NARRATIVE REVIEW

OPEN

Setting the Beta-Lactam Therapeutic Range for Critically Ill Patients: Is There a Floor or Even a Ceiling?

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OBJECTIVES: Beta-lactam antibiotics exhibit high interindividual variability in drug concentrations in patients with critical illness which led to an interest in the use of therapeutic drug monitoring to improve effectiveness and safety. To implement therapeutic drug monitoring, it is necessary to define the beta-lactam therapeutic range—in essence, what drug concentration would prompt a clinician to make dose adjustments up or down. This objective of this narrative review was to summarize evidence for the "floor" (for effectiveness) and "ceiling" (for toxicity) for the beta-lactam therapeutic range to be used with individualized therapeutic drug monitoring.

DATA SOURCES: Research articles were sourced from PubMed using search term combinations of "pharmacokinetics," "pharmacodynamics," "toxicity," "neurotoxicity," "therapeutic drug monitoring," "beta-lactam," "cefepime," "meropenem," "piperacillin/tazobactam," "ICU," and "critical illness."

STUDY SELECTION: Articles were selected if they included preclinical, translational, or clinical data on pharmacokinetic and pharmacodynamic thresholds for effectiveness and safety for beta-lactams in critical illness.

DATA SYNTHESIS: Experimental data indicate a beta-lactam concentration above the minimum inhibitory concentration of the organism for greater than or equal to 40–60% of the dosing interval is needed, but clinical data indicate that higher concentrations may be preferrable. In the first 48 hours of critical illness, a free beta-lactam concentration at or above the susceptibility breakpoint of the most likely pathogen for 100% of the dosing interval would be reasonable (typically based on *Pseudomonas aeruginosa*). After 48 hours, the lowest acceptable concentration could be tailored to 1–2× the observed minimum inhibitory concentration of the organism for 100% of the dosing interval (often a more susceptible organism). Neurotoxicity is the primary dose-dependent adverse effect of beta-lactams, but the evidence remains insufficient to link a specific drug concentration to greater risk.

CONCLUSIONS: As studies advance the understanding of beta-lactam exposure and response in critically ill patients, it is essential to clearly define the acceptable therapeutic range to guide regimen selection and adjustment.

KEY WORDS: adverse events; antibiotic; intensive care; pharmacodynamics; pharmacokinetics; seizures

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BACKGROUND

Antibiotic pharmacokinetic-pharmacodynamic (PKPD) optimization in critically ill patients was explicitly recommended in recent guidelines and consensus statements from several international organizations involved with pharmacology, anesthesia, critical care, and infectious diseases (1–3). One strategy for

PKPD optimization of beta-lactams is the use of therapeutic drug monitoring (TDM) or drug concentration testing. To successfully deploy TDM in practice and in research, it is first necessary to define the preferred beta-lactam therapeutic range—in essence, what drug concentration should prompt the clinician to make dose adjustments up or down. This step is a necessary precursor for any beta-lactam TDM program, even if not yet widely available. The purpose for this narrative review was to summarize the evidence for the "floor" (for effectiveness) and the "ceiling" (for toxicity) of the beta-lactam therapeutic range and identify reasonable thresholds for critically ill patients.

FINDING THE FLOOR: A LOWER LIMIT THRESHOLD FOR BETA-LACTAM PKPD OPTIMIZATION

Rationale for Setting a Floor

There are two primary motivations for establishing an acceptable lower limit for beta-lactam concentrations: microbiological success and clinical success.

Microbiologic success not only reflects eradication of the present infection but also prevention of resistance for the patient and the community in the future. Once bacteria express or acquire new resistance genes, reverse evolution is uncommon. These resistance profiles may be amplified or transferred to otherwise susceptible bacterial populations which facilitates the spread of resistance (4). Estimates indicate that by 2050, resistant bacteria could contribute to 10,000,000 deaths annually worldwide (5, 6). *Pseudomonas aeruginosa* in particular is now isolated in 18% of Gram-negative infections in the ICU, and rates of resistance to broad-spectrum beta-lactams (e.g., cefepime, piperacillin/tazobactam, meropenem) have climbed to 30% (7, 8). This is especially worrisome because antibiotic development has stalled (9–11). Global health organizations recognize antibiotic resistance as a public health crisis and recommend efforts directed at prevention, appropriateness, preservation, and innovation (6, 9). Many of these are long-term priorities, but PKPD optimization is an immediate solution to preserve the existing antibiotics in our armamentarium.

