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MODEL-INFORMED PRECISION DOSING AT THE BEDSIDE: CAN BAYESIAN TOOLS REDEFINE ANTIMICROBIAL THERAPY IN THE CRITICALLY ILL?

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ABSTRACT

Standard antimicrobial doses fail a measurable fraction of critically ill patients: in the DALI point-prevalence study, 16% of infected patients did not keep free β-lactam concentrations above the MIC for even half of the dosing interval, and those patients had lower odds of a good outcome. Bayesian model-informed precision dosing (MIPD) combines a population pharmacokinetic model with patient covariates and one or two measured concentrations to forecast exposure and propose a dose. This narrative review examines whether the approach has changed outcomes at the bedside. For vancomycin, Bayesian AUC-guided dosing has become the method preferred by the 2020 consensus guideline and has been associated with less nephrotoxicity. For β-lactams and ciprofloxacin the picture is different. Three randomised trials with 889 analysed patients (TARGET, DOLPHIN and AutoKinetics) found no improvement in organ dysfunction, length of stay or mortality, and in the largest target attainment did not improve either. The trials share weaknesses: late dose advice, unvalidated models, capped doses and unselected populations. Bayesian tools have refined how exposure is estimated; they have not yet been tested in a form that could redefine therapy. The design that would test them is described.

Keywords: model-informed precision dosing; Bayesian forecasting; therapeutic drug monitoring; critical illness; sepsis; beta-lactams; vancomycin; pharmacokinetics; intensive care units.

1. Introduction

Antimicrobial doses printed in a product label are derived from volunteers and from patients who are not critically ill. Sepsis changes almost every determinant of drug exposure at once. Capillary leak and fluid resuscitation expand the volume of distribution of hydrophilic drugs, renal clearance can be either abolished or raised above normal, and both shift within hours [1]. The consequence was quantified by the DALI study, a point-prevalence survey of eight β-lactams in 384 patients across 68 hospitals: of the 248 patients treated for infection, 16% failed to maintain free concentrations above the minimum inhibitory concentration (MIC) for 50% of the dosing interval, and that group was 32% less likely to have a positive clinical outcome (odds ratio 0.68, p = 0.009) [2]. Renal hyperfiltration is one mechanism. In a four-centre cohort of 281 intensive care unit (ICU) patients with normal plasma creatinine, who contributed 1660 measured creatinine clearances, augmented renal clearance (at least 130 mL/min/1.73 m²) proved common soon after admission [3].

Guidelines have responded with principle more than with method. The 2021 Surviving Sepsis Campaign guideline issues a best-practice statement that dosing should be optimised according to pharmacokinetic and pharmacodynamic (PK/PD) properties, without specifying how [4]. A position paper endorsed by four international societies went further and recommended routine therapeutic drug monitoring (TDM) in critically ill adults for aminoglycosides, β-lactams, linezolid, teicoplanin, vancomycin and voriconazole [1]. French guidelines for β-lactams in the ICU, written by an 18-member panel, advise personalised dosing, prolonged or continuous infusion and TDM, with free concentrations held above the MIC of the causative organism for the whole dosing interval [5].

Conventional TDM answers a narrow question: was this concentration, at this time, inside a range? It says little about what dose to give next when the patient is not at steady state, when sampling was mistimed, or when clearance is changing. Bayesian forecasting was devised to close that gap. The statistical basis was set out by Sheiner and colleagues in 1979 [6], and its modern clinical form is called model-informed precision dosing (MIPD): a mathematical framework that integrates several sources of information about a patient to individualise a regimen [7]. Software that performs the calculation at the bedside is now widely available [8], yet a 2017 analysis asked why MIPD had still not become ordinary practice [9], and the question remains fair.

Two developments make the question timely. Three randomised trials of individualised dosing in the ICU reported within a single year, all without a clinical benefit [10,11,12]. In 2024 the largest trial yet conducted of β-lactam administration, with 7031 patients, and its companion meta-analysis shifted the standard of care toward prolonged infusion [13,14]. Any claim for Bayesian dosing now has to be made against that background.

The title of this review poses a stronger question than whether Bayesian tools are elegant. It asks whether they can redefine therapy, which means changing what happens to patients. The review therefore follows the evidence in the order a sceptical clinician would: what the tools do, where they have already changed practice, what the randomised trials in critically ill patients found, why those trials turned out as they did, and what would have to be true for a future trial to give a different answer. The argument advanced is that Bayesian MIPD has so far improved the estimation of exposure more than it has improved outcomes, and that the reasons are mostly problems of implementation and trial design that can be named and fixed.

2. Scope and Approach

This is a narrative review. Literature was identified between 16 and 17 November 2026 through searches of PubMed-indexed records and publisher pages using combinations of the terms model-informed precision dosing, Bayesian forecasting, dosing software, therapeutic drug monitoring, critically ill, intensive care, sepsis, β-lactam, vancomycin and ciprofloxacin, followed by citation tracking from recent reviews and from the editorials accompanying the main trials. Priority was given to randomised and prospective controlled studies in adult ICU patients, to systematic reviews with meta-analysis, to external evaluations of population pharmacokinetic models, and to consensus guidelines. Antifungal, antiviral and paediatric dosing were outside scope except where a study enrolled mixed populations.

