



Review Article

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Pharmacometrics for Organ Dysfunction and Rapidly Changing Physiology

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ABSTRACT

Organ dysfunction is often translated into dosing through categorical renal or hepatic impairment, yet critical illness and organ support can change clearance and distribution faster than those categories update. To map how pharmacometric studies represent organ dysfunction and rapidly changing physiology, emphasizing temporal covariates, dynamic clearance, model transportability, therapeutic drug monitoring, and model-informed precision dosing. Evidence from 2017–2025 was sought using structured pharmacokinetic/pharmacometric searches combined with renal, hepatic, critical-illness, extracorporeal-support, and dynamic-physiology terms. The operational ledger identified 87 records; 19 duplicates were removed, 68 records were screened, 37 full texts were assessed, and 23 eligible evidence reports entered the synthesis. Renal dysfunction can affect filtration, secretion, and drug clearance; hepatic dysfunction can alter transport, metabolism, flow-related determinants, and exposure in mechanism-dependent ways. Critical illness and organ support add changing distribution, intrinsic clearance, and extracorporeal clearance. External evaluation and concentration-informed Bayesian updating can improve prediction, but performance remains model- and context-specific. Pharmacometric interpretation is strongest when organ dysfunction is treated as a time-indexed exposure-generating state rather than a diagnosis alone. A proposed state–trajectory–decision-horizon framework separates observed physiology, model assumptions, forecast uncertainty, and dose action without assuming that dynamic models are universally superior.

Keywords: Pharmacometrics, Organ dysfunction, Model-informed precision dosing, Time-varying covariates, Dynamic clearance, Critical illness

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INTRODUCTION

Pharmacometrics links population pharmacokinetics, physiologically based pharmacokinetic modeling, therapeutic drug monitoring, and individualized dose selection. Model-informed precision dosing combines prior knowledge with patient information, but its usefulness depends on model qualification, data timeliness, and the clinical decision being supported [1–3]. These requirements become particularly important when physiology changes during treatment.

Organ dysfunction is commonly represented by a renal-function estimate, hepatic severity category, or critical-illness label. Such descriptors can collapse distinct processes. Critical illness may alter distribution, protein binding, perfusion, renal elimination, and nonrenal clearance simultaneously, with direction and magnitude varying by drug, disease phase, and treatment context [4]. Creatinine may lag acute change, liver scores may

incompletely reflect transporter or flow changes, and organ support may add clearance not represented by intrinsic function.

This review therefore distinguishes current organ-function state from its trajectory and from the dosing decision horizon. The state–trajectory–decision-horizon construct is proposed here as an organizing synthesis, not a validated clinical algorithm. The review asks when dynamic representation is supported, when static categories remain adequate, and where uncertainty prevents strong individual prediction.

MATERIALS AND METHODS

This scoping review followed PRISMA-ScR reporting principles [5] and mapped evidence rather than pooling effects. Eligible publications were charted for organ-function context, model type, population, temporal structure, covariates, concentration feedback, validation approach, and dose-decision relevance.

The evidence window was 1 January 2017 through 31 December 2025. Final bibliographic and DOI verification was performed on 31 August 2026 without admitting 2026 publications. Reviews and methodological sources could support interpretation, but eligible evidence reports were counted separately.

Review scope and eligibility

Eligible evidence addressed PK, PD, pharmacometric, or model-informed dosing questions in renal dysfunction, hepatic dysfunction, critical illness, extracorporeal support, concurrent impairment, or clinically relevant physiological transition. Population PK, PBPK, PK/PD, external model evaluation, Bayesian forecasting, and clinically oriented simulation studies were eligible when they informed exposure or dosing.

Records were excluded if organ dysfunction was incidental, usable pharmacometric or exposure analysis was absent, publication fell outside 2017–2025, or the journal failed the prespecified Q1 criterion in a relevant category.

Search strategy

The PubMed/MEDLINE logic combined *pharmacokinetic**, *pharmacometric**, *population pharmacokinetic**, *physiologically based pharmacokinetic**, or *model-informed precision dosing with renal impairment, kidney dysfunction, hepatic impairment, liver dysfunction, critical illness, ECMO, CRRT, continuous renal replacement therapy, or organ dysfunction*, restricted to 2017–2025. DOI/publisher-index searching and citation chaining supplemented retrieval.

The operational ledger contained 61 PubMed/MEDLINE records, 14 supplementary DOI/publisher-index records, and 12 citation-chained records: 87 before deduplication. Nineteen duplicates were removed, leaving 68 records; 31 were excluded at title/abstract screening. All 37 reports sought were retrieved and assessed. Fourteen full texts were excluded: five for insufficient direct relevance, four for absence of usable pharmacometric/PKPD exposure analysis, three for failure of the Q1 journal criterion, and two for publication outside the window. Twenty-three eligible evidence reports remained.

