Neurocrit Care (2022) 37:73–80
https://doi.org/10.1007/s12028-022-01442-1

NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Incidence and Predictive Factors Associated with Beta-Lactam Neurotoxicity in the Critically Ill: A Retrospective Cohort Study

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Abstract

Background: Beta-lactam neurotoxicity is a relatively uncommon yet clinically significant adverse effect in critically ill patients. This study sought to define the incidence of neurotoxicity, derive a prediction model for beta-lactam neurotoxicity, and then validate the model in an independent cohort of critically ill adults.

Methods: This retrospective cohort study evaluated critically ill patients treated with ≥ 48 h of cefepime, piperacillin/tazobactam, or meropenem. Two separate cohorts were created: a derivation cohort and a validation cohort. Patients were screened for beta-lactam neurotoxicity by using search terms and diagnosis codes, followed by clinical adjudication using a standardized adverse event scoring tool. Multivariable regression models and least absolute shrinkage and selection operator were used to identify surrogates for neurotoxicity and develop a multivariable prediction model.

Results: The overall incidence of beta-lactam neurotoxicity was 2.6% ($n/N = 34/1323$) in the derivation cohort and 2.1% in the validation cohort ($n/N = 16/767$). The final multivariable neurotoxicity assessment tool included weight, Charlson comorbidity score, age, and estimated creatinine clearance as predictors of neurotoxicity. Incidence of neurotoxicity reached 4% in those with a body mass index more than 30 kg/m^2. Use of the candidate variables in the neurotoxicity assessment tool suggested that a score more than 35 would identify a patient at high risk for neurotoxicity with 75% sensitivity and 54% specificity.

Conclusions: In this single center cohort of critically ill patients, beta-lactam neurotoxicity was demonstrated less frequently than previously reported. We identified obesity as a novel risk factor for the development of neurotoxicity. The prediction model needs to be further refined before it can be used in clinical practice as a tool to avoid drug-related harm.

Keywords: Cefepime, Piperacillin/tazobactam, Antibiotic, Encephalopathy

Introduction

Widespread use of beta-lactam antibiotics for critically ill patients has resulted in the recognition of their potential for rare but serious drug-associated neurotoxicity. The reported incidence of this adverse event has varied significantly within the literature, ranging from 7 to 23%, likely secondary to a lack of standardized diagnostic criteria [1–3]. Symptoms of beta-lactam neurotoxicity include confusion, myoclonus, seizures, encephalopathy, decreased consciousness, and electroencephalogram (EEG) changes [2, 4]. Critically ill patients often have many reasons for altered mental status, thus the diagnosis of beta-lactam neurotoxicity is ambiguous and the

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time to intervention is often delayed. A delayed diagnosis may postpone discontinuation of the offending drug, leading to long-term, possibly irreversible consequences [5, 6]. Among the beta-lactam antibiotics, risks associated with those that cover *Pseudomonas aeruginosa* (i.e., cefepime, meropenem, piperacillin/tazobactam) are of greatest relevance in critically ill patients [7].

Although the exact mechanism of neurotoxicity is unknown, evidence has suggested that it is because of the competitive inhibition of gamma amino-butyric acid on neuronal receptors, leading to a blockade of inhibitory signals, culminating in an overexcitation of the central nervous system [8]. Several approaches for predicting and diagnosing beta-lactam neurotoxicity have been attempted. Symptom onset must occur after initiation of the beta-lactam and is more likely if discontinuation of the beta-lactam resolves the neurological symptoms, and other potentially neurotoxic drugs have been ruled out as contributors [4, 9]. Previously identified risk factors for neurotoxicity include older age, higher drug doses, reduced kidney function, and baseline cognitive impairment [6, 10]. Some retrospective studies have proposed that kidney function and drug levels can be used as predictors of beta-lactam neurotoxicity, but results have been discrepant and beta-lactam drug level monitoring is not common practice. Many of these studies are too small to fully vet predictors and the validation of predictive models is missing [11–15].

