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Encephalopathy in mechanically ventilated adult patients in the intensive care unit: the role of β-Lactam overdosing

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Declarations

Ethics approval and consent to participate: This observational prospective study was approved by the Institutional Review Board of the French intensive care medicine society (CE SRLF 17-48) and written and oral information about the study was given to the patients. The data were anonymously collected from medical files in a secure database declared to the National Commission for Information Technology and Civil Liberties.

Consent for publication: Not applicable

Data availability statement: The dataset used and analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions: Dr Gendreau, Dr Razazi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Gendreau, Dr Benelli, Dr Cintrat, Pr Guillaume Carteaux, Pr Nicolas de Prost, Dr Anne Hulin, Dr Pressiat, Dr Razazi, and Dr Mekontso Dessap contributed to initial study design, analysis, and interpretation of data. Dr Arrestier, Dr Bay, Dr Chantelot, Dr Labedade, Dr Moncomble, Dr Gendreau, Dr Benelli, Dr Cintrat, and the ADEL study group participated to data extraction and analysis. Dr Gendreau, Dr Benelli, Dr Cintrat, Dr Razazi contributed to drafting of the submitted article. Dr Gendreau, Dr Benelli, Dr Cintrat, Dr Razazi, Dr Dufranc, Dr Arrestier, Dr Bay, Dr Chantelot, Dr Labedade, Dr Moncomble, Pr Guillaume Carteaux, Pr Nicolas de Prost, Dr Anne Hulin, Dr Pressiat, and Dr Mekontso Dessap contributed to critical revisions for intellectual content, and providing final approval of the version to be published.

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Abstract

Introduction: Delirium is common in ICU and the neurotoxicity induced by antibiotics could be at least in part responsible for it. This study explored the association between βLactam overdosing and persistent coma or delirium in patients under mechanical ventilation.

Methods: All adult patients admitted in ICU receiving continuous sedation were included. βLactam's concentrations were collected during sedation, and up to 48 hours after end of continuous sedation. Antibiotic dosings were performed 24 hours after initiation or after changing the dose or every 48 hours. Overdosing was defined as βLactam concentrations above the target for the most resistant pathogen empirically considered, therefore 8 times its clinical breakpoint (BP) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The primary outcome was encephalopathy, defined as either delirium or persistent coma during the 48 hours following sedation removal.

Results: 224 mechanically ventilated patients were prospectively included, and 190 patients assessed for primary outcome. 58% of patients presented an encephalopathy (30/111 persistent coma and 81/111 delirium), and had longer ventilation duration, more extubation failure, longer ICU length of stay, and higher mortality. βLactam overdosing rate was similar in patients with or without encephalopathy. Factors associated with encephalopathy were age, sedation duration and SOFA score. A subgroup analysis suggested an association of encephalopathy with overdosing when defined as per published neurotoxic thresholds.

Conclusions: βLactam's overdosing was not associated with occurrence of encephalopathy. These data highlight the complexity of delayed awakening and may suggest to broadening the identification of neurotoxic thresholds of individual antibiotics in further studies.

Key words: Delirium, coma, antibiotics, therapeutic drug monitoring, encephalopathy, neurotoxicity

Introduction

Delirium in critical care settings is a common yet not well characterized manifestation of brain dysfunction. It is either hypoactive or agitated, and could manifest by reduced psychomotor activity, fluctuating alertness, attentional and judgmental disorders, temporal and spatial disorientation, sleep-wake cycle disorders, or psychomotor agitation [1]. It can be routinely assessed by the Confusion Assessment Method for the ICU (CAM-ICU)[2] or Intensive Care Delirium Screening Checklist (ICDSC) [3]. Delirium was reported in up to 80% of mechanically ventilated patients [2,4]. Delirium is associated with higher mortality [5], longer durations of mechanical ventilation, longer lengths of stay [6] in ICU and the hospital [7], higher costs, and a higher risk of cognitive impairment in survivors [8]. The pathophysiology of delirium is not yet fully clarified, and multiple associated factors have been described, including age, previous history of dementia or hypertension, sepsis, cephalosporin's consumption [9], and mechanical ventilation [10]. Amongst mechanically ventilated patients, delayed awakening is a manifestations of encephalopathy, defined as either coma or delirium. After cardiac arrest, delayed awakening was defined after more than 48 h after sedation removal, and was associated with unfavorable 3-months outcome [11]. Persistent coma has been already previously assessed as side effect attributed to an overdosing of antibiotics[12].