Another reason to set a "floor" for the beta-lactam therapeutic range is to identify the lower limit most closely associated with clinical success. Whereas microbiologic success in vitro is largely a function of the antibiotic's activity against bacteria, clinical success is influenced by host factors such as immunosuppression (12) and physiologic reserve. One explanation for the 20–30% mortality that still exists in sepsis and septic shock is the interpatient variability in antibiotic exposure observed with standard therapy (13, 14). The current approach to beta-lactam dosing in ICU patients is a "one size fits all" strategy taken from data in the product information derived from noncritically ill patients (15) or small population-based studies in the ICU. Wide interindividual variability in the pharmacokinetics of critically ill patients has been observed with these strategies (16–18). With standard dosing in critically ill patients, at least 30-fold variation in beta-lactam trough concentrations occurred, which renders the clinical and microbiologic effects unpredictable (18–21). Beta-lactam concentrations may fall below an acceptable threshold as early as 90 minutes into the 6–12 hours dosing interval (22). Patients with low beta-lactam concentrations exhibit a 1.5-fold higher risk of clinical failure, need for antibiotic escalation, antibiotic reinitiation, or death (18). These issues are the central motivation for beta-lactam TDM.

PKPD Indices in General

Broadly, antibiotics have been classified as "concentration dependent" or "time dependent" based on their PKPD (23). Concentration-dependent agents (e.g., aminoglycosides, fluoroquinolones) exhibit a direct relationship between drug concentrations and bactericidal activity. In general, the pharmacodynamic index most closely associated with concentration-dependent killing is the ratio of the maximum drug concentration (Cmax) to the minimum inhibitory concentration (MIC) of the organism (see also **Table 1** for definitions). For time-dependent agents (e.g., beta-lactams), there is a minimum concentration required for antibacterial activity, but activity plateaus at higher concentrations. The time that the free drug fraction exceeds the MIC during the dosing interval ($fT_{>MIC}$) is the pharmacodynamic index most closely associated with time-dependent killing (**Fig. 1**). Often, only total drug concentrations are measured (bound and unbound drug); thus, time that the total drug concentration is above the MIC ($T_{>MIC}$) may be used as a surrogate for $fT_{>MIC}$ especially for beta-lactams with low protein binding. A third group merges these two concepts and

TABLE 1.
Pharmacokinetic and Pharmacodynamic Terminology Used for Antibiotics (24)

Term	Brief Description
Breakpoint	Concentrations that distinguish strains where there is a high likelihood of treatment success from those where failure is more likely (25).
Clinical success	Effect of the drug on the host, directly related not only to the drug-bacteria pair, but host susceptibility factors (i.e., immunosuppression, physiologic reserve) (9).
Cmax	Peak concentration observed after drug administration.
MIC	Minimum inhibitory concentration.
Microbiological success	Antimicrobial efficacy of the drug (9).
PAE	Postantibiotic effect; suppression of microbial growth after drug exposure (26); in vitro, this is assessed as the relative time required for bacterial counts to increase 1 $\log_{10}$ above the counts observed immediately after washing off the antibiotics compared with controls (24).
PKPD index	Pharmacokinetic/pharmacodynamic index; quantitative relationship between a pharmacokinetic variable (i.e., Cmax) and a microbiologic variable (i.e., MIC), also referred to as a PKPD index.
$fT_{>MIC}$	Percentage of time in 24 hr that the free drug concentration exceeds the MIC at steady state conditions.
$T_{>MIC}$	Percentage of time in 24 hr that the drug concentration (bound and unbound drug) exceeds the MIC at steady state conditions. May be used as a surrogate for $fT_{>MIC}$ especially for beta-lactams with low protein binding.

is pharmacodynamically defined by the optimal area under the concentration time curve (AUC) to MIC ratio (e.g., macrolides) (27). It is evident that it is not just amount of drug but also the shape of the concentration time curve that determine the clinical and microbiological effects (4, 28).