Given the variable incidence reported within the literature and heterogeneous definitions for neurotoxicity, our study objective was to rigorously define the incidence of this adverse drug reaction within a cohort of critically ill patients. We then aimed to derive and validate a prediction tool by using confirmed neurotoxicity cases that could be used at the bedside to identify patients at high risk for future drug-related harm.

Methods

Overview

This retrospective cohort study evaluated adult patients treated with an antipseudomonal beta-lactam (cefepime, piperacillin/tazobactam, or meropenem) in the medical or surgical intensive care unit (ICU) at Mayo Clinic Hospital in Rochester, Minnesota. The derivation cohort was selected from patients treated between January 1, 2008, and September 1, 2013. The validation cohort included patients admitted from January 1, 2018, to December 1, 2020. The objectives were to (1) determine the incidence of beta-lactam neurotoxicity in a cohort of critically ill patients by using a standardized approach and (2) derive and validate a multivariable prediction model for beta-lactam neurotoxicity. The model was created to serve as a screening tool for beta-lactam neurotoxicity based on clinical characteristics at the time of beta-lactam initiation in the ICU. This study was approved by the Mayo Clinic Investigational Review Board (number 14-007857).

Patient Selection

Included patients were treated with one of the study beta-lactams for at least 48 h and did not receive more than one dose of any other beta-lactam in the 1 week preceding the course of interest. The 48-h cutoff was chosen on the basis of previous case series and reviews that have shown the development of neurotoxicity to occur most often beyond 2 days of therapy [1, 2, 9, 16]. To limit the potential for other plausible causes of acute neurologic dysfunction, patients were excluded if they presented with active alcohol or drug withdrawal, a history of hepatic encephalopathy, dementia, or epilepsy, or an admitting diagnosis of drug overdose, stroke, traumatic brain injury, central nervous system infection, intracranial hemorrhage, or seizure based on clinical notes. Patients with documented delirium [Confusion Assessment Method for the ICU (CAM-ICU) positive] or Glasgow Coma Scale scores < 8 within 48 h of beta-lactam initiation were also excluded. To avoid potential confounders, patients were excluded if they received concomitant continuous infusion paralytics, were deeply sedated (defined by a Richmond Agitation Sedation Scale score of ≤ -4 for two consecutive readings in the 48 h prior to beta-lactam initiation), or if they received benzodiazepines at a dosage in excess of 20 mg/day of lorazepam equivalents within 48 h of beta-lactam initiation. The authors chose this dose cutoff on the basis of previously demonstrated risk of delirium at dosages of lorazepam exceeding 20 mg/day [17]. Finally, pregnant women, incarcerated patients, and patients not consenting to the use of their medical records for research were excluded [18].

Definitions and Data Collection

To identify the outcome of neurotoxicity, we performed an initial screening of diagnosis codes and electronic health record terms to identify possible neurotoxicity cases. Search terms included, but were not limited to, "hallucination," "cognitive impairment," "altered consciousness," "depressed consciousness," "seizure," "myoclonus," "confusion," and "neurotoxicity." A manual review of 10% ($n = 132$) of the derivation cohort was performed to assess the inclusivity of this approach. No additional terms or suspected neurotoxicity cases were identified in the manual review. The full cohort was then screened with these search terms. For patients who screened positive, the electronic health records were manually reviewed independently and in triplicate by two clinical pharmacists and one neurointensivist by

using the Naranjo Adverse Drug Reaction Probability Scale [19] (Supplemental Table 1) to confirm beta-lactam neurotoxicity. Criteria for beta-lactam neurotoxicity included signs and symptoms of neurotoxicity beginning at least 48 h after beta-lactam initiation, lack of an alternative cause of neurotoxicity, and absolute or partial reversal of neurologic symptoms on discontinuation of the beta-lactam. Possible alternative causes of neurotoxicity that were evaluated for included elevated blood urea nitrogen, elevated ammonia, abnormal electrolytes, oversedation, or concurrent benzodiazepine use. Patients who were scored as "definite" or "probable" according to the Naranjo scale by two out of three investigators were labeled as confirmed neurotoxicity cases (full scoring guide found in Supplemental Table 1). This threshold was considered reasonable, as the objective was to develop a screening tool that favors a more inclusive case definition.