Model and population coding

Renal-function coding was treated as a model choice rather than neutral preprocessing. Equations for filtration, creatinine clearance, body size, and fat-free mass can alter covariate interpretation across populations [6]. We therefore coded the function measure, whether it was updated over time, and whether extracorporeal clearance was represented separately.

Model qualification was coded independently from model class. Population-PK implementation recommendations emphasize model selection, external evaluation, software, and clinical workflow as related but distinct requirements [7], while bedside MIPD requires a qualified prior model, timely patient data, and an actionable target [8]. Mechanistic complexity was therefore not treated as equivalent to clinical usefulness.

Evidence charting

Evidence was charted at observation, model, and decision levels. Observations included organ-function measurements, concentrations, support settings, and clinical state; model fields included structural assumptions, covariates, time dependence, and uncertainty; decision fields recorded dose, sampling, target-attainment, or interpretive uses. EHR-integrated support illustrates how predictions can enter workflow without itself proving clinical benefit [9].

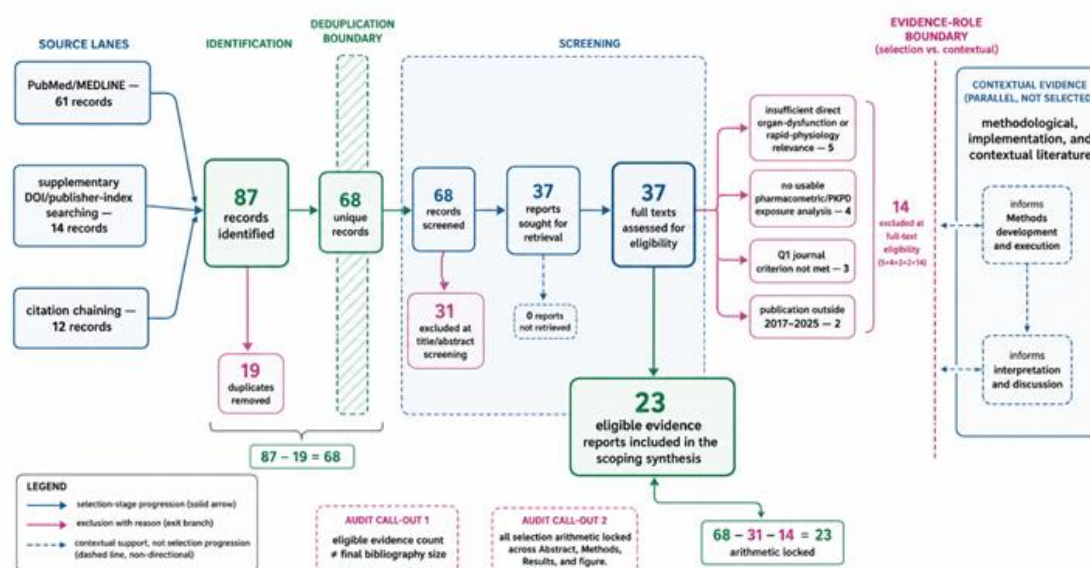
Temporal information was coded separately because models can be updated as practice data accumulate [10], while external evaluations show that performance can change after transport to new patients [11]. Apparent precision was therefore flagged when a covariate was stale, device clearance was omitted, external evaluation was absent, or concentration feedback arrived after the relevant decision.

The warning patterns are more informative when their corrective tests and residual limitations can be compared directly; the resulting exception-first triage is summarized below.

Table 1. Failure-mode triage for evidence charting in rapidly changing organ-function pharmacometrics

Misleading pattern	Evidence structure	Boundary and consequence	Misleading pattern	Evidence structure	Boundary and consequence
Stable label during active change	Likely origin Covariate predates current physiology Dose implication Forecast anchored to obsolete clearance	Monitoring signal New concentrations diverge from prediction Validation step Re-estimate with updated covariate Residual consequence Current measurement may still lag trajectory	Apparent renal effect includes device clearance	Likely origin Intrinsic and extracorporeal elimination combined Dose implication Dose change attributed to kidney alone	Monitoring signal Exposure changes after support modification Validation step Model device and intrinsic clearance separately Residual consequence Device settings remain time-varying
Good internal fit, poor transported prediction	Likely origin Development domain differs from target population Dose implication False confidence in individual dose	Monitoring signal Systematic a priori forecast error Validation step External evaluation Residual consequence Local calibration may remain necessary	Bayesian correction treated as mechanistic proof	Likely origin Feedback compensates for structural error Dose implication Useful forecast assigned wrong mechanism	Monitoring signal Posterior improves while structure remains discordant Validation step Compare with mechanism-sensitive information Residual consequence Predictive and mechanistic validity remain distinct
Sparse or delayed sampling	Likely origin Informative transition missed Dose implication Estimate represents an earlier state	Monitoring signal Unstable posterior or wide uncertainty Validation step Evaluate alternative sampling times Residual consequence Structural non-identifiability may persist	Single severity category	Likely origin Clinical classification too coarse Dose implication Different pathways treated as equivalent	Monitoring signal Exposure discordance within category Validation step Test pathway-specific predictors Residual consequence No universal replacement marker is established

Note: The categories are proposed synthesis, not validated scores or rankings.



