relevant for drugs with substantial pharmacokinetic variability and an interpretable concentration–effect or concentration–toxicity relationship. In critically ill patients receiving β -lactams, therapeutic drug monitoring (TDM) has been advocated as a means of identifying underexposure or excessive exposure that cannot be inferred reliably from renal estimates alone, although evidence for improvement in hard clinical outcomes remains less certain [24]. The value of TDM therefore lies first in clarifying exposure, not in proving that a particular dosing adjustment will improve outcome. Exposure-guided dosing also illustrates why renal function should be treated as one covariate within a wider pharmacokinetic problem. Vancomycin AUC-targeted dosing models integrate renal function with body size and other covariates to estimate the regimen required to achieve a specified exposure range [25]. Model-informed updating can move the decision further toward the individual patient by incorporating measured concentrations; in a piperacillin scenario analysis, a posteriori model-informed dosing improved target attainment relative to empirical approaches within the analyzed dataset [26]. Such results support iterative exposure updating, but they remain model- and drug-dependent and should not be translated into a claim of universal clinical benefit.

TDM itself can also disagree with other signals. A concentration may be uninterpretable if sampling time is uncertain, the pharmacokinetic target is poorly validated, the assay turnaround is too slow for the changing physiology, or dialysis and redistribution have altered the sampled compartment. International guidance on antimicrobial TDM therefore emphasizes drug selection, sampling, target definition, and implementation conditions rather than indiscriminate monitoring [27]. Within renal-dose reconciliation, measured exposure should consequently receive greater interpretive weight only when the measurement is timely, analytically reliable, pharmacologically meaningful, and connected to a defensible target.

This requirement changes how discordance should be handled. A concentration that contradicts an eGFR-based expectation should first prompt verification of dose history, sampling time, assay validity, distribution phase,

dialysis timing, and the exposure metric being interpreted. Only then should the disagreement be treated as evidence that the renal estimate poorly represents current drug clearance. Conversely, an apparently reassuring concentration should not freeze the regimen when kidney function is continuing to change. Exposure is a time-stamped observation, and its authority diminishes as physiology, dialysis delivery, fluid balance, or dosing changes after sampling. TDM therefore contributes most when embedded in a repeated assessment loop rather than used as a single corrective test.

Clinical response and toxicity as reassessment signals

Clinical response and toxicity are the outcomes toward which dosing is ultimately directed, but they are noisy signals of renal clearance. Worsening kidney function during vancomycin therapy, for example, cannot be attributed to a single baseline eGFR or concentration because AKI risk reflects multiple patient, treatment, and exposure-related variables. A multicenter prediction study of vancomycin-associated AKI demonstrated that toxicity risk is multivariable rather than reducible to renal-function category alone [28]. Clinical deterioration should therefore prompt reassessment without automatically proving that the current dose caused toxicity.

The same distinction applies to apparent treatment success or failure. A systematic review of β -lactam TDM in deep-seated infections found that the evidence linking pharmacokinetic/pharmacodynamic optimization to clinical outcomes remains limited and heterogeneous [29]. Meta-analytic evidence in critically ill patients likewise supports a clearer effect of TDM on target attainment than on hard clinical outcomes [30]. These findings matter conceptually: exposure is closer to dose than clinical outcome is, whereas outcome is also shaped by disease severity, source control, pathogen susceptibility, concomitant therapy, timing of treatment, and host response. Clinical response can therefore challenge an apparently satisfactory renal dose, but it cannot by itself identify which pharmacokinetic assumption is wrong.

Even the laboratory signal interpreted as toxicity may require adjudication. Real-world oncology data show that treatment-associated increases in serum creatinine can represent pseudo-worsening of kidney function rather than true loss of filtration [31]. A dose reduction made solely in response to such a creatinine rise could therefore move exposure in the wrong direction. In a dynamic reconciliation process, toxicity and response function as feedback signals: they trigger re-examination of renal trajectory, exposure, competing causes, and the validity of the measurements already being used.

The temporal position of clinical response is also important. Early nonresponse may precede an informative exposure measurement, whereas late toxicity may reflect accumulation that occurred after the renal estimate used for the original regimen. Conversely, improvement can occur despite an exposure estimate outside a conventional target because response is not determined by concentration alone. The practical implication is not to downgrade clinical observation, but to classify it correctly: response and toxicity are downstream evidence that can strengthen, weaken, or redirect a dosing hypothesis. They should rarely be allowed to retroactively redefine kidney function without independent support.