For derivation and validation of the multivariable model, candidate predictors were identified from information available at the time of ICU admission and/or prior to beta-lactam initiation. Patient demographics and baseline characteristics, and severity of illness scores including the Charlson comorbidity index, Acute Physiology and Chronic Health Evaluation III score, the Sequential Organ Failure score, and Glasgow Coma Scale score were collected at ICU admission [20–22]. At beta-lactam initiation, medication name, dose, and administration frequency were collected. For those experiencing neurotoxicity, concomitant sedation and intravenous opioid analgesia at the time of the toxic event were obtained to assess for possible confounders (Supplemental Table 2). Renal replacement therapy during admission was extracted from the electronic health record. Baseline creatinine clearance was calculated according to the Cockcroft-Gault equation, and kidney dysfunction was defined as an estimated creatinine clearance (eCrCl) < 60 mL/min. The Cockcroft-Gault equation was used to assess beta-lactam dose appropriateness (Supplemental Table 3) [23–25]. Finally, any EEG monitoring, consultation of the neurology service, or mortality occurring after beta-lactam initiation was also extracted from the medical record.

Statistical Analysis

Continuous data were described using means with standard deviations or medians and interquartile ranges according to the normality of the distribution. The timing and cumulative incidence of neurotoxicity was assessed visually with Kaplan–Meier curves. Univariate and multivariable logistic regression models were used to identify potential predictors of clinically adjudicated neurotoxicity. Variable selection for the multivariable model was based on previously reported clinical factors of interest and least absolute shrinkage and selection operator techniques. The best prediction model identified in the derivation cohort was then tested in the validation cohort. Discrimination of the predictive model was determined by using the concordance index (C statistic). The C statistic ranges from 0.5 to 1, where 0.5 infers that the model is no better than a coin flip in predicting the outcome and a C statistic of 1 would indicate perfect ability to differentiate between positive and negative outcomes. Given the expected large proportion of true negatives in the cohort, we also used the area under the precision recall curve (AUPRC) to further characterize discrimination. The AUPRC baseline is the frequency of positive cases (i.e., 5% positive cases correspond to a baseline AUPRC of 0.05). An increase above this baseline would be considered an improvement with the model. A graph of predicted probability from the model versus observed probability in the validation cohort was used to assess the calibration of the statistical model, as was the Hosmer–Lemeshow test. Reporting of the prediction model was done according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement [26].

Results

Patient Characteristics

A total of 1323 patients treated at Mayo Clinic in Rochester between 2008 and 2013 were included in the derivation cohort (Fig. 1). The most common reason for exclusion was presence of an alternative explanation for altered mental status. The mean ± standard deviation age at inclusion was 65 ± 16 years, with 54% men and a median Acute Physiology and Chronic Health Evaluation III score of 73 (interquartile range 59–91) (Table 1). The selection of beta-lactam therapy within this cohort was as follows, piperacillin/tazobactam: $n = 514$ (39%); cefepime: $n = 429$ (32%); and meropenem: $n = 388$ (29%). Estimated creatinine clearance at the time of beta-lactam initiation was 75 (47–115) mL/min. Five hundred and twenty-four (40%) patients had an eCrCl < 60 mL/min at beta-lactam initiation. Doses of beta-lactams were assessed for appropriateness based on prespecified dosing ranges according to eCrCl [23–25] (Supplemental Table 3). In the derivation cohort, 90% of patients were on appropriately dosed beta-lactams (Table 1). The validation cohort included 767 patients. Baseline characteristics were similar to those in the derivation cohort, and 91% of patients were on appropriately dosed antibiotics (Supplemental Table 4).