RESULTS AND DISCUSSION

Twenty-three eligible evidence reports entered the mapped synthesis, spanning PBPK, population PK, external evaluation, clinical organ-impairment studies, and simulation-based pharmacometrics. Reviews and implementation papers were used for context but did not alter the eligible-report count.

Renal evidence showed multiple mechanisms. PBPK demonstrated transporter-mediated effects beyond filtration [12]. In critically ill patients, eGFR influenced imipenem clearance [13], while piperacillin modeling linked renal function with exposure and target attainment [14]. External piperacillin evaluation showed variable a priori performance and improvement with concentration-informed Bayesian updating [15]. Meropenem evaluation in CRRT similarly showed the value of therapeutic drug monitoring [16]. ECMO studies suggested parameter-specific effects for amikacin [17] and highlighted uncertainty when ECMO and CRRT overlapped for fluconazole [18]. These observations fit the broader transition from conventional therapeutic drug monitoring toward model-informed antibiotic dosing [19].

Renal dysfunction

Renal dysfunction should not be equated with filtration alone. For transporter-dependent drugs, reduced kidney function can alter active secretion and exposure beyond changes predicted from filtration [12]. This is pathway-specific evidence, not justification for a universal renal correction.

Renal function also changes during treatment. Imipenem and piperacillin studies show that renal descriptors can materially influence clearance and target attainment [13, 14], but their numerical relationships are not transferable across drugs, infusion strategies, and targets. When CRRT begins, extracorporeal elimination adds a second clearance pathway, and meropenem model evaluation shows why transportability cannot be assumed across support settings [16].

The proposed renal-state synthesis therefore distinguishes stable reduction, active decline, recovery, marker–concentration discordance, and transition to renal replacement support. Because the same renal estimate can imply different dose actions depending on direction and timing, these states require explicit temporal comparison.

Table 2. Temporal renal states that change the meaning of dose adaptation

Exposure concern Time lag	Covariate trajectory Assumption Unresolved question	Main uncertainty
Entering renal state Stable chronic reduction		

Exposure concern Persistent accumulation Time lag or feedback Usually limited	Covariate trajectory Approximately flat	Pathway-specific effects
	Assumption requiring scrutiny Current function represents dosing interval	
	Unresolved question When is a static category sufficient?	
	Entering renal state Rapid decline	
Exposure concern Prior dose reflects higher clearance Time lag or feedback Marker may lag	Covariate trajectory Downward	Speed of change
	Assumption requiring scrutiny Latest marker equals current clearance	
	Unresolved question How much trajectory information is needed?	
	Entering renal state Recovery	
Exposure concern Dose reduction may cause underexposure Time lag or feedback Concentration reflects prior low-clearance state	Covariate trajectory Upward	Recovery rate
	Assumption requiring scrutiny Previous low clearance persists	
	Unresolved question When should the prior be discounted?	
	Entering renal state Marker–concentration discordance	
Exposure concern Exposure differs from renal estimate Time lag or feedback Concentration gives delayed correction	Covariate trajectory Uncertain	Structural error versus measurement error
	Assumption requiring scrutiny Renal marker dominates clearance	
	Unresolved question Is discordance physiological or model-based?	
	Entering renal state Renal replacement transition	
Exposure concern Intrinsic and device clearance coexist Time lag or feedback Support changes may precede TDM	Covariate trajectory Step change	Settings and residual function
	Assumption requiring scrutiny Device clearance is fixed	
	Unresolved question How frequently must both states be updated?	

Note: These states are proposed synthesis and are not validated dosing categories.

Hepatic dysfunction

Hepatic dysfunction cannot always be represented by a single reduction in clearance because blood flow, protein binding, enzyme activity, transport, and shunting may change differently. Clinical transporter analysis, PBPK representation of portal shunting, and extended-clearance modeling collectively show that exposure depends on the drug's dominant pathways and the physiological changes represented [20–22].

A cross-drug analysis found differential sensitivity of clearance mechanisms to hepatic disease progression [23]. In a separate amprelosetine study, a quantitative hepatic-function measure predicted pharmacokinetics better than Child-Pugh classification [24]. This supports investigation of continuous function measures but not a universal replacement for clinical severity scores.