No new pooled analysis was performed. The three randomised trials that tested a dosing intervention against standard care differ in the intervention itself (TDM without software, TDM with Bayesian software, and model predictions driven by electronic health record data), in the drugs studied and in the primary endpoint (organ dysfunction score, ICU length of stay, and pharmacokinetic target attainment). A single summary estimate across them would average over three different questions. Published meta-analyses of TDM-guided dosing are instead summarised in Section 5.3. Every numerical value in the text, tables and figures is taken from the cited source at the precision reported there.

3. How a Bayesian Dosing Tool Works

A Bayesian dosing tool begins with a population pharmacokinetic model: equations for clearance and volume of distribution, the covariates that shift them (renal function, body weight, renal replacement therapy), and the amount of variability between patients that the covariates leave unexplained. Before any drug concentration is measured, the model can already suggest a dose from the covariates alone. This is a priori dosing. Its precision is limited by the unexplained variability, which in critical illness is large. In a retrospective single-centre study of 78 patients summarised in a recent review, the probability of attaining the target was 29% when regimens were predicted from covariates alone

and 83% once measured concentrations were used [15].

Once a concentration is measured, the tool updates. Maximum a posteriori estimation finds the individual clearance and volume that best reconcile two things: the measured concentration, weighted by assay and model error, and the population distribution, which acts as the prior. A concentration that is plausible under the population model moves the estimate little. An unexpected one moves it more, but not all the way, because a single sample is never fully trusted. With the individual parameters in hand, the tool simulates the concentration-time course under any candidate regimen and reports which regimen is most likely to meet the chosen target (Figure 1).

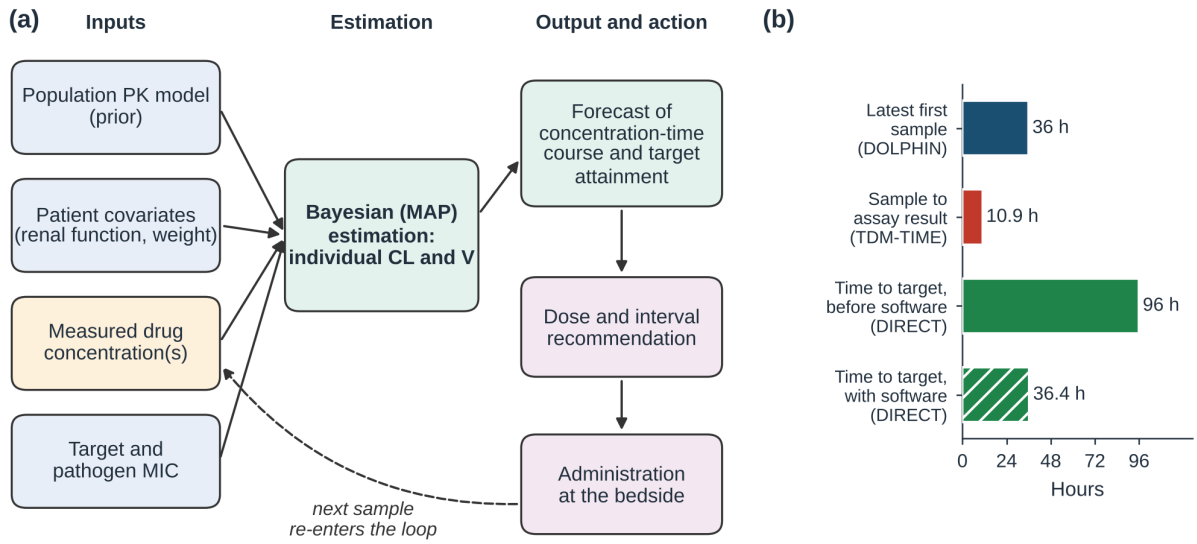


Figure 1. Bayesian model-informed precision dosing as a feedback loop, and the delays that limit it at the bedside. (a) A population pharmacokinetic model supplies the prior; patient covariates and one or more measured concentrations update it by maximum a posteriori (MAP) estimation into individual clearance (CL) and volume of distribution (V), from which the concentration-time course and the probability of attaining the pharmacodynamic target are forecast for candidate regimens. The recommended dose is given and the next sample re-enters the loop. (b) Time elapsed from the first antibiotic dose in three clinical studies: latest permitted time of the first sample in the DOLPHIN trial (36 h) [11]; median time from sampling to an available β-lactam assay result in the TDM-TIME feasibility study (10.9 h, n = 30) [16]; and median time to target exposure, among antibiotic courses that missed the target at 24 h, before (96 h) and after (36.4 h) introduction of Bayesian dosing software in the DIRECT study [17]. Bars are the values reported in each source; no error bars are shown because the sources report them in different forms. MIC, minimum inhibitory concentration; EHR, electronic health record.

Three properties follow from this arithmetic and explain the appeal of the method. Sampling need not wait for steady state, since the model accounts for where on the accumulation curve the sample fell. Sampling times need not be exact, only recorded. And the target can be an exposure that is never measured directly, such as the 24 h area under the concentration-time curve

(AUC), which the tool computes from the individual parameters [7].