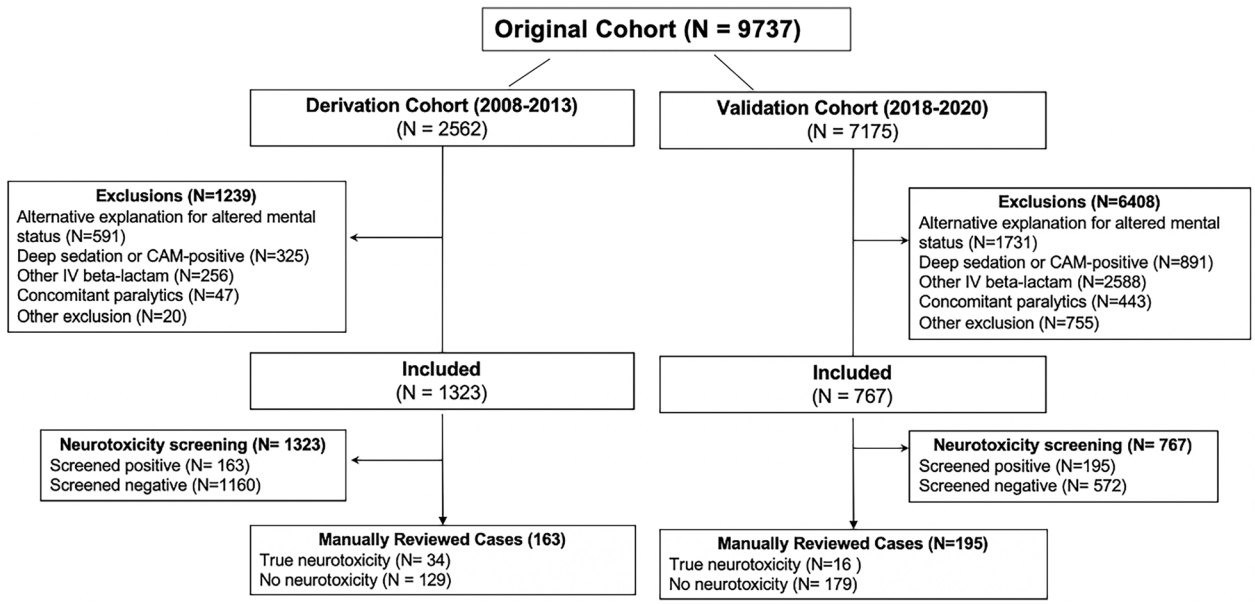

Fig. 1 Study flow diagram of derivation and validation cohorts of patients in the ICU receiving beta-lactams. The final derivation cohort after applying exclusion criteria was 1323 patients, 34 of whom had neurotoxicity. The final validation cohort included 767 patients, with true neurotoxicity identified in 16 patients. *CAM* Confusion Assessment Method, *ICU* intensive care unit, *IV* Intravenous

Cumulative Incidence of Neurotoxicity

After applying the initial screening criteria using search terms and diagnosis codes, 163 patients (12.3%) in the derivation cohort screened positive for possible neurotoxicity. Independent and thorough chart review of these 163 cases was done in triplicate and resulted in a frequency of clinically adjudicated neurotoxicity within the derivation cohort of 2.6% ($n=34$). Of those with neurotoxicity, 14 (41%) were treated with cefepime, 8 (24%) with meropenem, and 12 (35%) with piperacillin/tazobactam. The mean time to neurotoxicity development was approximately 2.5 days from the start of therapy (Fig. 2). Within the validation cohort, 195 patients (25%) screened positive for possible neurotoxicity, with a final neurotoxicity incidence of 2.1% ($n=16$) as verified by clinical adjudication. Continuous infusion benzodiazepine use was rare in patients with neurotoxicity, but most had exposure to sedatives or analgesics (Supplemental Table 2).