The impact of antibiotics on delirium is still uncertain in ICU. Neurotoxicity induced by antibiotics is known since 1945 [13], and was associated with higher antibiotic's concentrations [14]. β-Lactams are the most commonly prescribed antimicrobials in intensive care unit (ICU) settings [15]. Pharmacokinetics of all molecules including beta-lactams are modified in critical care settings due to either increased volume of distribution, capillary leakage, hypoalbuminemia, and renal insufficiency [16], with a risk of overdosing or underdosing. Antimicrobial exposure could be responsible for neurological deterioration, especially in the presence of acute renal failure [16,17]. During sepsis, it is recommended to optimize dosing strategies of β-Lactam antibiotics[18], and French guidelines recommended a target of 4 to 8 times the minimum inhibitory concentration (MIC) of the identified or suspected germ in patient hospitalized in intensive care unit[19], and daily doses of antibiotics are often greatly increased [20]. The wide pharmacokinetic variability of beta-lactams in critically ill patients provides a significant challenge to clinicians in ensuring appropriate antibiotic doses are prescribed. Therapeutic drug monitoring is therefore recommended to improve clinical cure and avoid toxicity.

Encephalopathy in mechanically ventilated patients could be attributed to β-Lactams neurotoxicity in case of overdosing [12]. However, this association is still unproven. This study explored the association between β-Lactam overdosing and acute encephalopathy defined as persistent coma or delirium in patients under mechanical ventilation.

Material and methods

All patients admitted in the medical ICU of a French tertiary hospital and receiving continuous sedation were screened for inclusion. Patients were excluded if they met one or more of the following criteria: <18 years old, women with pregnancy, patients with conditions that would make assessments for encephalopathy unreliable (hearing loss, non-comprehension of French, known or suspected severe neurologic disease such as from an anoxic and severe dementia or psychosis), admission for alcohol withdrawal syndrome or cardiac arrest.

The following data were collected: anthropometric data (age, sex, weight, height), comorbidities (cardiac, respiratory, renal failure, chronic dialysis, diabetes, immunosuppression, neurological pathology, psychiatric pathology, addictions), long term use of psychoactive drugs (i.e., benzodiazepine, neuroleptics or serotonin reuptake inhibitor), sepsis-related organ failure assessment SOFA score [21], infection-related parameters (i.e., site of infection, microorganism), reason for ICU admission, date of sedation discontinuation, temperature, and biological parameters at ICU admission.

Sedation and delirium assessment

All patients underwent a standardized nurse-driven analgesia and sedation strategy. Sedation was administered continuously. Pain and sedation management followed the PADIS guidelines. Pain in mechanically ventilated patients was assessed using the Behavioral Pain Scale (BPS), one of the most reliable tools for evaluating pain in critically ill adults unable to self-report. Sedation was managed through a nurse-driven, protocolized approach aimed at achieving and maintaining a light level of sedation. According to the ICU protocol, for patients not receiving neuromuscular blocking agents, sedation doses were titrated by nurses during each round based on the Richmond Agitation–Sedation Scale (RASS), targeting a score between –1 and +1. Daily sedation awakening was performed, although systematic daily interruption was not implemented. An assessment-driven protocol was applied, mandating regular evaluation of pain and sedation using both BPS and RASS, providing explicit guidance on medication selection and dosing, and prioritizing analgesia before sedation—an “analgesia-first” approach. Early mobility and exercise were encouraged in our unit. Antibiotic therapy was carried out according to the department's protocol and adapted to kidney function after a 24-hours of full dose in case of septic shock or sepsis. Antibiotic residuals were collected every 48 hours or 24 h after any dose adjustment. Characterization of the state of consciousness (by the RASS score) [22], and delirium

assessment (using the Confusion Assessment Method for ICU (CAM- ICU) score) [2] were performed twice daily on all assessable patients over the period by trained nurses or physicians [23]. Mental status on each day was classified as normal, delirious, or comatose.