Which target the tool is asked to hit depends on the drug class. β-Lactams are time-dependent: the index is the fraction of the dosing interval during which the free concentration exceeds the MIC, and recommendations for the critically ill run from 100% of the interval above the MIC [5] to the four-fold multiple used in the TARGET trial [10]. Vancomycin efficacy and nephrotoxicity both track the 24 h AUC [18,19]. The tool therefore reads a different quantity off the individual curve for each class, a concentration relative to the MIC for a β-lactam and an integral for vancomycin, while the Bayesian step stays the same. This generality is why one software platform can cover many drugs. It is also why a platform's performance for one drug says nothing about its performance for another.

The same arithmetic exposes the method's dependencies. The forecast is only as good as the prior, and a model built in one population may describe another badly. The target must be specified by the user, including the MIC against which exposure is judged. The loop also runs at the speed of its slowest step, which in most hospitals is the assay. Keizer and colleagues noted in 2018 that the diagnostics pharmacometricians use to accept a model for drug development are not the ones that establish whether it forecasts well for the next patient, and that MIPD needs its own standards of predictive performance [8]. Each of these dependencies reappears in the clinical trials discussed below.

4. Vancomycin: Where Bayesian Dosing Became the Standard

Vancomycin is the one antimicrobial for which Bayesian dosing has moved from option to recommendation. The 2020 consensus guideline from four United States societies abandoned trough-only monitoring at 15 to 20 mg/L and named Bayesian software, built on a richly sampled prior model and applied to one or two concentrations, as the preferred way to estimate the AUC [18]. The recommended exposure is an AUC to MIC ratio of 400 to 600, assuming an MIC of 1 mg/L. Two samples are preferred, one drawn 1 to 2 h after the infusion and one at the end of the dosing interval, although the Bayesian estimate can be made from a single trough. Because it does not require steady state, target attainment can be assessed early in a course [18].

The shift rested on safety more than on cure. A meta-analysis of eight observational studies with 2491 patients found that an AUC below approximately 650 mg·h/L was associated with less acute kidney injury, both when measured over the first 24 h (odds ratio 0.36, 95% CI 0.23 to 0.56) and over the second (0.45, 0.27 to 0.75), and that AUC-guided monitoring carried a lower risk than trough-guided monitoring (0.68, 0.46 to 0.99) [19]. The prospective evidence most often cited is the three-year study by Neely and colleagues in 252 adults. In the first year clinicians targeted troughs; in the second and third the study team dosed with the BestDose Bayesian software to an AUC/MIC of at least 400 with a ceiling AUC of 800 mg·h/L. Only 19% of trough concentrations were in the

therapeutic range, against 70% of AUCs. Across the three years nephrotoxicity occurred in 8%, 0% and 2% of patients, duration of therapy fell from 8.2 to 5.4 and 4.7 days, and fewer additional blood samples were drawn per patient[20].

How far does this support the larger claim? Less far than it is usually made to. The Neely study compared sequential years, not randomised groups, and the case mix differed: pneumonia and bacteraemia were significantly more frequent in the third year than in the first two [20]. The meta-analytic comparison of monitoring strategies drew on two studies only [19]. The enrolled adults were not selected for critical illness. What vancomycin shows is that a Bayesian tool can deliver a lower, better-controlled exposure and that the lower exposure is safer for the kidney. It is a result about avoiding toxicity from a drug with a narrow margin, obtained with a target (AUC) that cannot be read from a single trough. β-Lactams present the opposite problem: a wide margin, a target defined by time above a threshold, and a concern about too little drug more than too much.

Even for vancomycin, the choice of model matters in the ICU. When 31 published population models were tested against data from 292 hospitalised patients, forecasting performance varied widely; the best-performing model showed a relative bias of -4.41% but a relative root mean squared error of 44.3% [21]. A companion evaluation restricted to ICU patients found only four models clinically acceptable with Bayesian forecasting, and showed that renal replacement therapy and sex altered the performance of the leading model [22]. A tool that is preferred by guidelines is therefore still a tool whose embedded model has to be checked against the patients it will be used on.

5. β-Lactams and Ciprofloxacin: The Randomised Evidence

5.1. Three Trials

Between February and November 2022, three randomised trials reported on individualised dosing of β-lactams, and in two cases ciprofloxacin, in critically ill adults (Table 1). They were not three tests of the same intervention, and the differences are instructive.

Table 1. Controlled studies of individualised antimicrobial dosing discussed in this review. Target attainment and clinical outcomes are given as intervention versus comparator.