Accordingly, hepatic model coding should retain the distinction between clinical classification and the pharmacokinetically active mechanism. The practical question is whether the available descriptor captures enough pathway variation for the intended compound and decision horizon.

Critical illness and organ support

Critical illness combines unstable intrinsic physiology with treatment-induced clearance. Piperacillin external evaluation showed variable a priori prediction and improved individual forecasts after measured concentrations were incorporated [15]. Meropenem evaluation during CRRT likewise demonstrated the value of concentration

feedback and residual renal information [16]. Bayesian updating is therefore useful for managing uncertainty, but posterior correction does not prove that the underlying model structure is mechanistically correct. ECMO adds another layer because circuit-related effects need not influence clearance and distribution equally. In the amikacin VA-ECMO population, renal dysfunction was a major clearance determinant while ECMO-associated effects were more evident in distribution [17]. In the small fluconazole ECMO/CRRT study, simultaneous support modalities created overlapping patient- and device-related determinants [18]. These studies argue against a universal ECMO or CRRT correction factor. Model-informed antibiotic dosing can integrate prior models, concentrations, and covariates [19], but each update remains bounded by model quality, sampling, exposure target, and clinical state. Rapidly changing physiology therefore requires attention not only to which covariates are present, but to when they changed, how quickly the model can detect the change, and whether a resulting dose recommendation remains valid long enough to act on it.

Rapid physiological transitions

The most difficult dosing states are often not severe but stable impairment; they are periods in which the patient is moving between physiological states. Concurrent moderate renal and hepatic impairment altered zibotentan exposure in a dedicated clinical study, illustrating that combined dysfunction cannot always be reconstructed safely from isolated organ-specific assumptions [25]. Mechanistic PBPK-PD work with siRNA therapeutics likewise shows how organ-function changes can be propagated through disposition and response models, although simulated states remain predictions rather than clinical validation [26].

The proposed state–trajectory–decision-horizon framework therefore distinguishes three quantities. State represents the physiology and support conditions measured at a particular time. Trajectory represents the direction, speed, persistence, and reversibility of change. Decision horizon represents the interval over which a dose recommendation must remain sufficiently valid to be clinically useful. A current laboratory value may describe state adequately while providing little information about trajectory.

This distinction becomes important during evolving acute kidney injury, recovery after organ support, changing hepatic perfusion, initiation or withdrawal of CRRT, and simultaneous changes in distribution and clearance. A model should not automatically convert every physiological change into a dose change; rather, it should establish whether the change materially affects the exposure metric, whether the effect is observable before the next decision, and whether intervention is justified.

The relationships among measured state, changing physiology, pharmacometric prediction, and dose action are compressed in **Figure 2**.

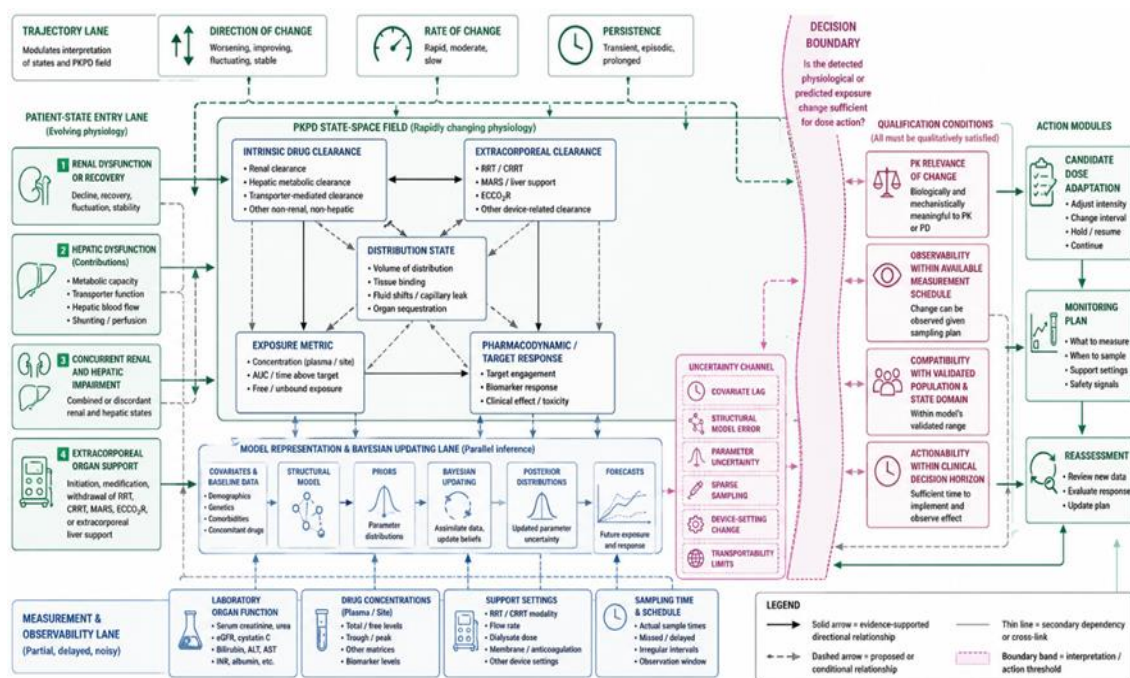


Figure 2. When a current organ-function measurement stops representing the dosing state