Evolution and outcome included date of discharge from the ICU, length of ventilation and ICU stay, and vital status (alive or dead). Antibiotics' concentrations collected at any time before the end of continuous sedation and up to 48 hours after end of continuous sedation, were taken into account for the analysis of the primary endpoint, as well as concentrations collected during the 48 hours preceding the end of continuous sedation (Figure 1).

The main outcome was the occurrence of acute encephalopathy, defined as either delirium (assessed by the CAM-ICU score) or persistent coma (defined by RASS score of -4 and -5) during the 48 hours following sedation removal. Explorations of encephalopathy included electroencephalogram (EEG), cerebral tomodensitometry (TDM) or magnetic resonance imaging (MRI). If multiple explorations were performed, the closest to the sedation discontinuation were retained.

Antibiotics

Antibiotic dosage and route of administration were chosen by the treating physician according to ICU protocol. Aztreonam, meropenem, piperacillin, cefepime, ceftazidime, and cefoxitin were administered with 4 hours extended infusion. β-Lactam concentration measurements were performed 24 hours after initiation or dose change and every 48 hours. The plasma concentrations of β-Lactam were determined by a validated method using high-performance liquid chromatography (HPLC) coupled with UV detection at 230, 260 and 295 nm. Internal and external quality controls were regularly performed during the study period. Blood samples were obtained just before infusion of the drug (trough concentrations) and after at least the fourth dose for intermittent administration β-Lactam, and at least after 24 hours of administration (steady state concentration) for continuous administration β-Lactam.

β-Lactam overdosing was defined as documentation of antibiotic concentrations above the target for the most resistant pathogen empirically considered, i.e., 8 times its clinical breakpoint (BP) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [24]; for Oxacillin/Cloxacillin and Cefazolin, we considered thresholds of 50 mg/l and 80 mg/L, respectively, as the available fraction for antibiotic efficacy (unbound to albumin) in healthy patients is known to be reduced[12]. Overdosing was assessed during sedation and until 48 hours after sedation discontinuation (Figure 1). Sensitivity analyses used a 10 times BP threshold[25] and considered overdosing occurring two days before and after sedation cessation (Figure 1). We also assessed the role of overdosing on persistent coma

and delirium separately. A subgroup analysis focused on antibiotics with published neurotoxic thresholds [12,26–28] (see Table.A.1, Appendix).

Statistical analysis

Results are reported as median and interquartile range (25^{th}-75^{th} percentiles) or numbers with percentages. Initial bivariate statistical comparisons were conducted using χ^2 or Fisher's exact tests for categorical data and Mann-Whitney *U* test for continuous data. The primary endpoint was to compare the occurrence of encephalopathy (delirium assessed by CAM-ICU or RASS <-3 during 48 hours after sedation discontinuation) between patients with or without antibiotic overdosing. Uni and multivariable logistic regression models were built with overdosing and variables associated in literature with encephalopathy and death, including age, hypertension, immunosuppression, Serotonin Reuptake Inhibitor treatment, sedation duration, SOFA score, acute respiratory failure, acute kidney injury and renal replacement therapy, hemoglobin, urea, bilirubin, prothrombin time, hypernatremia, and encephalopathy.

Collinearity was assessed by variance inflation factor (VIF <3) [29]. Analyses were performed using R (The R Foundation for Statistical Computing, Vienna, Austria). Two-sided p-values <0.05 were considered significant.

Sensitivity analysis were conducted on the main outcome, with exclusion of patients admitted for neurological reason (n=51) and patients who never received antibiotics (n=7).