Study	Design and setting	Patients analysed	Drugs	Intervention	Target attainment	Main clinical result
Neely 2018 [20]	Prospective, three sequential years; hospitalised adults	252	Vancomycin	Bayesian AUC-guided dosing (BestDose) vs trough-guided	70% of AUCs vs 19% of troughs in range	Nephrotoxicity 8% (year 1) vs 0% and 2% (years 2, 3)
Hagel 2022, TARGET [10]	Randomised; 13 ICUs, Germany	249	Piperacillin/tazobactam, continuous infusion	Daily TDM, no dosing software, vs fixed dose	37.3% vs 14.6%	Mean SOFA 7.9 vs 8.2 (p = 0.39); 28-day mortality 21.6% vs 25.8%

Study	Design and setting	Patients analysed	Drugs	Intervention	Target attainment	Main clinical result
						(p = 0.44)
Ewoldt 2022, DOLPHIN [11]	Randomised, open-label; 8 hospitals, the Netherlands	388	β-Lactams, ciprofloxacin, intermittent infusion	TDM with Bayesian software (InsightRX) vs standard dosing	Day 1: 55.6% vs 60.9%; day 3: 59.5% vs 60.4%	Median ICU stay 10 vs 8 days (IRR 1.16, 95% CI 0.96 to 1.41; p = 0.13)
Roggeveen 2022 [12]	Randomised; 2 centres, the Netherlands	252	Ciprofloxacin, vancomycin, meropenem, ceftriaxone	Bedside decision support from EHR data (AutoKinetics) vs standard	Ciprofloxacin 69% vs 3%; no gain for the other three	No significant difference in mortality, ICU stay or kidney injury
Chai 2024, DIRECT [17]	Prospective, non-randomised, before-after; 3 adult and 1 paediatric ICU	54 participants (61 courses) below target at 24 h	Antibiotics for sepsis, including β-lactams	Bayesian software (ID-ODS) vs prior practice	Time to target 36.4 h vs 96 h (p < 0.01)	Not powered for clinical outcomes

AUC, area under the concentration-time curve; EHR, electronic health record; ICU, intensive care unit; IRR, incidence rate ratio; SOFA, Sequential Organ Failure Assessment; TDM, therapeutic drug monitoring.

TARGET tested TDM alone. Across 13 German ICUs, 254 adults with sepsis or septic shock were randomised and 249 were evaluable. All received piperacillin/tazobactam by continuous infusion; in the intervention arm the dose was adjusted daily to bring free piperacillin to four times the MIC, within a tolerance of 20%, and in the control arm it was fixed. Mean daily SOFA score over ten days was 7.9 with TDM and 8.2 without (p = 0.39). Mortality at 28 days was 21.6% against 25.8% (p = 0.44), and clinical cure at the end of therapy was recorded in 21 of 59 against 12 of 69 assessable patients, neither difference being significant. Target attainment improved from 14.6% to 37.3% of days (odds ratio 4.5, 95% CI 2.9 to 6.9) [10]. Read that last figure again. Even with a daily measured concentration and a continuous infusion, patients were inside the target window on barely more than one day in three. The investigators stated that no dosing algorithm or software had been used and that attainment might have been higher with one [10]. TARGET thus defined the opening that a Bayesian tool was supposed to fill.

DOLPHIN tested the tool. In eight Dutch hospitals, ICU patients starting a β-lactam or ciprofloxacin by intermittent infusion were randomised to standard dosing or to MIPD, in which measured concentrations were entered into commercial Bayesian software and a dose and interval were recommended. The analysis included 388 patients, 189 assigned to MIPD and 199 to standard dosing, with a median age of 64 years. Median ICU length of stay, the primary outcome, was 10 days with MIPD and 8 days with standard dosing (incidence rate ratio 1.16, 95% CI 0.96 to 1.41; p = 0.13). No secondary outcome differed. The pharmacokinetic result is the more striking one: target attainment was

55.6% against 60.9% on the first sampling day, before any advice could act, and 59.5% against 60.4% on day 3, after it had [11]. The intervention did not change the variable through which it was meant to work (Figure 2).

Two features of the design bear on that result. Dosing in the standard arm was not frozen: attending physicians could adjust it freely under local guidelines, while blood was sampled on the same schedule and analysed later in bulk [11]. And the editorial accompanying the trial observed that attainment in the MIPD arm never exceeded 71.4% at any sampling moment [23]. DOLPHIN was the first multicentre trial of MIPD in critically ill patients [23]. It is best read as a test of one implementation under routine conditions, and what it established is that adding software to a sample taken on the first or second day of treatment is not enough.