Prediction Model Development

Four variables were significantly associated with neurotoxicity in univariate models: higher weight ($p=0.003$), higher body mass index (BMI) ($p=0.003$), higher Charlson comorbidity score ($p=0.036$), and older age ($p=0.008$). Although eCrCl was not found to be statistically different at the univariate level ($p=0.49$), the neurotoxicity group was found to have a clinically meaningful numerical difference of a 14 mL/min lower median eCrCl than the nonneurotoxic group. Patients receiving dialysis within 12 h were excluded for model derivation. In multivariable modeling, a parsimonious model with clinically relevant inputs included age, weight, Charlson comorbidity score, and eCrCl. The final prediction equation illustrating risk of neurotoxicity is as follows:

$$\text{Neurotoxicity Assessment Tool(NAT)} = (0.28 \times \text{Age}) + (0.17 \times \text{weight}) + (0.51 \times \text{Charlson Score}) - (0.02 \times \text{eCrCL})$$

The C statistic of the model in the derivation cohort was 0.71 and the AUPRC was 0.09. A Hosmer–Lemeshow goodness of fit test was done to assess model calibration, which showed no significant lack of fit ($p=0.5$; Supplemental Figure 1). A NAT score of 35 was selected as the optimal cutoff for the screening tool (Supplemental Table 5).

Table 1 Patient characteristics

Characteristic	Derivation cohort				
	Total ($N=1323$)[a]	Patients with neurotoxicity ($n=34$)	Patients without neurotoxicity ($n=1289$)	Odds ratio (95% CI)	*p* value
Male sex	709 (54%)	19 (56%)	690 (54%)		0.79
Non-Hispanic White	1229 (93%)	34 (100%)	1195 (93%)	5.45 (0.33–90.98)	0.24
Age, *n* (SD) (years)	65 (16)	72 (12)	64 (16)	1.43 (1.10–1.86)	0.008
Weight (kg)	80 (67, 98)	90 (73, 109)	80 (66, 98)	1.14 (1.05–1.24)	0.003
BMI (kg/m^2)	27 (23, 33)	30 (27, 36)	27 (23, 32)	1.04 (1.01–1.07)	0.003
< 18.5	91 (7%)	1 (1%)	90 (99%)		
≥ 18.5–25	402 (30%)	6 (2%)	400 (99%)		
≥ 25–30	376 (28%)	9 (2%)	367 (98%)		
> 30	454 (34%)	18 (4%)	436 (96)		
ICU type					
MICU	462 (35%)	10 (29%)	452 (35%)	Reference	
Mixed medical/surgical	283 (21%)	6 (18%)	277 (22%)	0.98 (0.35–2.72)	0.97
SICU	578 (44%)	18 (53%)	560 (43%)	1.45 (0.66–3.18)	0.35
APACHE III	73 (59, 91)	80 (68, 106)	73 (59, 90)	1.12 (0.99–1.27)[b]	0.084
SOFA	6 (4, 9)	7 (5, 9)	6 (4, 9)	1.04 (0.95–1.13)	0.42
Charlson comorbidity score at ICU admission	6 (4, 9)	8 (6, 10)	6 (4, 9)	1.10 (1.01–1.19)	0.036
Creatinine clearance at ICU admission (mL/min)	75 (47, 115)	61 (35, 103)	76 (48, 115)	0.98 (0.91–1.05)[b]	0.49
< 60 mL/min[c]	522 (40%)	18 (53%)	504 (39%)		
ESRD on dialysis prior to admission	33 (3%)	1 (3%)	32 (3%)	1.75 (0.89–3.47)	0.11
On dialysis within 12 h of beta-lactam start	78 (6%)	2 (6%)	76 (6%)	1.00 (0.24–4.24)	0.99
Beta-lactam selection					
Cefepime	425 (32%)	14 (41%)	411 (32%)	Reference	
Meropenem	387 (29%)	8 (24%)	379 (29%)	0.62 (0.26–1.49)	0.29
Piperacillin/tazobactam	511 (39%)	12 (35%)	499 (39%)	0.71 (0.32–1.54)	0.38
Beta-lactam treatment duration (h)	140 (84, 210)	145 (88, 193)	138 (84, 210)	0.99 (0.96–1.02)[b]	0.52
Beta-lactam dose appropriateness[d]					
Appropriate	1194 (90%)	31 (91%)	1163 (90%)	Reference	
Dose too high	17 (1%)	0 (0%)	17 (1%)	1.06 (0.06–19.46)	0.97
Dose too low	112 (9%)	3 (9%)	109 (9%)	1.18 (0.38–3.64)	0.77