Time-varying covariates

A time-varying covariate is clinically valuable only when its evolution carries information about future exposure that is not already captured adequately by the existing model and measurements. PBPK studies of tipifarnib and topiramate illustrate how organ-impairment scenarios can be explored mechanistically, while clinical and population evidence for aficamten demonstrates the counterpoint that organ impairment does not inevitably create a clinically important PK change [27–29].

This review therefore proposes separating four temporal properties: current covariate value, direction of change, delay between physiology and biomarker response, and persistence relative to the next dose decision. These properties prevent “time varying” from becoming a purely statistical label.

Table 3. Temporal covariate states that can alter forecast meaning without automatically requiring dose change

Stable covariate Monotonic deterioration Monotonic recovery Abrupt support transition Oscillating or poorly observed state					
Temporal pattern	Stable covariate	Monotonic deterioration	Monotonic recovery	Abrupt support transition	Oscillating or poorly observed state
PK information carried	Current physiological level	Declining functional capacity	Increasing functional capacity	New extrinsic clearance or physiology	Uncertain physiological driver
Exposure interpretation	Conventional covariate relationship may suffice	Future clearance may differ from current estimate	Prior low-clearance estimate may overpredict exposure	Previous model state may become obsolete	Point estimate can be misleading
Feedback or lag	Minimal	Biomarker may lag	Drug concentration may reflect earlier state	Device change can precede measurement	Multiple lagged signals
Trajectory question	Is stability credible across the dosing interval?	How quickly is the trajectory progressing?	Is recovery sustained?	Is the new state persistent?	Is variation biological or measurement-related?
Decision consequence	Maintain model unless exposure disagrees	Shorten reassessment horizon	Reconsider previous dose reduction	Recalculate state before acting	Preserve uncertainty rather than force adjustment

Note: This temporal classification is proposed and carries no validated scoring system.

Dynamic clearance models

Dynamic clearance models are most defensible when their structural complexity corresponds to a physiological process that matters for the drug. Clinical-PBPK analysis of entrectinib illustrates that hepatic impairment may alter exposure through several mechanisms rather than a single metabolic-capacity scalar [30]. During CRRT, population modeling of trimethoprim/sulfamethoxazole similarly requires separation of residual intrinsic renal elimination from extracorporeal removal [31].

The central modeling problem is therefore reconciliation: whether changing concentrations reflect a true clearance transition, delayed observation, changing distribution, device clearance, model misspecification, or some combination. Structural flexibility alone cannot solve poor observability.

Table 4. Evidence reconciliation before assigning a dynamic clearance mechanism

Observed pattern	What is observable Monitoring evidence	Dose implication Framework endpoint	Validation criterion Clinical state
Scientific anchor	What is observable Monitoring evidence	Dose implication Framework endpoint	Validation criterion Clinical state

Concentration rises as renal function worsens	What is observable Exposure and renal trajectory align Monitoring evidence Serial concentrations	Dose implication Lower clearance plausible Framework endpoint Dynamic clearance interpretation supported	Validation criterion Reproduce trajectory prospectively within patient Clinical state Intrinsic decline
Concentration changes after CRRT modification	What is observable Exposure follows support change Monitoring evidence Device settings plus concentrations	Dose implication Extracorporeal contribution plausible Framework endpoint Device clearance retained explicitly	Validation criterion Model intrinsic and device pathways separately Clinical state Organ support transition
Posterior fit improves but physiology remains discordant	What is observable Predictive correction only Monitoring evidence Repeated Bayesian updates	Dose implication Dose may still be usable Framework endpoint Prediction separated from mechanism	Validation criterion External physiological discriminator Clinical state Model–mechanism discordance
Exposure remains stable despite impairment category	What is observable Little pharmacokinetic consequence detected Monitoring evidence Exposure metric remains acceptable	Dose implication Adjustment may be unnecessary Framework endpoint No automatic dose change	Validation criterion Confirm relevant severity and pathway Clinical state Stable impairment
Predicted clearance changes without informative observations	What is observable Model output predominates Monitoring evidence Sparse or delayed sampling	Dose implication High decision uncertainty Framework endpoint Defer strong mechanistic inference	Validation criterion Obtain discriminating measurement Clinical state Poor observability

Note: The reconciliation endpoints are proposed interpretive categories rather than validated clinical rules.