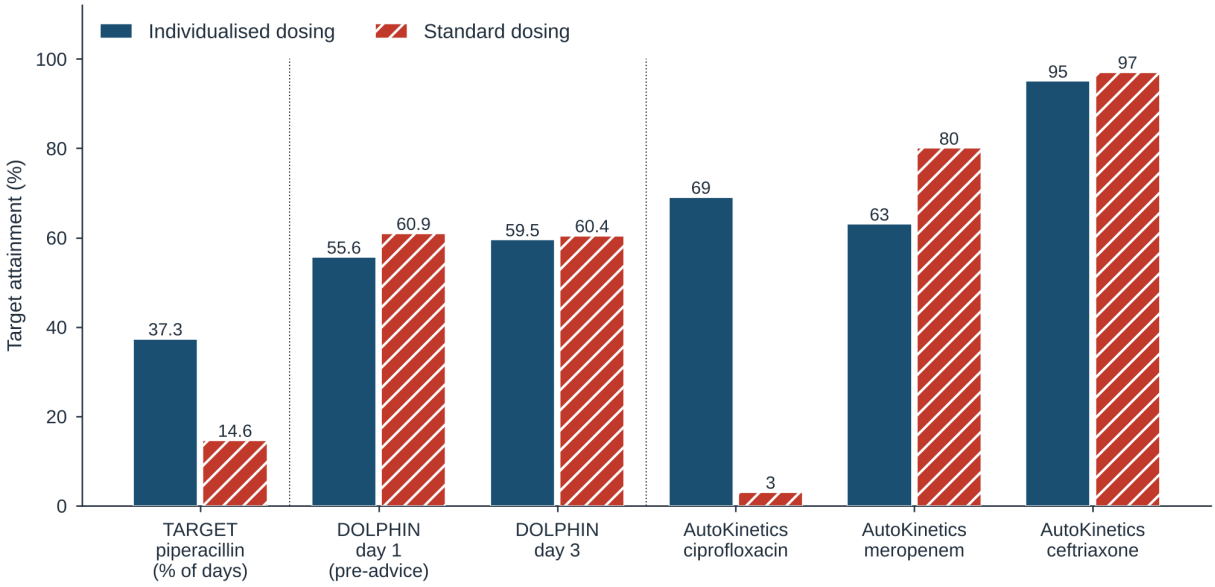


Figure 2. Pharmacokinetic target attainment with individualised versus standard dosing in the three randomised trials. Bars show the percentage of patients (or, for TARGET, of treatment days) meeting the trial's own target in the intervention arm and the comparator arm. TARGET: daily TDM of piperacillin without software [10]. DOLPHIN: Bayesian software with TDM, first sampling day (day 1, before dose advice) and day 3 [11]. AutoKinetics: bedside decision support, attainment in the first 24 h for ciprofloxacin [12], meropenem and ceftriaxone as tabulated in [15]. Targets were defined differently in each trial (a concentration window around four times the MIC in TARGET; drug-specific pharmacodynamic targets in DOLPHIN and AutoKinetics), so bar heights are comparable within a trial and not between trials.

The third trial removed the assay from the loop. AutoKinetics is a decision-support system that feeds electronic health record data into pharmacokinetic models and displays a dose recommendation at the bedside in real time. In two Dutch centres, patients with infection and either a lactate above 2 mmol/L or a vasopressor requirement were randomised to AutoKinetics or standard dosing of ciprofloxacin, vancomycin, meropenem or ceftriaxone; recruitment stopped at 252 patients because of the COVID-19 pandemic. For ciprofloxacin, the 24 h target was reached in 69% of the intervention group and 3% of controls (odds ratio 62.5), and it was reached

26 h sooner (95% CI 18 to 42 h). For the other three drugs attainment did not improve, and for meropenem it was numerically lower with the intervention (63% against 80%) [12,15]. Mortality, ICU stay and acute kidney injury did not differ, and higher dosing did not increase harm [12]. The accompanying economic evaluation found higher societal costs in the intervention group (EUR 42,684 against EUR 39,475) and a probability of cost-effectiveness below 60% at most willingness-to-pay thresholds, and concluded that the system as implemented could not be recommended on economic grounds [24].

5.2. Non-Randomised Evidence

One prospective study points the other way on the pharmacokinetic endpoint. In the DIRECT study, conducted in three adult ICUs and one paediatric ICU, clinicians trained in the ID-ODS Bayesian software issued dose recommendations for patients with sepsis in a second phase, after a first phase of observation. Sixty-one antibiotic courses in 54 participants had missed target exposure within 24 h of starting treatment, 36 in the first phase and 18 in the second. Among those, the median time to reach target fell from 96 h to 36.4 h ($p < 0.01$) [17]. The design was before-after and not randomised, the comparison concerns the subgroup that began below target, and the authors called for trials of clinical outcome. Even so, the result isolates what the software is good at: rescuing the patient who has been shown to be under-exposed.

Smaller series tabulated in a 2026 review show the same pattern. Two prospective cohorts using ID-ODS, of 70 and 25 patients, recorded 24 h attainment of 85% and 86% for piperacillin/tazobactam and 95% and 100% for meropenem, without a comparator. A retrospective cohort of 140 patients found clinical cure in 60% with model-guided dosing against 52% with standard dosing, and hospital mortality of 39% against 36%, neither difference being significant [15].

5.3. Meta-Analyses

Two systematic reviews with different inclusion rules reach different conclusions, and the difference is itself informative. Pai Mangalore and colleagues pooled randomised and observational studies of β-lactam TDM in critically ill patients and found associations with clinical cure (relative risk 1.17, 95% CI 1.04 to 1.31), microbiological cure (1.14, 1.03 to 1.27), less treatment failure (0.79, 0.66 to 0.94) and target attainment (1.85, 1.08 to 3.16), but none with mortality or length of stay [25]. Takahashi and colleagues restricted the analysis to randomised trials of TDM-based regimens in critically ill patients. Five trials with 1011 patients contributed to 28-day mortality, for which the risk ratio was 0.94 (95% CI 0.77 to 1.14; I^2 = 0%); in-hospital mortality (0.96, 0.76 to 1.20), clinical cure (1.23, 0.91 to 1.67) and day-1 target attainment (1.14, 0.88 to 1.48) were likewise not significantly different [26]. When observational studies are removed, the benefit on cure loses significance while the point estimates stay on the favourable side of unity. That pattern is what confounding by indication would produce. It is also what an underpowered set of trials with

weak interventions would produce, and the data cannot yet distinguish the two readings. A 2026 review confined to β-lactam MIPD in critical care reached the same position: possible gains in target attainment and cure, no demonstrated reduction in mortality, and heterogeneity of design too great for a firm conclusion [15].