Reconciling discordant renal-dosing signals

Discordance becomes clinically important when two or more reasonable dosing signals imply different actions. The solution is not to average them or automatically privilege the most familiar renal metric. An integrated analysis supporting ribociclib dosing in renal impairment illustrates that pharmacokinetic, safety, and efficacy information can be interpreted together when a dedicated renal-impairment study and broader patient-trial evidence do not tell exactly the same story [32]. This is a useful proof of principle for evidence integration, although it does not validate a bedside reconciliation algorithm.

Contemporary regulatory thinking similarly recognizes that renal-impairment assessment may draw on several complementary evidence sources rather than one conventional study design [33]. Translating that principle to clinical care requires an additional temporal dimension: the most informative signal may change during the same admission. A recent creatinine trajectory may be more relevant during evolving AKI; extracorporeal clearance may dominate during active dialysis; a valid concentration may become more informative once exposure can be interpreted; and clinical response may later challenge the adequacy or safety of the working regimen.

Drug-specific behavior prevents the reconciliation process from becoming a universal hierarchy. Population pharmacokinetic analysis of trimethoprim/sulfamethoxazole shows that renal insufficiency and CRRT can affect the two components differently [34]. ICU exposure data for the same fixed combination further illustrate how

renal function and body size can make a nominally simple regimen difficult to individualize [35]. These examples support the need to reconcile signals at the level of the actual drug or drug components rather than at the level of “renal dosing” in the abstract.

A useful adjudication question is therefore not “Which renal value is correct?” but “Which observed signal is most informative for the dosing risk that exists now?” If the immediate hazard is accumulation during deteriorating function, recent trajectory and exposure may deserve greater attention than a delayed categorical label. If dialysis has just started or changed, prescription and timing information become central. If a concentration conflicts with clinical response, target validity and competing explanations require review before another dose change. This proposed approach preserves reversibility: the provisional action is linked to explicit monitoring and a condition under which it should be withdrawn.

Table 1 operationalizes the article’s proposed adjudication logic for recurrent patterns of renal-dose discordance.

Table 1. Renal-dose discordance adjudication register for provisional action and reversal

Signal combination	Why discordant	Most time-sensitive risk	Provisional dosing response	Monitoring	Trigger for reversal
eGFR falls; exposure unchanged	Marker lag or non-GFR creatinine effect	Unnecessary underexposure	Avoid reflex reduction; verify trajectory	Repeat renal markers; exposure if valid	Exposure rises or independent injury evidence appears
eGFR improves; exposure remains high	Clearance recovery lags estimate	Toxic accumulation	Maintain caution; reassess interval/dose	Concentration trend; toxicity	Exposure falls with stable recovery
AKI resolving; clearance appears high	Recovery or augmented clearance	Underexposure	Reconsider prior conservative regimen	Measured clearance/exposure where feasible	Clearance or exposure falls again
Dialysis prescription changes	Extracorporeal clearance changes	Under- or overexposure	Re-time or revise regimen provisionally	Dialysis details; timed concentrations	Modality/timing returns or exposure contradicts assumption
Exposure and clinical response disagree	PK target or outcome interpretation uncertain	Wrong causal attribution	Reassess target and competing causes	Exposure, efficacy, toxicity, context	New evidence identifies dominant explanation

Note: Entries describe the proposed reconciliation logic of this Current Opinion; they are not validated dosing rules or quantitative thresholds.

The proposed dynamic renal-dose reconciliation model

The proposed Dynamic Renal-Dose Reconciliation Model begins by separating five signal classes that are often collapsed in practice: estimated filtration, kidney-function trajectory, extracorporeal clearance, measured or inferred drug exposure, and clinical response or toxicity. The first task is not to rank them permanently but to ask what each signal measures at the present time. Biomarker discordance [4], pseudo-worsening of creatinine [7], differences between endogenous markers and measured kidney function [13], and the multidimensional determinants of CRRT pharmacokinetics [20] all show why apparently comparable “renal” signals can represent different processes.