Ethical considerations

This observational prospective study was approved by the Institutional Review Board of the French intensive care medicine society (IRB00014135, manuscript number: CE SRLF 17-48). Written and oral information about the study was given to the patients, and written informed consent was waived in accordance with French law, and was approved by the Institutional Review Board of the French intensive care medicine society (IRB00014135, manuscript number: CE SRLF 17-48). All research was performed in accordance with relevant guidelines/regulations. The data were anonymously collected from medical files in a secure database declared to the National Commission for Information Technology and Civil Liberties.

Results

Patients

Between November 2017 and March 2019, 329 patients were screened for inclusion criteria, and 224 mechanically ventilated patients were prospectively included in this study. 34 patients were further excluded because they never had sedation cessation (27/34) or no neurological assessment after sedation cessation (7/34), leaving 190 patients for analysis (Figure 2). Characteristics of excluded patients are summarized in Table.A.2, Appendix.

Encephalopathy

111 patients (58%) experienced encephalopathy, including 30/111 (27%) with persistent coma and 81/111 (73%) with delirium (Table 1). Patients with and without encephalopathy had similar characteristics at baseline except for older age, more hypertension, and less serotonin reuptake inhibitor as baseline treatment in the former group (Table 1). Upon ICU admission, patients with encephalopathy also had more organ failures (higher SOFA score), including acute kidney failure, as compared to their counterparts (Table 1). At time of sedation cessation, patients with encephalopathy had longer sedation duration, higher values of blood urea, creatinine, sodium, and lactates as compared to those without encephalopathy (Table 2). Neurological exams were performed in 72 (65%) patients with encephalopathy and included tomodensitometry (N=65/111), MRI (24/111) and/or EEG (52/111) (Table 2). Ischemic or hemorrhagic stroke were found in 4 (16%) patients without encephalopathy versus 25 (36%) patients with encephalopathy (p: 0.06).

β-Lactam concentration

Seven patients didn't received β-Lactam. β-Lactam concentration could be assessed in 140/183 (77%) patients (46 patients were assessed once, 41 patients twice, 25 patients 3 times, 28 patients more than 3 times). Results for antibiotic concentration assessment are summarized in Table 2 and Figure 3. The main β-Lactams with blood concentration assessment were amoxicillin (109/349, 31%) and piperacillin (100/349, 29%). There was no significant difference in age between patients with overdose and those without (p = 0.2). However, acute kidney injury was more prevalent among patients with overdose (n = 28, 72%) compared to those without overdose (n = 58, 54%; p = 0.049). Overdosing (above 8 times the worst pathogen breakpoint) occurred in 39/147 (27%) patients that could be assessed. Overdosing rate did not significantly differ between patients with encephalopathy and those without in the main analysis [14/58 (24%) vs 25/89 (28%), p=0.6], and in sensitivity analyses (considering the 10 times BP threshold

and/or cases occurring within two days of sedation cessation) (Table 2). The separate analysis of delirium and prolonged coma found a trend towards more patients with overdosing in the group with vs without prolonged coma [10/24(42%) vs 29/123(24%), p=0.07], while overdosing was similar in patients with or without delirium [15/65(23%) vs 24/82 (29%), p=0.4]. In the subgroup analysis focusing on β-Lactams with published neurotoxic thresholds, overdosing defined as per these thresholds was more frequent in patients with encephalopathy as compared to those without [22/69 (32%) vs 7/50 (14%), p=0.02] (Table 2). There was a high proportion of acute encephalopathy amongst patients exposed to amoxicillin (62%, n=60), piperacillin (66%, n=53), cefotaxime (65%, n=34), imipenem (69%, n=16), cefepime (78%, n=9), and oxacillin (100%, n=4) (see Fig.A.1, Appendix). Evolution of daily RASS score wasn't different in patients with or without overdosing, as presented in Fig.A.2, Appendix.

Outcome and risk factors

Patients with encephalopathy had less extubation success, longer ventilation duration and ICU length of stay, and a higher mortality as compared to their counterparts (Table 2). The association of encephalopathy with mortality persisted in multivariable analysis (see Table.A.3, Appendix). Factors associated with encephalopathy by multivariable analysis included age, sedation duration and SOFA score upon admission (Table 3).