Evidence

In Vitro and Preclinical Models. In historical studies, it was challenging to untangle the optimal pharmacodynamic index for an antibiotic because the Cmax:MIC ratio, the AUC:MIC ratio, and the $T_{>MIC}$ were strongly correlated. In the 1940–1950s, Eagle et al (29) demonstrated in a mouse thigh infection model with *Streptococcus pyogenes* that the $T_{>MIC}$ for penicillin G predicted microbiological and clinical success. In the 1980–1990s, the seminal work of Craig and Ebert (30) with a neutropenic mouse thigh model extended these findings to provide detailed PKPD information across a variety of drugs, bacteria, and regimens. For beta-lactams, the $T_{>MIC}$ was consistently the pharmacodynamic index most associated with decreases in bacterial burden (**Fig. 2**). It is from these initial in vitro analyses with beta-lactams against *P. aeruginosa* and *Escherichia coli* that a threshold of 40–60% $T_{>MIC}$ to suppress bacterial growth was identified as a possible floor for the beta-lactam therapeutic window with concentrations up to 4× the MIC leading to maximal bactericidal activity. Gram-positive infections including with *Staphylococcus* species and *Streptococcus* species required lower exposure than Gram-negative infections, likely evidence of a modest postantibiotic effect. These data have since been reproduced (31).

In summary, based solely on the in vitro and preclinical evidence, $T_{>MIC}$ greater than 40–60% appears to be a reasonable "floor" pharmacodynamic index for bacteriostatic activity of beta-lactam antibiotics. Higher concentrations increased the potential for bactericidal activity. Gram-positive infections require lower treatment thresholds than Gram-negative infections. Other host factors that warrant higher thresholds based on the experimental evidence include higher bacteria inocula or reduced immune function (12). Even concentrations above the MIC may still lead to acquired antibiotic resistance (32).

Clinical Models. Overall, clinical studies suggest that the threshold PKPD index needed for microbiological and clinical success may be higher than the greater than 40–60% $T_{>MIC}$ observed in the in vitro

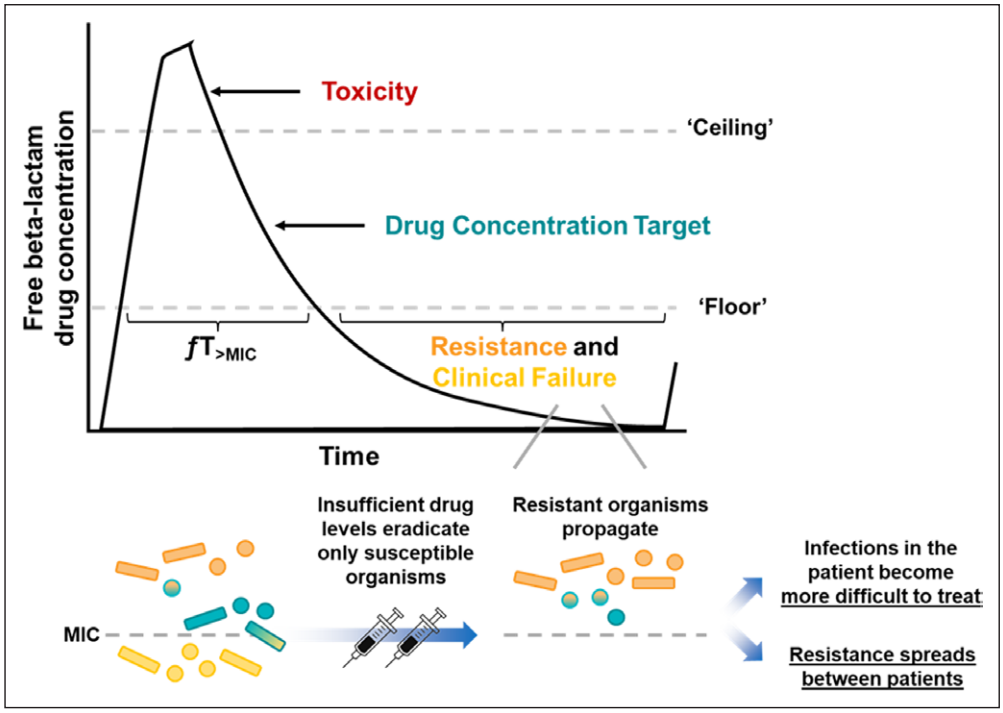

Figure 1. Conceptual model of the impact of beta-lactam drug concentrations on clinical and microbiologic outcomes. $fT_{>MIC}$: time the free drug concentration exceeds the minimum inhibitory concentration during the dosing interval.