The model then proposes four qualitative adjudication questions: How directly is the signal connected to clearance or exposure for this drug? How temporally close is it to the current dosing state? How reliable is the measurement or model in this patient? What clinically important risk follows if the signal is wrong? Dynamic-estimation work [16], exposure-based TDM [24], model-informed concentration updating [26], and integrated renal-impairment analyses [32] support the constituent logic, but the weighting of these questions is proposed here and has not been prospectively validated. No numerical score is implied.

The model also separates three levels that are easily conflated. At the measurement level, creatinine, cystatin C, measured clearance, dialysis prescription, and concentrations generate observations with different errors and delays. At the pharmacokinetic level, those observations are interpreted in relation to renal, extracorporeal, and nonrenal clearance and to distribution. At the clinical-decision level, the regimen is provisionally changed, maintained, or further investigated. A disagreement at one level should not automatically be converted into a

conclusion at another. For example, discordant biomarkers establish measurement uncertainty, not necessarily exposure error; an abnormal concentration establishes an exposure problem only if timing and target are valid; and toxicity establishes a clinical concern without proving renal causation.

Finally, the dose state remains revisable. RRT-associated concentration variability [23], multivariable toxicity risk [28], pseudo-worsening of creatinine [31], and difficult ICU exposure patterns [35] each illustrate situations in which later information can invalidate an earlier assumption. Reassessment therefore includes both escalation and downgrade pathways. A signal may gain weight as it becomes temporally closer or more direct, but it may also lose weight when the underlying physiology changes, the dialysis prescription is modified, sampling proves mistimed, or an alternative explanation becomes more plausible. **Figure 2** represents this logic as a recursive decision field rather than a one-way descent through renal categories.

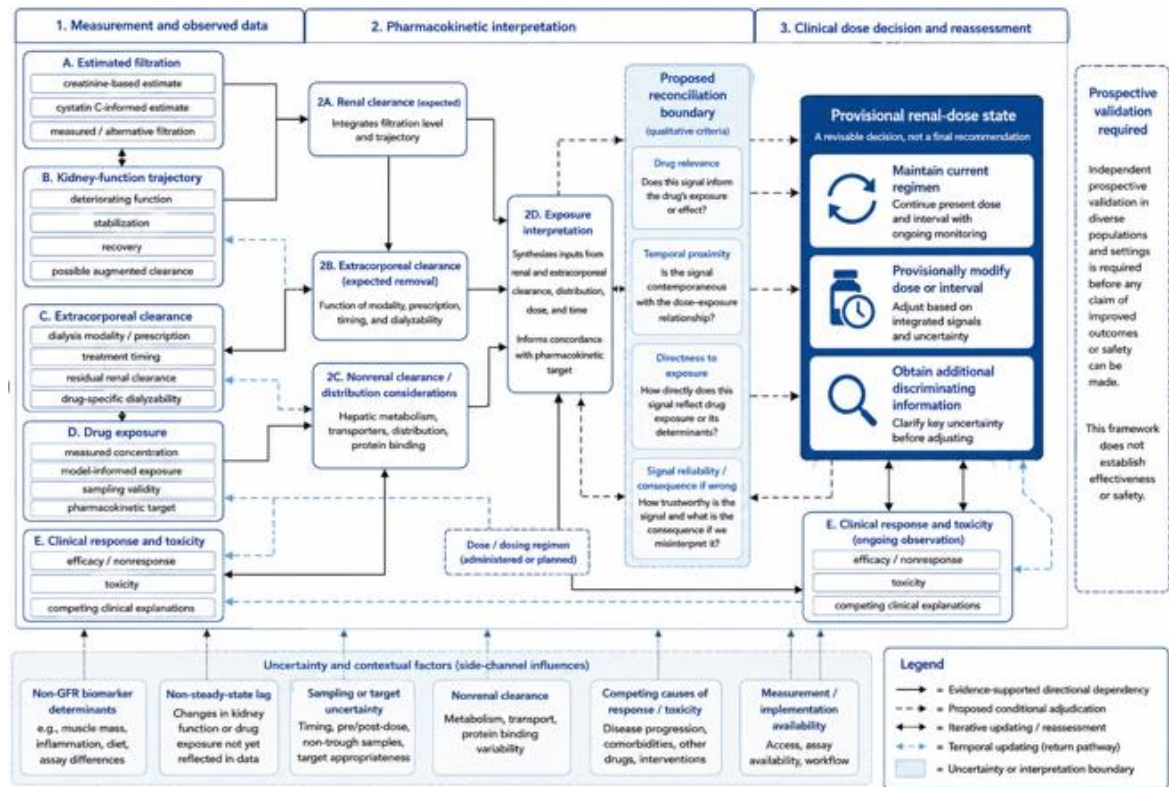


Figure 2. Renal Dose Decisions as a Revisable State Across Kidney Function, Dialysis, Exposure, and Response