5.4. Over-Exposure

Individualised dosing is usually argued from the risk of too little drug. The trials also bear on too much. In TARGET the odds of a piperacillin concentration above the target window were halved by TDM (odds ratio 0.5, 95% CI 0.2 to 0.9), whereas the reduction in concentrations below it did not reach significance (0.6, 0.3 to 1.2) [10]. AutoKinetics raised ciprofloxacin exposure without an increase in mortality or renal failure [12]. For vancomycin the whole clinical case rests on lowering exposure [19,20]. A tool that reliably trims the upper tail of the exposure distribution has value for drugs with concentration-related toxicity even if it never alters cure rates. That benefit is also easier to demonstrate, because the event (kidney injury, or a concentration above a toxicity threshold) lies closer to the intervention than survival does.

6. Why the Trials Found What They Found

A null trial of a plausible intervention has three possible explanations. The hypothesis is wrong, the intervention was not delivered, or the trial could not detect the effect. For Bayesian dosing of β-lactams, the published critiques and secondary analyses supply evidence for the second and third (Table 2).

Table 2. Points at which Bayesian dosing lost its effect in the randomised trials, with the supporting observation and a corresponding design remedy.

Point of failure	Observation	Remedy for a future trial
Timing of first advice	First sample up to 36 h after the first dose in DOLPHIN, with standard dosing until then [11,27]; median 10.9 h from sample to assay result in a 2026 feasibility study [16]	A priori model-based dose from the first administration; assay result within one dosing interval
Model fitness	A priori bias of 24 piperacillin models ranged from -135.6% to 78.3% in 561 ICU patients [28]; models used in DOLPHIN lacked published external evaluation [27]	Externally evaluated models, or automated model selection and averaging [29]
Dose ceiling	Protocol maxima (18 g piperacillin/tazobactam, 6 g meropenem per day); 40% non-attainment but 13.3% dose changes at the fifth sampling day [27]	Permit doses above label where the forecast requires and toxicity monitoring is in place
Target and MIC	A single MIC measurement cannot be determined accurately enough to guide dose [30]; attainment in the MIPD arm stayed between 55.6% and 71.4% [23]	Targets set against epidemiological cut-off values, with an upper bound for toxicity
Population	Unselected ICU patients; a subgroup signal in those with baseline SOFA below 8 [31]	Enrichment for sepsis with predicted pharmacokinetic extremes
Endpoint	ICU stay and SOFA respond to many influences besides antibiotic exposure; procalcitonin course did not differ between arms [32]	Clinical cure or mortality in a trial sized for a modest effect
Comparator	Prolonged infusion is itself associated with lower 90-day mortality [14]	Test MIPD on top of continuous infusion

6.1. The Intervention Arrived Late

Sepsis is decided early. In DOLPHIN the first sample could be drawn as late as 36 h after the first dose, the assay had a turnaround target of a further 12 h, and until then both arms received the same standard regimen [11,16]. A correspondence from a pharmacometric group made the point directly: for the period that matters most, there was effectively no difference between the two groups [27]. The editorial that accompanied the trial argued that timely refinement requires a short turnaround between sampling and reported result [23]. That requirement is hard to meet outside a research setting. A 2026 feasibility study of real-time β-lactam monitoring in 30 critically ill patients with lower respiratory infection obtained a result within two dosing intervals of sampling in 20 patients (67%), with a median of 10.9 h from sample to result [16]. The DIRECT data show the other side of the same coin: where software was applied to patients known to be below target, time to target fell by more than half [17]. Speed, not the Bayesian calculation, was the limiting reagent.

6.2. The Models Were Not Shown to Fit

A Bayesian forecast inherits the errors of its prior. The largest external evaluation in this field assembled 3654 piperacillin concentrations from 561 ICU patients at 11 centres and tested 24 published models. Predicting from covariates alone, the median prediction error ranged from -135.6% to 78.3% between models and the median absolute error from 35.7% to 135.6%. Adding TDM samples improved every model, and a small number were identified as suitable for clinical use [28]. Two implications follow. Choosing a model at random from the literature is unsafe. And the models embedded in the software used in DOLPHIN had, according to the critics, no publicly available external validation, while an independent evaluation of the meropenem models involved had shown high bias or low precision [27]. A trial of MIPD with a poorly fitting model is a trial of the model.

6.3. The Recommended Dose Could Not Always Be Given

DOLPHIN capped daily doses, at 18 g for piperacillin/tazobactam and 6 g for meropenem. The same correspondence noted that at the fifth sampling day 40% of patients in the MIPD arm were still below target while only 13.3% had their dose adjusted [27]. A forecast that calls for a dose the protocol forbids changes nothing. This is a design choice with a defensible motive, since supra-label doses carry risk, but it converts a test of precision dosing into a test of dose reduction and modest rearrangement.