and experimental data (18, 20, 26, 33–37), but findings are inconsistent (20, 38, 39). Illustrative studies that explore the relationship between PKPD indices of anti-Pseudomonal beta-lactams and clinical outcomes in adults are summarized in **Table S1** (http://links.lww.com/CCX/A654) (18, 20, 26, 33, 34, 37–41). Only slightly above the experimental thresholds, greater than 68–74% $fT_{>MIC}$ during the dosing interval best predicted survival in 180 adults treated with cefepime for a Gram-negative bacteremia (41). The Defining Antibiotic Levels in ICU study showed that a free beta-lactam concentration above the MIC for 50% and 100% of the dosing interval (50% $fT_{>MIC}$ and 100% $fT_{>MIC}$) was associated with a 1.02- and 1.56-fold greater likelihood of a favorable clinical outcome (18). This matches the data from other studies in critically ill adults, patients with sepsis, and the elderly that suggested a threshold of at least 75–100% $fT_{>MIC}$ predicted favorable treatment response (34, 35, 37). Select small studies have argued for higher thresholds yet, on the order of 4× the MIC for 100% of the dosing interval (33, 40). In one such example, data from 36 adults treated with cefepime indicated a drug concentration greater than 4.3-times the MIC for the dosing interval best achieved microbiologic success (33). These data have limitations (4). Many are small single-center evaluations. Others lack direct patient sampling and assume pharmacokinetic variables for patients based on population models. Compared with the experimental literature, which often uses a neutropenic animal model to isolate the precise effect of the antibiotic and the associated PKPD variables on a single organism, in practice, the conditions are much more variable. Critically ill patients experience extensive pharmacokinetic changes, diminished physiologic reserve, and varying degrees of immunosuppression. Infections are often disseminated, involve difficult to penetrate sites, are polymicrobial, or are culture negative (42). Studies also differ in whether they report free (unbound) or total (bound and unbound) drug concentrations which is important as the free drug fraction exerts the physiologic effects. In critical illness where hypoalbuminemia is common (16, 17), estimated free concentrations for highly protein bound beta-lactams (i.e., ceftriaxone, flucloxacillin) differ considerably from observed free concentrations (43). These studies also may include resistant organisms or concurrent use of several active drugs (i.e., dual therapy) (42). Finally, selected endpoints, their associated definitions, and degree of adjudication vary. Most studies include a marker of microbiologic success, but in only rare circumstances are follow-up cultures available to demonstrate bacterial eradication.

Summary Threshold for the "Floor"

Overall, a wide range of thresholds have been suggested to optimize clinical and microbiologic response to beta-lactams. The preclinical thresholds of greater than 40–60% $T_{>MIC}$ appear to be the minimum acceptable amount, and when this cannot be reached, we

suggest considering the drug-bacteria pair as nonsusceptible. Based on the available evidence, in critically ill patients, it appears that two lower limit thresholds for beta-lactams are reasonable depending on the time course (within the first 48 hr or after approximately 48 hr). This approach is consistent with one recently proposed in the literature that has yet to be prospectively validated (44).

Early in critical illness microbiologic information is rarely available, and the clinical trajectory is unknown. A standard approach is to select a threshold based on the breakpoint of the most resistant possible pathogen (typically *Pseudmonas* species; examples in **Table 2**) (18, 20, 45, 46). The breakpoint reflects the concentration at or below which the bacteria are considered susceptible to antibiotic treatment. During the first 48 hours of critical illness, we propose a minimum acceptable free beta-lactam concentration of 1× the breakpoint of the most likely pathogen for 100% of the dosing interval. In other words, for a patient treated with cefepime, this would correspond to a trough concentration of at least 8 mg/L, the breakpoint for *P. aeruginosa* (46). Free beta-lactam concentrations of at least 4× the breakpoint for 100% of the dosing interval may achieve superior clinical and microbiologic outcomes (33, 40). Drug concentrations identified in a TDM program that considerably exceed this threshold may warrant a dose reduction. After 48 hours, additional patient information is often available. At this time, the "floor" could be tailored to 1–2× the observed MIC of the organism for 100% of the dosing interval. For example, if a *Proteus mirabilis* bloodstream infection is identified, the "floor" for cefepime concentrations could be liberalized to 2–4 mg/L.