Boundary conditions and evidence gaps

The proposed model is most vulnerable when the available signals are simultaneously weak. No endogenous filtration marker is universally reliable across changing physiology, and even well-validated equations retain population- and context-dependent error [11]. Critical illness can further separate creatinine or cystatin C from measured kidney function [13], while oncology provides an example in which body composition and treatment-related effects complicate conventional estimation [15]. The model therefore cannot solve measurement error simply by asking clinicians to reconcile more measurements.

Exposure-based adjudication also has limited reach. CRRT pharmacokinetic evidence remains heterogeneous across drugs, modalities, and study methods [20]. TDM is informative only for selected therapies with interpretable targets and feasible sampling [24], and international recommendations acknowledge substantial differences in evidence strength and implementation requirements across antimicrobials [27]. Moreover, systematic outcome evidence remains uncertain for several TDM applications [29]. A measured concentration can therefore be more direct than eGFR without becoming an infallible decision endpoint.

Health-system constraints are part of the boundary rather than an afterthought. Timely cystatin C testing, measured clearance, specialized assays, pharmacometric software, pharmacist or clinical-pharmacology support, and detailed dialysis documentation are not equally available across institutions. Even when a measurement is

technically available, laboratory turnaround may be too slow for an unstable AKI trajectory. A reconciliation process that requires every signal for every patient would therefore be impractical and could create false precision. The proposed model instead implies selective escalation of information: additional measurement is most defensible when disagreement is clinically consequential and the result is capable of changing the provisional regimen.

The principal research need is prospective testing of the reconciliation process itself. Model-informed dosing studies can evaluate exposure-target attainment [26], and toxicity models can identify multivariable risk patterns [28], but neither establishes that the proposed cross-signal adjudication strategy improves patient outcomes. Integrated clinical-pharmacology cases demonstrate that divergent renal evidence can be combined coherently [32], while difficult ICU dosing examples show why such integration may be necessary [35]. Future evaluations should test prespecified discordance states across AKI development and recovery, augmented clearance, intermittent and continuous dialysis, and multiple drug classes; compare decisions against exposure and patient-centered outcomes; examine disagreement between clinicians; and determine whether added measurements, modeling, staffing, and assay infrastructure produce sufficiently actionable information across different health systems.

Conclusion

Renal dose adjustment under dynamic kidney function is better understood as a recurrent interpretation problem than as a one-time assignment to a filtration category. Estimated GFR and creatinine clearance remain essential, but their dosing relevance depends on the physiological state, biomarker assumptions, drug-specific clearance pathways, and timing of measurement. AKI introduces lag and trajectory; recovery may produce unexpectedly high clearance; dialysis contributes a separable and time-dependent extracorporeal pathway; therapeutic drug monitoring can move assessment closer to actual exposure for selected drugs; and clinical response or toxicity can reveal that an apparently coherent pharmacokinetic interpretation requires reconsideration.

The Dynamic Renal-Dose Reconciliation Model proposed here organizes these signals without claiming that one should always dominate. Its central principle is conditional updating: interpret each signal according to what it measures, how current it is, how directly it relates to the drug's exposure, and what risk follows from accepting it incorrectly. A dose decision should remain provisional when the underlying physiology is moving, and the reason for acting should remain linked to a reason for reversing that action.

Important boundaries remain. Many drugs lack validated exposure targets, dialysis prescriptions vary, biomarkers have nonrenal determinants, clinical outcomes have competing causes, and the proposed reconciliation logic has not been prospectively validated. Measurement and modeling resources also differ among health systems. Its value at present is therefore conceptual: to make discordance explicit, prevent different renal and pharmacokinetic signals from being treated as interchangeable, and define a testable structure for future work on dynamic renal dosing.

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