APACHE Acute Physiology and Chronic Health Evaluation, *BMI* body mass index, *CI* confidence interval, *CrCl* Cockcroft-Gault creatinine clearance, *ESRD* end stage renal disease, *ICU* intensive care unit, *MICU* medical intensive care unit, *SD* standard deviation, *SICU* surgical intensive care unit, *SOFA* Sequential Organ Failure Assessment

[a] Values expressed as counts (percentages) or medians (interquartile ranges) unless noted

[b] Per 10-unit increase

[c] Creatinine clearance only calculated for patients not on dialysis (total 1246 patients)

[d] Assessed based on appropriate ranges outlined in Supplemental Table 3

Model Validation

Application of the best performing model in the validation cohort resulted in a C statistic of 0.62 and an AUPRC of 0.04. Predicted versus observed probability of neurotoxicity showed no significant lack of fit ($p=0.13$; Supplemental Figure 2). Select variables were available for this cohort that were otherwise unavailable during derivation including cystatin C concentration within 1 week of beta-lactam initiation and Sequential Organ Failure scores at ICU admission. Neither of these characteristics differed significantly between patients who did experience neurotoxicity and patients who did not experience neurotoxicity. Of those that did experience neurotoxicity within the validation cohort, 13%

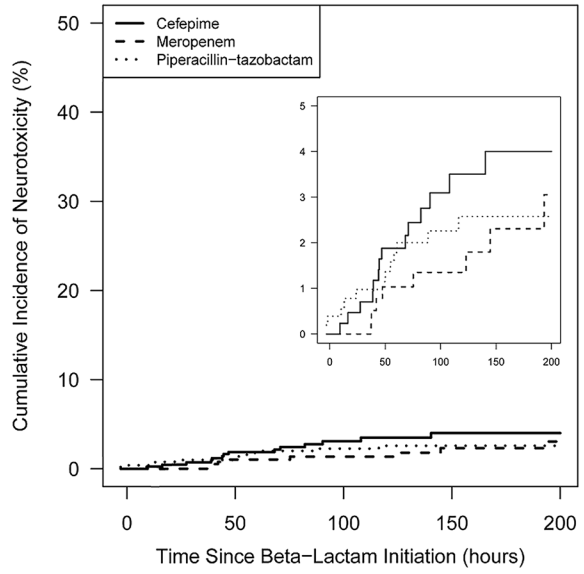

Fig. 2 Incidence of neurotoxicity. Cumulative incidence of neurotoxicity in derivation cohort patients ($n = 34$). The highest incidence of neurotoxicity was found in patients on cefepime, and toxicity occurred at a median of 2 days into beta-lactam therapy

($n = 2$) were on inappropriate antibiotic doses based on their kidney function. Mortality was not significantly different between patients with neurotoxicity and those without (Table 1 and Supplemental Table 4).

Discussion

In this large retrospective study, we determined the incidence of beta-lactam neurotoxicity using two distinct cohorts with a relatively high severity of illness. We derived and independently validated a prediction model (NAT) to identify patients at a higher risk for neurotoxicity on the basis of clinical characteristics. All cases of neurotoxicity were clinically adjudicated using a standardized adverse drug reaction scale. The cumulative incidence of clinically adjudicated beta-lactam neurotoxicity was 2–3%. The final NAT model included age, Charlson comorbidity score, weight, and baseline eCrCl as clinically important predictors of the development of neurotoxicity. The NAT model had good discrimination in the derivation cohort and fair discrimination in the validation cohort with no issues observed with calibration.