FINDING THE CEILING: DEFINING THE THRESHOLD FOR BETA-LACTAM TOXICITY

Although effective antibiotic dosing in the ICU may warrant use of doses above package insert recommendations, exposure to supratherapeutic beta-lactam concentrations has consequences. A growing body of evidence indicates that beta-lactams may cause significant toxicity in select patients, such as those in the ICU (47). Reported adverse effects include neurotoxicity, nephrotoxicity, hepatotoxicity, and cytopenias. To limit risk for these toxicities, published protocols for pilot beta-lactam TDM programs have recommended dose-reductions if beta-lactam trough concentrations exceed six to 10 times the MIC (3, 48–50). This approach is somewhat counterintuitive as toxicity should be independent of bacterial susceptibility. Still, in adults, approximately 25% of patients required a dose reduction based on these thresholds after the first concentration check (49). We summarize evidence for each of these toxicities and the suggested thresholds for drug exposure associated with their occurrence.

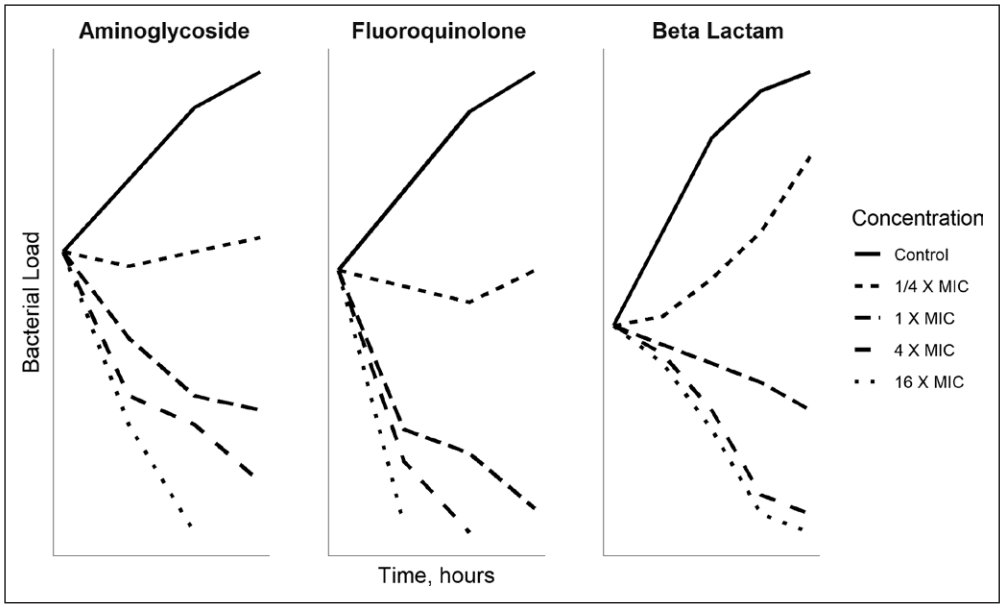

Figure 2. Example time-kill curves for *Pseudomonas aeruginosa* with three antibiotics of different classes at varying concentrations. For beta-lactams, exposure of the bacteria to a concentration 1× the minimum inhibitory concentration (MIC) of the organism is bactericidal. Drug concentrations greater than 4× the MIC of the organism elicit no additional increase in bacterial killing. For aminoglycosides and fluoroquinolones increases in drug exposure increases bacterial kill (23).

Neurotoxicity

Beta-lactams can have deleterious effects on the CNS. Nearly 70 years ago, intrathecal injection of benzylpenicillin caused significant paresthesia in monkeys (51) and electroencephalogram-confirmed

TABLE 2.
Example Thresholds for Drug Concentrations Based on Published Susceptibility Breakpoints for Select Organisms

Drug-Organism Pair	One Times the Breakpoint, mg/L	Four Times the Breakpoint, mg/L
Piperacillin/tazobactam		
Pseudomonas species	16/4	64/16
Proteus species	16/4	64/16
Cefepime		
Pseudomonas species	8	32
Proteus species	2	8
Meropenem		
Pseudomonas species	2	8
Proteus species	1	4

seizures when injected intracortically (52). Since then, these observations have been reproduced and documented with other beta-lactams. Cephalosporins and carbapenems especially exhibit ictogenic potential in preclinical models (53, 54). A systematic review recently estimated that cefepime neurotoxicity occurs in approximately one case of every 480 cefepime courses (55), but other reports suggest the frequency is much higher (56). Reports of beta-lactam neurotoxicity described in patients include decreased levels of consciousness, nonconvulsive status epilepticus, myoclonus, and new-onset psychiatric symptoms (57, 58). Aggregated data suggest that risk factors for neurotoxicity include age, baseline cognitive dysfunction, and factors that contribute to heightened drug exposure, such as inappropriate dosing and kidney dysfunction (59).