Sensitivity analysis

β-Lactam overdosing was not associated with encephalopathy when excluding patients admitted for neurological reason (see Table.A.4, Appendix), or patients who never received antibiotics (see Table.A.5, Appendix). Only age and sedation duration were consistently associated with encephalopathy.

Discussion

We herein report the occurrence of encephalopathy at sedation cessation in a majority of mechanically ventilated patients, mostly presenting as delirium. β-Lactam overdosing (as defined by a 8 times BP) was not associated with encephalopathy. However, a subgroup analysis suggested an association of encephalopathy with overdosing when defined as per published neurotoxic thresholds.

Encephalopathy

In this study, encephalopathy was independently associated with mortality, as well as length of stay and ventilation duration, as previously reported [6]. The main expression of encephalopathy in the present study was delirium, with an incidence (43%) in accordance with previous reports [7], stressing the need to tackle this multifactorial and dreaded complication of ICU stay. Sedation protocols, pain monitoring and treatment, an early mobilization are the key points of delirium prevention. Haloperidol for prevention of delirium didn't show benefit on mortality and length of stay in a randomized controlled trial [30]. Although dexmedetomidine was previously associated with a reduced risk of delirium [31], recent results suggested an increased 90-day mortality in patients <65 years old [32]. Exploratory studies with conflicting results involved melatonin [33], risperidone [34] and ketamine [35,36], and these molecules deserve further investigations. It was previously reported that benzodiazepine could be protective against neurotoxicity induced by piperacillin [14], an association not evidenced in our study. In our study, only age and SOFA score upon admission were independently associated with encephalopathy. These findings are in accordance with previous studies on sepsis-associated encephalopathy [37]. Indeed, alteration in mental status is often multifactorial, and it could suggest that accumulation of sedative drugs in the brain is potentiated in case of advanced age, liver and kidney failure especially with the reported alteration of the blood-brain barrier in critically-ill patients, resulting in a greater sensitivity of the brain to drug concentration[37]. Sedatives and antibiotics can interact through several mechanisms. First, some of these drugs are both eliminated renally, which can lead to the accumulation of both agents in patients with impaired kidney function. In addition, antibiotics may potentiate sedative-induced respiratory depression. Experimental studies in rats have also shown that penicillin can reduce the number of benzodiazepine receptors, leading to decreased inhibitory neurotransmission and altered neuronal excitability[38].

Encephalopathy manifested as persistent coma in only one third of cases. A previous study considering side effects attributed to oxacillin and cloxacillin overdose found similar features, with 8 cases of delirium and 3 of persistent coma [12]. As persistent coma is usually excluded from studies on delirium, this clinical entity and its association with antibiotics are still poorly characterized.

Antibiotic neurotoxicity

Clinical manifestations of antibiotic-induced neurotoxicity are wide, with either altered mental status, seizures, hallucinations or confusion, focal neurological defect or coma [39,40]. Neurotoxicity threshold were assessed with different definitions for neurotoxicity in previous studies, including neurological defect, confusion, depressed level

of consciousness, hallucinations, or seizures[41], increased neurological SOFA[14], abnormal electroencephalograph[14], or any clinical symptoms of neurotoxicity[28]; none of these studies used delirium nor persistent coma.

The diagnosis of neurotoxicity is therefore highly challenging in critically-ill patients as no specific sign exists. The underlying mechanism of β-Lactam neurological adverse drug reactions is not fully known but could involve GABA pathway. β-lactam antibiotics are believed to interfere with GABAergic neurotransmission through their β-lactam ring, which bears structural resemblance to GABA. This interaction results in competitive antagonism at GABA(A) receptors, thereby reducing inhibitory synaptic activity and promoting neuronal hyperexcitability[42]. Most frequently implicated classes of antibiotics are cephalosporin, penicillin, carbapenem, quinolone, and macrolide. Available data previously suggested that, among the beta-lactam antibiotics, cefepime, might carry the highest risk of mental status change and encephalopathy [17]. In this study, only 5% of patients received cefepime before neurological assessment, which prevented any further analysis on these associations.