Much of the current neurotoxicity literature has centered on cefepime, where the reported incidence of neurotoxicity ranges from 7 to 23% in critically ill patients [1, 2]. The incidence of neurotoxicity in this study was much lower at 2–3%. For the subset of patients receiving cefepime, the incidence was 3–4%. Several possible reasons exist for this observed difference, likely due to the approach to defining the endpoint [1, 27]. Identification of beta-lactam neurotoxicity is often based on clinical features and occasionally EEG data. The heterogeneity in the presentation makes it difficult to compare across studies. Previous studies have allowed features such as headache and somnolence as part of the definition for neurotoxicity [1]. In the present study, we used a multilayered approach including a broad review of electronic health records using search terms, and a detailed manual evaluation of the chart with application of the standardized Naranjo criteria. Additionally, individuals with any other likely explanations for altered mental status at the time of the onset of neurological symptoms were excluded (e.g., stroke, renal or hepatic encephalopathy, drug intoxication or withdrawal). This rigorous case definition likely explains the lower incidence of neurotoxicity in the present study.

Model inputs identified in previous literature reflect features which could heighten susceptibility to adverse drug effects (i.e., advanced age, baseline cognitive dysfunction), as well as factors that directly affect the drug exposure (i.e., higher drug doses, poorer kidney function) [6, 10]. The predictors identified in this study largely reflect this phenomenon with the addition of weight as a novel predictor for neurotoxicity. When stratifying patients from the derivation cohort who experienced neurotoxicity by BMI ranges, there was a slight increase in risk with advancing BMI (1% for BMI < 18.5 kg/m^2 to 4% for BMI > 30 kg/m^2). Weight-adjusted total daily doses were comparable across the cohort and therefore inappropriate dosing does not explain the association of neurotoxicity with higher weight. It is conceivable that obesity could affect the lipophilicity and volume of distribution of beta-lactams [28–30]. Confirmation of this association and exploration of the underlying mechanism requires further study. Drug dosing was not included in the prediction model in this study because 90% of patients were on beta-lactam doses deemed appropriate for their eCrCl. At the study center, clinical pharmacists are actively involved with drug management and adjustments in the critically ill. Coupled with electronic health record based clinical decision support which provides drug dosing guidance to prescribing clinicians, inappropriate dosing in this cohort was infrequent.

Surprisingly, reduced kidney function was not found to be a predictor for neurotoxicity in univariate analysis, which differs from previous literature [1, 2, 16, 27]. In the setting of reduced kidney function, beta-lactam clearance can be significantly reduced and passage of drug through the blood–brain barrier becomes more likely [2, 11]. Yet, we found no significant association despite evaluating kidney function in several ways including eCrCl at baseline, eCrCl as part of the dose appropriateness calculation, and need for dialysis modeled as both a binary and

time-dependent variable. Reasons for the lack of a consistent relationship between impaired kidney function and beta-lactam neurotoxicity in this study are unclear. It might be a function of the relatively small sample size of patients with neurotoxicity. Between those with toxicity and without, we observed a nonsignificant 14 mL/min difference in eCrCl, which is clinically meaningful. The association may have been significant with a higher event rate. Another possibility is that our strict exclusion criteria and use of an adverse drug reaction score that required assessment of "other contributors" may have decreased the likelihood of attributing the neurological changes to the antibiotic in patients with kidney dysfunction. Although kidney dysfunction has been associated with beta-lactam neurotoxicity, some reports have demonstrated that neurotoxicity is not exclusive to patients with kidney impairment, which is supported by our study results [14, 15]. Previous literature has also demonstrated evidence of neurotoxicity in patients with adequate kidney function, suggesting that eCrCl alone is not an optimal predictor for neurotoxicity [14, 15].

It is worth mentioning that model inputs were not selected based on C statistic alone, but rather with the mindset that the prediction model would be used as a screening tool. Accordingly, we prioritized model sensitivity over specificity and specifically selected inputs that would be available upon admission to the ICU or beta-lactam start. A cutoff of 35 was chosen for the prediction model, such that a score at or above this value would predict neurotoxicity with at least 75% sensitivity and 54% specificity. At this score cutoff, model sensitivity is maximized and the opportunity for potential cases of toxicity to be missed is minimized. Clinically relevant inputs were selected using least absolute shrinkage and selection operator, which is consistent with best practice recommendations [31]. The model was chosen to be parsimonious and practical and total number of inputs was constrained by the number of incident neurotoxicity cases.