Mechanism. Beta-lactams inhibit the γ-aminobutyric acid A ($GABA_A$) receptor (60). Inhibition appears to be competitive in the case of cephalosporins and noncompetitive for penicillins (61, 62). Although beta-lactams are structurally distinct from γ-aminobutyric acid, certain agents like cefazolin and benzylpenicillin have pharmacophores with similar properties to pentylenetetrazol, a convulsant active at the $GABA_A$ receptor (**Fig. S1**, http://links.lww.com/CCX/A654) (59). Some of the most ictogenic beta-lactams have clinically meaningful degrees of blood-brain barrier penetration which may potentiate this risk (cefazolin 0.7–10%, benzylpenicillin 2%, imipenem 20%) (54, 63, 64). The pentylenetetrazol mouse model (65) is a common method for evaluating the proconvulsive effects of beta-lactams. The convulsive activity of pentylenetetrazol is determined alone and after the IV injection of subtoxic doses of a beta-lactam (65). The corneal kindled mouse model has also been used to evaluate beta-lactam neurotoxicity (66). Work with these animal models clearly supports the existence of a dose-response for neurotoxicity with beta-lactams, but to date, these findings have not translated to clear estimates of neurotoxicity risk at specific beta-lactam concentrations in patients.

Evidence of an Exposure-Response Relationship. Beta-lactam neurotoxicity has been associated with supratherapeutic drug concentrations in patients, but the thresholds most associated with concern remain debated. Importantly, given the difficulty with sampling, systemic beta-lactam concentrations are used as a surrogate to approximate exposure in the CNS.

In a cohort of 378 hospitalized patients, serum trough concentrations of piperacillin (n = 223), meropenem (n = 94), and flucloxacillin (n = 61) were significantly higher in those who experienced toxicity than in those who did not (67). Threshold concentrations that conferred a 50% risk of neurotoxicity were 361 mg/L for piperacillin, 64 mg/L for meropenem, and 125 mg/L for flucloxacillin. A study of 53 patients in the ICU suggested a lower threshold for piperacillin of 157 mg/L (68). Toxicity has not been universally linked to higher drug concentrations, however. A cohort of 300 hospitalized patients treated with imipenem found a 2.6% incidence of neurotoxicity. No clear relationship was observed between drug concentration and toxicity (5.2 vs 4.8 mg/L; p = 0.78) (69). A small study of critically ill patients who received meropenem or piperacillin-tazobactam found no association between incidence of seizure and use of higher than approved drug doses. Plasma concentrations were not reported (70).

One of the most studied beta-lactams in critically ill adults is cefepime. Systematic reviews and cohort studies of hospitalized patients have reported the mean serum concentration of cefepime in neurotoxic patients between 36 mg/L and 63 mg/L, approximately five to eight times the breakpoint for *P. aeruginosa* of 8 mg/L (56, 57, 71–73). Lower thresholds have also been reported (73, 74). It appears, at least with

cefepime, that neurotoxicity may not only be related to episodic supratherapeutic concentrations but also total exposure factoring in duration of therapy. A systematic review of cefepime neurotoxicity cases reported the median time to symptom onset was 4 days (interquartile range, 2–6 d) (56). Days on therapy, a surrogate for total exposure, has predicted neurotoxicity in certain analyses (75, 76), but results have been mixed (71, 72). Considering one of the largest risk factors for developing neurotoxicity is kidney dysfunction, progressive accumulation of medication over time may lead to sustained toxic exposure, although this remains speculative.

The preponderance of evidence suggests that excessive dosing or exposure to supratherapeutic beta-lactam concentrations potentiates the risk for neurotoxicity. Thus, it remains prudent to not greatly exceed doses needed to achieve effective bactericidal beta-lactam concentrations. Future study will be needed to determine if method of administration (prolonged vs short infusion) alters the incidence of neurotoxicity.