Clinical dose adaptation

Precision dosing is not only a model-selection problem; it is also a measurement-timing problem. Simulation of amikacin MIPD shows that sampling design influences how reliably an exposure target can be estimated [32]. Longitudinal modeling of brentuximab vedotin further demonstrates that pharmacokinetic parameters can vary with time and patient context [33], although that population should not be treated as direct evidence for adult organ failure.

Dose adaptation should therefore integrate the freshest clinically meaningful covariates, sufficiently informative drug concentrations, model transportability, and the anticipated duration of the predicted physiological state. A recommendation that is accurate for a state that has already changed is operationally inaccurate.

The mapped evidence argues against treating organ dysfunction as a universally static modifier of clearance. Renal impairment may involve filtration, secretion, recovery, acute decline, or extracorporeal removal. Hepatic dysfunction may alter enzymes, transport, perfusion, shunting, and other physiological determinants. Critical illness can combine these processes while also changing volume of distribution, support settings, and measurement reliability.

The proposed state–trajectory–decision-horizon framework does not require dynamic modeling for every patient. Stable physiology, predictable elimination, and adequately validated conventional models may make additional temporal complexity unnecessary. Its purpose is instead to identify circumstances in which a static descriptor risks becoming stale before the associated dosing decision is completed.

A second distinction concerns prediction versus explanation. Bayesian updating can improve individual forecasts even when the prior model is structurally imperfect. Conversely, a physiologically elaborate PBPK model can remain uncertain in an unvalidated severe or rapidly changing state. Predictive usefulness, mechanistic credibility, and clinical actionability must therefore be assessed separately.

This distinction is particularly important for model transport. External evaluations show that a model with acceptable development performance may behave differently in another population, support environment, assay context, or sampling schedule. Consequently, dynamic models should be judged against the intended clinical state rather than against complexity alone.

Research gaps

Prospective evidence remains limited for patients moving rapidly between organ-function states, especially when severe dysfunction, multiple organs, ECMO, and renal replacement therapy overlap. Such populations are difficult to study but are precisely those in which static assumptions may be least reliable.

Further work should compare models using clinically relevant forecast horizons, evaluate how rapidly new measurements should discount older physiological information, and distinguish predictive correction from mechanistic validity. Studies should also determine when a simpler externally validated model performs as well as a mechanistically richer alternative.

Hepatic-impairment PBPK development continues to face uncertainty in physiological scaling, pathway representation, disease severity, and model qualification [34]. Similar qualification problems apply to renal recovery and changing extracorporeal support. Validation should therefore include not only average exposure prediction but also state transitions, external populations, and measurement schedules that resemble intended clinical use.

CONCLUSION

Organ dysfunction becomes a pharmacometric challenge when physiological change occurs on the same timescale as drug exposure and dose decision-making. Renal and hepatic impairment, critical illness, and organ support can alter different components of disposition, while laboratory and concentration measurements may describe those changes with delay.

The proposed state–trajectory–decision-horizon framework separates current physiology, its direction of change, model uncertainty, and the period over which a dosing recommendation must remain useful. It does not replace established renal or hepatic dosing approaches and is not a validated clinical algorithm. Rather, it identifies when static descriptors may be insufficient and when additional temporal information, concentration feedback, external validation, or explicit representation of extracorporeal clearance is needed.

The central implication is that more dynamic modeling is not automatically better. The appropriate model is the simplest adequately validated representation that preserves the physiological changes relevant to exposure and supports a decision before the patient's state changes again.

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REFERENCES

1. Minichmayr IK, Dreesen E, Centanni M, Wang Z, Hoffert Y, Friberg LE, et al. Model-informed precision dosing: State of the art and future perspectives. *Adv Drug Deliv Rev.* 2024;215:115421. doi:10.1016/j.addr.2024.115421
2. Darwich AS, Ogungbenro K, Vinks AA, Powell JR, Reny JL, Marsousi N, et al. Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future. *Clin Pharmacol Ther.* 2017;101(5):646-56. doi:10.1002/cpt.659
3. Heimbach T, Chen Y, Chen J, Dixit V, Parrott N, Peters SA, et al. Physiologically-based pharmacokinetic modeling in renal and hepatic impairment populations: A pharmaceutical industry perspective. *Clin Pharmacol Ther.* 2021;110(2):297-310. doi:10.1002/cpt.2125
4. Morales Castro D, Dresser L, Granton J, Fan E. Pharmacokinetic alterations associated with critical illness. *Clin Pharmacokinet.* 2023;62(2):209-20. doi:10.1007/s40262-023-01213-x
5. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Ann Intern Med.* 2018;169(7):467-73. doi:10.7326/M18-0850