Antibiotic overdosing

In this study, 27% patients had β-Lactam overdosing (above 8 times the BP) during sedation. Previous reports on overdosing in ICU are scarce, with a prevalence ranging from 9% [43] to 81% [44]. Our main definition of β-Lactam overdosing used a threshold of 8 times the BP. This definition may not be fully relevant for toxicity, because it is primary derived from an efficacy (but not tolerance) parameter. This may at least in part explain why despite therapeutic drug monitoring improved treatment response, it did not alter adverse drug events related to antibiotics [45]. The scientific evidence strongly supports maintaining β-lactam concentrations above the MIC for 100% of the dosing interval. However, data demonstrating a benefit of maintaining concentrations 100% of the time above 4× MIC are more heterogeneous. Moreover, as MIC values are often unavailable, clinicians frequently use the highest breakpoint of the microorganisms targeted by the antibiotic, which results in targets that are substantially higher than the actual MIC of the identified pathogen. Therapeutic drug monitoring (TDM) likely allows for the rapid detection of under- or overdosing, although randomized studies have not demonstrated a survival benefit. A continuous infusion aiming for approximately 4× MIC appears sufficient to ensure clinical efficacy. Interestingly, in a subgroup analysis, overdosing defined as per published thresholds of neurotoxicity showed a significant association with encephalopathy. However, the important number of missing values precluded a multivariable analysis with this definition. Taken together, these findings suggest the need for large observational studies to assess specific toxicity thresholds for individual β-Lactams, using a consensual definition for neurotoxicity.

Strengths and limitations

To our knowledge, this is the first study attempting to assess prospectively a broad association between β-Lactam overdosing and encephalopathy. Our study presents some limitations. β-Lactams dosing was not available for all patients, especially for the subgroup with published neurotoxicity thresholds. We lacked power to investigate neurotoxicity related to specific antibiotics, including cefepime. Finally, renal function was assessed using creatinine levels upon admission, but variations during the hospital stay may not have been accounted for.

Conclusions

An encephalopathy occurred in a majority of mechanically ventilated patients at sedation cessation, and mainly manifesting as delirium. β-Lactam overdosing (as defined by an 8 times BP threshold) was not associated with encephalopathy. However, a subgroup analysis suggested an association of encephalopathy with overdosing when defined as per published neurotoxic thresholds. These observations highlight the complexity of encephalopathy in ICU, and may support the need for large prospective studies to depict the neurotoxicity thresholds of specific antibiotics.

List of abbreviations

BP	breakpoint
CAM-ICU	Confusion Assessment Method for the ICU
EEG	electroencephalogram
EUCAST	the European Committee on Antimicrobial Susceptibility Testing
HPLC	high-performance liquid chromatography
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive care unit
MIC	minimum inhibitory concentration
MRI	magnetic resonance imaging
RASS	Richmond Agitation-Sedation Scale
SOFA	Sepsis-related Organ Failure Assessment
TDM	tomodensitometry

Tables and figures

Table 1. Demographic data

Table 2. Treatments and evolution

Table 3. Univariate and multivariate analysis of factors associated with encephalopathy

Figure 1. Time-line of the study

Figure 2. Flow chart of patients included

Figure 3. β-Lactams dosing available before and 48 hours after sedation discontinuation