Nephrotoxicity

Mechanism. Nephrotoxicity has been described with beta-lactams, but the true mechanistic and dose-response relationship is less clear than with neurotoxicity. Acute tubulointerstitial nephritis (AIN) is the primary pattern of drug-associated nephrotoxicity observed with beta-lactams which has a subacute, type B, idiosyncratic presentation (77). Beta-lactam–induced AIN is thought to be hapten-mediated, where reactive metabolites of the beta-lactam structure bind to albumin, activate an antigen-presenting cell, and stimulate T cells into activity (78, 79). Certain beta-lactams, such as imipenem (without cilastatin), cephaloridine, and cephaloglycin, have also been reported to cause direct mitochondrial damage in renal tubular cells. Acylation metabolites of these antibiotics disrupt mitochondrial electron transport, impairing cellular respiration and ultimately leading to tubular necrosis (80). This mitochondrial toxicity is mitigated by tubular secretion inhibitors like probenecid or cilastatin in the case of imipenem (81).

Evidence of an Exposure-Response Relationship. Dose-dependence of beta-lactam nephrotoxicity has not been shown, which is consistent with the immune-mediated idiosyncratic injury pattern. The previously mentioned cohort which compared plasma concentrations of piperacillin, meropenem, and flucloxacillin evaluated drug concentrations in patients who experienced acute kidney injury (AKI). Trough concentrations for piperacillin and meropenem, both renally eliminated beta-lactams, were significantly higher in patients with AKI. Trough concentrations were not higher for flucloxacillin, a primarily hepatically cleared drug. In this one study, thresholds associated with a 50% risk of AKI were 453 mg/L for piperacillin (higher than for neurotoxicity) and 44 mg/L for meropenem (lower than for neurotoxicity) (67). As renally eliminated drugs, high concentrations may be the result of AKI or may directly lead to its development; this requires future study.

Hepatotoxicity

Specific beta-lactams, including flucloxacillin, oxacillin, amoxicillin, and amoxicillin-clavulanate, have been implicated in cases of drug-induced liver injury (DILI). DILI appears rare with cephalosporin antibiotics (82).

Mechanism. Hepatoxicity appears to be T-cell mediated, similar to AIN, where beta-lactam ring components bind to albumin and drive inflammatory activity, particularly for hepatically cleared agents such as flucloxacillin (83). Other suggested mechanisms include direct hepatocellular damage and stasis leading to drug precipitation (84, 85).

Evidence of an Exposure-Response Relationship. Plasma drug concentrations were comparable in patients who did and did not experience DILI in the setting of piperacillin, meropenem, or flucloxacillin (67). These observations support the suspected idiosyncratic nature of this toxicity. Genetic factors appear to potentiate the risk of beta-lactam DILI (86, 87).

Cytopenias

Beta-lactams have been associated with drug-associated neutropenia/agranulocytosis, leukopenia, thrombocytopenia, and hemolytic anemia (85). Beta-lactam–associated cytopenias remain rare, and various drugs have been implicated including penicillins, cephalosporins, and carbapenems.

Mechanism. The exact pathogenesis of beta-lactam associated cytopenias is unknown, but they appear mediated by immunoallergic or toxic mechanisms

(88). Some have argued for an autoimmune component; others have suggested direct damage to the bone marrow. For hemolytic anemia, beta-lactams may trigger development of one or two different types of hemolyzing antibodies (drug dependent and drug independent) (89). An additional mechanism purported is hydrolysis degradation products of beta-lactam antibiotics directly inhibiting DNA polymerase (90).

Evidence of an Exposure-Response Relationship. The relationship between beta-lactam concentrations and development of cytopenias has not been well described. Although this adverse reaction likely has an immune-mediated and idiosyncratic component, it does appear that high drug exposure may be a risk factor (88). Early work suggested that beta-lactam degradation products may play a role in causing cytopenias rather than the parent compound. In vitro studies in K-562 cells demonstrated that ceftazidime at concentrations far above therapeutic levels in humans (750 μg/mL) led to impaired granulopoiesis, an effect that was significantly enhanced when ceftazidime was allowed to incubate in cell medium for 144 hours (91). An explanation for the more substantial cytopenia that occurs with sustained incubation may be that longer durations of therapy, rather than transiently high exposures, allows for degradation of the beta-lactam ring via hydrolysis and exposure to toxic degradation products (92, 93). A systematic review of piperacillin-/tazobactam-associated hematologic adverse effects indicated that most cases occurred after at least 2 weeks of therapy (94). We are unaware of any specific studies in humans linking observed beta-lactam concentrations to cytopenia(s).