6.4. The Target Was Uncertain

Every forecast is judged against a target, and for β-lactams the target is a multiple of the MIC held for a fraction of the dosing interval. The optimal multiple is not agreed [15]. The MIC is a weaker anchor than it appears: Mouton and colleagues argued that routine laboratories cannot measure an individual MIC accurately enough to drive dose adjustment, because the inherent variation of the assay spans the range over which doses would change, and that this variation must be

allowed for to avoid under-dosing [30]. TARGET handled empirical therapy by assuming the epidemiological cut-off for *Pseudomonas aeruginosa*, 16 mg/L, which makes four times the MIC a demanding 64 mg/L [10]. A precise estimate of exposure compared against an imprecise threshold yields an imprecise decision.

6.5. Population and Endpoint Diluted the Effect

Most ICU patients given standard β-lactam doses reach conventional targets; in DOLPHIN about 60% did so in the control arm [11]. Only the remainder can benefit from being moved, and only if under-exposure was what stood between them and recovery. Randomising all comers therefore dilutes any effect by more than half before the trial begins. A post hoc analysis of DOLPHIN divided patients by baseline characteristics and reported lower 28-day mortality with MIPD among those whose SOFA score was below 8 [31]. Subgroup findings from a neutral trial generate hypotheses and nothing more, but this one suggests that the patients most likely to respond are not necessarily the sickest, in whom organ failure may be driven by factors no antibiotic concentration will reverse. Endpoints compound the problem. ICU length of stay depends on bed availability, withdrawal decisions and non-infectious complications. Mortality is the endpoint that matters, but TARGET observed only 59 deaths at 28 days among its 249 patients [10], and the 1.9 percentage point difference in 90-day mortality in BLING III fell short of significance with 7031 [13]. Trials of a few hundred patients can detect only effects larger than any dosing strategy has plausibly produced. A secondary analysis of 662 procalcitonin measurements from 351 DOLPHIN patients found no difference in the biomarker's course between arms [32], which is consistent with an intervention that did not change exposure.

6.6. The Ceiling Set by Infusion Strategy

A final consideration concerns what MIPD is being added to. The BLING III trial randomised 7031 patients with sepsis in 104 ICUs to continuous or intermittent infusion of piperacillin/tazobactam or meropenem; 90-day mortality was 24.9% and 26.8% respectively, a difference that did not reach statistical significance, with a higher rate of clinical cure in the continuous arm [13]. The meta-analysis that incorporated it, covering 18 trials and 9108 patients, estimated a risk ratio for 90-day mortality of 0.86 (95% credible interval 0.72 to 0.98) with prolonged infusion and a 99.1% posterior probability of benefit [14]. A simple change in how every patient receives the drug has, on this evidence, a mortality effect that no individualised dosing strategy has shown. DOLPHIN used intermittent infusion in both arms [11]. Whether Bayesian adjustment adds anything once continuous infusion is standard is an open question, and TARGET, which did use continuous infusion, suggests that large inter-patient variability persists under it [10].

7. Technical Advances Since the Trials

The methodological response to these failures has been faster than the clinical one. On model selection, Uster and colleagues derived two algorithms that remove the need for a human to choose the prior: one selects, for each patient, the best-fitting model from a candidate set as concentrations accrue, and the other averages the predictions of several models with weights that reflect their fit. Using vancomycin as the test case, in simulation and in a clinical dataset, both outperformed reliance on any single model [29]. The approach addresses the central weakness exposed by the piperacillin evaluation, since a set that contains at least one adequate model is easier to guarantee than a single correct choice.

A second line of work treats the prior as something a hospital can improve with its own data. Under continuous learning, an initial literature model is deployed and then re-estimated as routine clinical concentrations accumulate, so that it converges on the local population; a case study in paediatric vancomycin dosing examined how much additional data such tailoring requires [33]. A third replaces part of the Bayesian machinery. A hybrid of machine learning and pharmacokinetics, which selectively flattens the model prior, reduced root mean squared error by 5% to 18% relative to standard maximum a posteriori estimation [34]. Machine-learning classifiers have also been used to select or average models before any concentration is available, which is the phase in which the randomised trials were weakest [35].

Software has matured unevenly. A benchmarking study in which 22 experts weighted 103 criteria across eight categories, and then scored ten tools, found that all performed adequately but that integration with the electronic health record, standardised validation of software and models, and prospective evidence of clinical benefit were the outstanding deficiencies [36]. Those are the same three deficiencies the trials revealed. The ten tools comprised four commercial products (DoseMeRx, InsightRX Nova, MwPharm++ and PrecisePK) and six from non-commercial owners (AutoKinetics, BestDose, ID-ODS, NextDose, TDMx and Tucuxi). The experts rated privacy and data security as the most important category, with a mean score of 8.5 out of 10, and user-friendliness as the least, at 7.2 [36]. Sensor technology that would shorten the assay step, including minimally invasive microneedle-based devices, is under development but not in routine use [7].