6. O'Hanlon CJ, Holford N, Sumpter A, Al-Sallami HS. Consistent methods for fat-free mass, creatinine clearance, and glomerular filtration rate to describe renal function from neonates to adults. *CPT Pharmacometrics Syst Pharmacol.* 2023;12(3):401-12. doi:10.1002/psp4.12924
7. Berezowska M, Hayden IS, Brandon AM, Zats A, Patel M, Barnett S, et al. Recommended approaches for integration of population pharmacokinetic modelling with precision dosing in clinical practice. *Br J Clin Pharmacol.* 2025;91(4):1064-79. doi:10.1111/bcp.16335
8. Keizer RJ, Ter Heine R, Frymoyer A, Lesko LJ, Mangat R, Goswami S. Model-informed precision dosing at the bedside: Scientific challenges and opportunities. *CPT Pharmacometrics Syst Pharmacol.* 2018;7(12):785-7. doi:10.1002/psp4.12353
9. Vinks AA, Peck RW, Neely M, Mould DR. Development and implementation of electronic health record-integrated model-informed clinical decision support tools for the precision dosing of drugs. *Clin Pharmacol Ther.* 2020;107(1):129-35. doi:10.1002/cpt.1679
10. Maier C, de Wiljes J, Hartung N, Kloft C, Huisinga W. A continued learning approach for model-informed precision dosing: Updating models in clinical practice. *CPT Pharmacometrics Syst Pharmacol.* 2022;11(2):185-98. doi:10.1002/psp4.12745
11. Agema BC, Kocher T, Öztürk AB, Giraud EL, van Erp NP, de Winter BCM, et al. Selecting the best pharmacokinetic models for a priori model-informed precision dosing with model ensembling. *Clin Pharmacokinet.* 2024;63(10):1449-61. doi:10.1007/s40262-024-01425-9
12. Hsueh CH, Hsu V, Zhao P, Zhang L, Giacomini KM, Huang SM. PBPK modeling of the effect of reduced kidney function on the pharmacokinetics of drugs excreted renally by organic anion transporters. *Clin Pharmacol Ther.* 2018;103(3):485-92. doi:10.1002/cpt.750
13. de Velde F, de Winter BCM, Neely MN, Yamada WM, Koch BCP, Harbarth S, et al. Population pharmacokinetics of imipenem in critically ill patients: A parametric and nonparametric model converge on CKD-EPI estimated glomerular filtration rate as an impactful covariate. *Clin Pharmacokinet.* 2020;59(7):885-98. doi:10.1007/s40262-020-00859-1
14. Klastrop V, Thorsted A, Storgaard M, Christensen S, Friberg LE, Öbrink-Hansen K. Population pharmacokinetics of piperacillin following continuous infusion in critically ill patients and impact of renal function on target attainment. *Antimicrob Agents Chemother.* 2020;64(7). doi:10.1128/AAC.02556-19
15. Greppmair S, Brinkmann A, Roehr A, Frey O, Hagel S, Dorn C, et al. Towards model-informed precision dosing of piperacillin: Multicenter systematic external evaluation of pharmacokinetic models in critically ill adults with a focus on Bayesian forecasting. *Intensive Care Med.* 2023;49(8):966-76. doi:10.1007/s00134-023-07154-0
16. Schatz LM, Brinkmann A, Röhr A, Frey O, Greppmair S, Weinelt F, et al. Systematic evaluation of pharmacokinetic models for model-informed precision dosing of meropenem in critically ill patients undergoing continuous renal replacement therapy. *Antimicrob Agents Chemother.* 2023;67(5). doi:10.1128/aac.00104-23
17. Pressiat C, Kudela A, De Roux Q, Khoudour N, Alessandri C, Haouache H, et al. Population pharmacokinetics of amikacin in patients on veno-arterial extracorporeal membrane oxygenation. *Pharmaceutics.* 2022;14(2):289. doi:10.3390/pharmaceutics14020289
18. Novy E, Abdul-Aziz MH, Cheng V, Burrows F, Buscher H, Corley A, et al. Population pharmacokinetics of fluconazole in critically ill patients receiving extracorporeal membrane oxygenation and continuous renal replacement therapy: An ASAP ECMO study. *Antimicrob Agents Chemother.* 2024;68(1). doi:10.1128/aac.01201-23
19. Wicha SG, Mårtson AG, Nielsen EI, Koch BCP, Friberg LE, Alffenaar JW, et al. From therapeutic drug monitoring to model-informed precision dosing for antibiotics. *Clin Pharmacol Ther.* 2021;109(4):928-41. doi:10.1002/cpt.2202
20. Lin J, Kimoto E, Yamazaki S, Vourvahis M, Bergman A, Rodrigues AD, et al. Effect of hepatic impairment on OATP1B activity: Quantitative pharmacokinetic analysis of endogenous biomarker and substrate drugs. *Clin Pharmacol Ther.* 2023;113(5):1058-69. doi:10.1002/cpt.2829
21. Small BG, Hatley O, Jamei M, Gardner I, Johnson TN. Incorporation and performance verification of hepatic portal blood flow shunting in minimal and full PBPK models of liver cirrhosis. *Clin Pharmacol Ther.* 2023;114(6):1264-73. doi:10.1002/cpt.3032