Summary Threshold for the "Ceiling"

Critically ill patients treated with beta-lactams are at heightened risk for adverse effects in part due to advanced age, number and severity of comorbidities, acute organ dysfunction, and polypharmacy. Of the major reported beta-lactam toxicities, neurotoxicity has the strongest association with elevated drug concentrations, with the largest body of evidence for imipenem and cefepime. In patients with unexplained new-onset encephalopathy or seizures, a supratherapeutic beta-lactam concentration would suggest the antibiotic may be the culprit. Importantly, a "normal" serum beta-lactam concentration does not rule-out neurotoxicity as the CNS concentration may be very different than the peripheral concentration, and the patient may have other risk factors for toxicity. The preferred approach in cases of suspected neurotoxicity is drug discontinuation, but at a minimum, a dose adjustment is warranted. Toxic thresholds for beta-lactams remain an area in need of additional research. Nephrotoxicity and hepatotoxicity appear concentration independent. The exposure-response relationship between beta-lactams and cytopenias remains uncertain.

CLINICAL APPLICATION AND FUTURE DIRECTIONS

Although routine use of beta-lactam TDM is limited to a select number of academic centers at present, existing programs have demonstrated feasibility and the unmet need for therapeutic optimization. Critical care clinicians well understand the individual pharmacokinetic variability that exists in their populations. For drug dosing, oftentimes exposures vary 10- to 30-fold (95), and existing adjustment schemes (e.g., based on creatinine clearance) are insufficient to precisely achieve targets (18–21). In the ICU, 40–90% of patients who had TDM performed failed to achieve target beta-lactam levels (after 2-3 d of therapy). The majority of nontarget levels were low (49, 50, 96, 97), a risk for clinical and microbiologic failure. The absolute gain between optimized and suboptimal antibiotic exposures approaches 30% and is amplified in more serious illness (41, 98) especially in the presence of extracorporeal devices, high-volume resuscitation efforts, or acute changes to end-organ function like augmented renal clearance.

At the outset of therapy, aggressive dosing including use of loading doses could overcome pharmacokinetic changes that contribute to low concentrations (15–17, 22). Extended or continuous infusion may facilitate maintenance of desired drug concentrations. Although every patient may not require beta-lactam TDM, selection of patients most likely to benefit should become part of standard ICU care of critically ill patients with infections. Achievement of target drug concentrations is one of the most important and modifiable factors in improving infected patient outcomes (24, 25).

It is expected that it will take time for beta-lactam TDM to be fully adopted. Research is ongoing to inform best practices for implementation of beta-lactam TDM (99). The availability of assays can become more widespread as chromatography technology and

standard operating procedures are more widely distributed. In the earliest years, it is expected that most TDM programs will operate by comparing patient concentrations with individualized treatment goals (e.g., free concentration exceeds MIC for duration of therapy) and adjusting on the basis of individual results. We surmise, however, that much as computer flight software has become the standard for pilot flight, that computer programs that will aid in the understanding of concentration variability and allow stochastic control in the near future. That is, continuously updated predictions, based on patient antibiotic concentrations and individual features, will allow the clinician to envisage how dose adjustments for their unique patient will impact achievement of their target concentration (100). More work is needed to move the mathematical framework and computer programs from the realm of research to the actual patient bedside; however, the potential gains that can be achieved are considerable.

CONCLUSIONS

Beta-lactam individualization is important for optimizing the care of critically ill patients. When designing a beta-lactam TDM program, a minimum acceptable "floor" for free beta-lactam concentrations of 1× the breakpoint of the most likely pathogen for 100% of the dosing interval is reasonable. Although evidence suggests a dose-dependence between beta-lactam exposure and neurotoxicity, a clear "ceiling" has yet to be established and deserves further study. In the future, additional research is needed to describe best practices for implementation of beta-lactam TDM and their association with clinical and microbiologic outcomes.

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