A number of limitations exist within the current study. It was conducted at a single center therefore generalizability may be limited. Additionally, there is no way to verify with full certainty that identified patients with neurotoxicity did experience true neurotoxicity. We attempted to mitigate this limitation through extensive manual chart review, use of three independent reviewers, and a rigorous neurotoxicity definition. Despite the broad screening criteria used to identify possible neurotoxicity cases, it is also possible that not all cases of neurotoxicity were identified given that neurotoxicity is nonspecific in nature. Similarly, patients with past neurological diagnoses that could confound results were excluded based on diagnosis codes and search terms. The possibility remains that a portion of patients may have been inaccurately excluded based old diagnoses or inaccurate charting. We also excluded patients who developed neurotoxic symptoms within 48 h, as the likelihood for an alternative explanation would be higher. It is possible that true cases could have been excluded with this cutoff. Another limitation is that beta-lactam neurotoxicity was not universally detected, thus drug discontinuation did not occur in all cases, and this could have led to a falsely decreased final Naranjo score. Additionally, in cohorts with a low event rate, the C statistic may be inaccurate. To further characterize discrimination, we report the AUPRC, which demonstrated a modest improvement. Still yet, identified predictors in this study should be interpreted with caution. It should also be noted that the 10-year period between the derivation and validation cohorts may have affected the findings. Practice has changed significantly over the past 10 years including more purposeful antimicrobial stewardship (reflected in the lower frequency of meropenem use in the validation cohort), novel diagnostics to assess kidney function, and additional primary literature on beta-lactam neurotoxicity. Each of these may have affected the observed incidence of neurotoxicity and predictive associations. The similarities between the two cohorts in demographic characteristics, severity of illness, and observed incidence and distribution of toxicity across the drugs makes this less likely to have impacted the study findings. Finally, it is worth noting that the model performance did weaken significantly when applied to the validation cohort. Although the model still had fair discriminatory power in predicting neurotoxicity, further model optimization should be pursued in the future.

Conclusions

The incidence of neurotoxicity in this large retrospective study was found to be 2–3%. The final model for predicting neurotoxicity in the ICU included the following patient variables: age, Charlson comorbidity score, weight, and eCrCl. Additional evaluation is needed to determine whether implementation of this prediction model as a method of screening patients in the ICU prior to beta-lactam initiation may help to reduce drug-related harm.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12028-022-01442-1.

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Author contributions

NH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis. She helped to design the study, gather data on included patients with assistance from the members of the Mayo Clinic Anesthesia Clinical Research Unit team cited in the Acknowledgments, and draft the article. CI and SL assisted with study design. EB and DS assisted with study design, data collection, and contributed heavily to article drafting. KM helped to design the study and to review the statistical analysis. AAR, JF, SH, NH, and EB assisted with clinical adjudication of possible neurotoxicity cases. ADR and OG contributed to article editing and analysis. All authors reviewed the data, participated in discussions related to interpretation, and read and approved the final manuscript.

Source of support

This study was supported in part by the Mayo Clinic Department of Pharmacy, the National Institutes of Health National Center for Advancing Translational Sciences under Award Number UL1 TR002377, and the National Institute of Allergy and Infectious Diseases under Award Number K23AI143882 (PI; EFB). The aforementioned funding sources had no role in study development, data accrual, statistical analysis, or interpretation of study findings do not represent the official views of the National Institutes of Health.

Ethical approval/informed consent

This study was approved by the Mayo Clinic Investigational Review Board (number 14-007857), and all ethical guidelines have been adhered to.

Conflicts of interest

All authors report no conflicts of interest or financial relationships to disclose.

Publisher's Note

Received: 4 October 2021 Accepted: 4 January 2022
Published: 8 February 2022

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