22. Storelli F, Ladumor MK, Liang X, Lai Y, Chothe PP, Enogieru OJ, et al. Toward improved predictions of pharmacokinetics of transported drugs in hepatic impairment: Insights from the extended clearance model. *CPT Pharmacometrics Syst Pharmacol*. 2024;13(1):118-31. doi:10.1002/psp4.13062
23. Tang LWT, Varma MVS. Hepatic impairment and the differential effects on drug clearance mechanisms: Analysis of pharmacokinetic changes in disease state. *Clin Pharmacol Ther*. 2025;118(3):673-81. doi:10.1002/cpt.3643
24. Kanodia J, Giovinazzo H, Yates W, Bourdet DL, McRae MP, Helmke SM, et al. Hepatic dysfunction quantified by HepQuant DuO outperforms Child-Pugh classification in predicting the pharmacokinetics of ampreloxetine. *Clin Pharmacol Ther*. 2024;116(1):186-93. doi:10.1002/cpt.3265
25. Mercier AK, Sunnåker M, Ueckert S, Pawlik T, Henricson E, Molodetskyi O, et al. Pharmacokinetics and tolerability of zibotentan in patients with concurrent moderate renal and moderate hepatic impairment. *Clin Pharmacokinet*. 2023;62(12):1713-24. doi:10.1007/s40262-023-01306-7
26. Lumen A, Zhang X, Dutta S, Upreti VV. Predicting clinical pharmacokinetics/pharmacodynamics and impact of organ impairment on siRNA-based therapeutics using a mechanistic physiologically-based pharmacokinetic-pharmacodynamic model. *Clin Pharmacol Ther*. 2024;115(5):1054-64. doi:10.1002/cpt.3160
27. Okudaira N, Burt H, Mitra A. Tipifarnib physiologically-based pharmacokinetic modeling to assess drug-drug interaction, organ impairment, and biopharmaceutics in healthy subjects and cancer patients. *CPT Pharmacometrics Syst Pharmacol*. 2024;13(8):1366-79. doi:10.1002/psp4.13165
28. Chen S, Shen C, Tian Y, Peng Y, Hu J, Xie H, et al. Physiologically based pharmacokinetic modeling and simulation of topiramate in populations with renal and hepatic impairment and considerations for drug-drug interactions. *CPT Pharmacometrics Syst Pharmacol*. 2025;14(3):510-22. doi:10.1002/psp4.13292
29. Xu D, Lutz JD, Divanji P, Li J, Benattia Y, Griffith A, et al. Effect of hepatic impairment or renal impairment on the pharmacokinetics of aficamten. *Clin Pharmacokinet*. 2025;64(3):397-406. doi:10.1007/s40262-025-01481-9
30. Ozbey AC, Meneses-Lorente G, Simmons B, McCallum S, Annaert P, Parrott N, et al. Clinical exploration and physiologically based modelling of the impact of hepatic impairment on entrectinib pharmacokinetics. *Clin Pharmacokinet*. 2025;64(3):437-51. doi:10.1007/s40262-024-01468-y
31. Leegwater E, Baidjoe L, Wilms EB, Visser LG, Touw DJ, de Winter BCM, et al. Population pharmacokinetics of trimethoprim/sulfamethoxazole: Dosage optimization for patients with renal insufficiency or receiving continuous renal replacement therapy. *Clin Pharmacol Ther*. 2025;117(1):184-92. doi:10.1002/cpt.3421
32. Yamada T, Oda K, Nishihara M, Neo M. A simulation study on model-informed precision dosing of amikacin for achieving target area under the concentration-time curve. *Br J Clin Pharmacol*. 2024;90(4):1173-82. doi:10.1111/bcp.16002
33. Zhang D, Zhang Z, Lee A, Fenton K, Jain S, Garg A, et al. Time-varying brentuximab vedotin pharmacokinetics and weight-based dosing in paediatric patients despite lower exposure in those aged 2 to <6 and 6-11 years. *Br J Clin Pharmacol*. 2024;90(9):2299-313. doi:10.1111/bcp.16128
34. Qosa H, Younis IR, Sahasrabudhe V, Sharma A, Yan J, Galluppi G, et al. Opportunities and challenges of hepatic impairment physiologically based pharmacokinetic modeling in drug development—An IQ perspective. *Clin Pharmacol Ther*. 2025;117(6):1682-6. doi:10.1002/cpt.3601