These advances share a direction. Each moves effort from the measured concentration toward the prior, so that the first dose is better and dependence on a fast assay is less. None has been tested in a randomised trial with a clinical endpoint in critically ill adults, and the case studies on which they rest are mostly in vancomycin [29,33,35], a drug with a long history of routine monitoring and abundant data.

8. What a Decisive Trial Would Look Like

The evidence reviewed above specifies its own next experiment. The intervention should begin with the first dose, using an externally evaluated model or a model-averaging algorithm to set an a priori regimen from covariates, and should be refined by a concentration reported within one dosing interval. The software should be allowed to recommend doses above the label ceiling when the forecast requires them, with an explicit upper exposure limit to contain toxicity. Both arms should receive β-lactams by continuous infusion, because that is where standard care is heading and because the comparison of interest is MIPD against the best non-individualised practice. The population should be enriched for patients in whom pharmacokinetic extremes are likely: sepsis or septic shock in the first 24 h, augmented renal clearance or renal replacement therapy, and pathogens with reduced susceptibility. The primary endpoint should be clinical cure or mortality, and the sample size should be set for an effect smaller than the 4-point mortality difference that TARGET, with 249 patients, could not confirm [10].

Parts of this programme are in progress. The BULLSEYE trial is comparing standard with double dosing of β-lactams during the first 48 h of septic shock, a design that tests the early-exposure hypothesis directly and without waiting for an assay [37]. If doubling the dose for everyone improves outcome, the case for early individualisation is strengthened and the simplest form of it is already defined. If it does not, the hypothesis that under-exposure in the first two days drives mortality becomes harder to hold, and with it the main rationale for MIPD of β-lactams. A second trial, OPTIBETA, is a pragmatic open-label randomised comparison of TDM-guided and standard β-lactam dosing in patients with sepsis at a tertiary hospital in Spain, with time to clinical cure as its outcome [38].

There is also a narrower role that needs no further trial to justify. For vancomycin, Bayesian estimation gives a more reliable account of exposure than a single trough read against a range, and the consensus guideline already says so [18]; for aminoglycosides and the other agents with established monitoring, routine TDM is recommended in the critically ill and software is a natural way to interpret it [1]. In that role the tools are aids to estimation and safety. The claim under examination in this review is larger.

9. Implications for Current Practice

What should an ICU do while that trial is awaited? Four positions follow from the evidence.

Prolonged infusion of β-lactams comes first. It needs no assay and no software, and it is the only dosing strategy in this field with a pooled estimate for mortality whose credible interval excludes no effect [14].

For vancomycin, Bayesian AUC estimation is established practice under the current consensus guideline, and the remaining task is local: confirming that the model embedded in the chosen software forecasts acceptably in the unit's

own patients, particularly those receiving renal replacement therapy [18,22].

For β-lactams, measurement is recommended by the position paper and by national guidelines [1,5], but the randomised evidence does not support applying TDM or MIPD to every patient in the expectation of better outcomes [10,11,26]. A selective policy is easier to defend: augmented renal clearance, renal replacement therapy, infection with a less susceptible organism, or failure to improve. These are the circumstances in which the DALI and DIRECT data locate under-exposure [2,17], and in which a result returned in about eleven hours [16] still arrives in time to matter.

Finally, software should be treated as a device whose performance is a local empirical question. Before a Bayesian tool is used to change doses, its a priori and Bayesian predictions can be compared with stored concentrations from the unit, which is the procedure the external evaluations applied at scale [21,28]. A tool that fails that test should not be trusted on the strength of its interface.

None of this amounts to redefining therapy. It amounts to using an estimator where estimation is the bottleneck, and not asking it to compensate for late sampling, slow assays or protocols that forbid the dose it recommends.

10. Conclusion

Bayesian dosing tools do what they were designed to do: they turn sparse, mistimed concentrations into an individual estimate of exposure and a ranked set of regimens. For vancomycin that capability has changed guideline practice and has been associated with less kidney injury. For β-lactams and ciprofloxacin in the critically ill, three randomised trials have shown no improvement in organ dysfunction, length of stay or survival, and the trial that used Bayesian software did not improve target attainment. The explanation best supported by the published record is that the intervention reached patients late, relied on models of unproven fit, was prevented from recommending high doses, and was tested in unselected populations against endpoints with many other determinants. Bayesian tools have not redefined antimicrobial therapy in the ICU. Whether they can depends on a trial in which the model-based dose starts with the first administration, the model has been shown to fit, the assay returns within a dosing interval, and the comparator is continuous infusion. Until that trial reports, MIPD of β-lactams remains a well-reasoned hypothesis and prolonged infusion remains the dosing change with outcome evidence behind it.

Institutional Review Board Statement: Not applicable. This review analysed published literature only.

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; EHR, electronic health record; ICU, intensive care unit; IRR, incidence rate ratio; MAP, maximum a posteriori; MIC, minimum inhibitory concentration; MIPD, model-informed precision dosing; PK/PD,

pharmacokinetic/pharmacodynamic; SOFA, Sequential Organ Failure Assessment; TDM, therapeutic drug monitoring.

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