Table 1. Demographic data

Label	NA	No encephalopathy N= 79	Encephalopathy N= 111	Total **N= 190**	P value
Sex (male)	0	46 (58%)	77 (69%)	123 (65%)	0.1
BMI (med, IQR)	11	25.6 [22;33]	25.3 [23;30]	25.3 [23;31]	0.99
Age (med, IQR)	0	62 [47;69]	68.5 [59;78]	65.9 [55;73]	**<0.0001**
Past medical history					
COPD	0	14 (18%)	15 (14%)	29 (15%)	0.4
Obstructive sleep apnea	0	9 (12%)	10 (9%)	19 (10%)	0.5
Hypertension	0	36 (46%)	73 (66%)	109 (57%)	**0.006**
Cardiac insufficiency	0	11 (14%)	9 (8%)	20 (11%)	0.2
Neurological past history	0	12 (15%)	24 (22%)	36 (19%)	0.3
Stroke	0	10 (13%)	18 (16%)	28 (15%)	0.5
Mild cognitive impairment	0	2 (3%)	7 (6%)	9 (5%)	0.3
Epilepsy	0	4 (5%)	9 (8%)	13 (7%)	0.4
Cirrhosis	0	2 (3%)	2 (2%)	4 (2%)	>0.99
Immuno-depression	0	21 (27%)	22 (20%)	43 (23%)	0.3
Diabetes	0	23 (29%)	29 (26%)	52 (27%)	0.6
Chronic renal failure (<60 ml/min)	0	14 (18%)	17 (15%)	31 (16%)	0.7
Chronic RRT	0	5 (6%)	1 (1%)	6 (3%)	0.08
Psychiatric disorder	0	7 (9%)	4 (4%)	11 (6%)	0.2
Alcoholism	0	5 (6%)	14 (13%)	19 (10%)	0.2
Drug consumption	0	2 (3%)	2 (2%)	4 (2%)	> 0.99
Benzodiazepines	0	8 (10%)	8 (7%)	16 (8%)	0.5
Serotonin Reuptake Inhibitor	0	7 (9%)	2 (2%)	9 (5%)	**0.04**
Antipsychotic drug	0	3 (4%)	3 (3%)	6 (3%)	0.7
Corticoids	0	11 (14%)	12 (11%)	23 (12%)	0.5
Main reason for admission:					
Surgery	0	9 (11%)	6 (5%)	15 (8%)	0.3
Medical non neurological		51 (65%)	73 (66%)	124 (65%)	
Neurological		19 (24%)	32 (29%)	51 (27%)	
Organ failure upon admission					
SOFA score upon inclusion	0	7 [4;8]	8.0 [6;10]	7 [5;9]	**<0.0001**
Respiratory insufficiency	0	32 (41%)	52 (47%)	84 (44%)	0.5
Coma	0	14 (18%)	28 (25%)	42 (22%)	0.3
Other neurological impairment	0	7 (9%)	12 (11%)	19 (10%)	0.8
Sepsis	0	5 (6 %)	5 (5%)	10 (5%)	0.8
Shock	0	21 (27%)	26 (23%)	47 (25%)	0.6
Acute kidney injury	0	35 (44%)	68 (61%)	103 (54%)	**0.02**
RRT (acute and chronic)	0	10 (13%)	27 (24%)	37 (20%)	**0.05**
Infection upon admission	0	37 (47%)	60 (54%)	97 (51%)	0.3
Conditions upon admission					
Mean arterial pressure, mmHg (med, IQR)	0	88.0 [71;110]	87.0 [70;102]	88.0 [70;103]	0.6
Minimal temperature, °C , (med, IQR)	17	36.4 [35.9, 36.8]	36.4 [35.9, 37]	36.4 [35.9, 36.9]	>0.99
Maximal temperature, °C (med, IQR)	17	37.6 [37.1, 38.3]	37.8 [37.3, 38.6]	37.70 [37.2, 38.5]	0.2
Single room	10	18 (24%)	31 (29%)	49 (27%)	0.5
Sleeping pills	4	3 (4%)	5 (5%)	8 (4%)	>0.99
Propofol	4	26 (34%)	29 (27%)	55 (30%)	0.3
Midazolam	4	43 (56%)	71 (65%)	114 (61%)	0.2
Morphine	4	1 (1%)	0	1 (1%)	0.4
Sufentanil	4	54 (7%)	82 (75%)	136 (73%)	0.4
Dexmedetomidine	4	0	1 (1%)	1 (1%)	>0.99
Neuroleptics	4	0	0	0	-
Catecholamine upon admission					
Epinephrine		0	1 (1%)	1 (1%)	0.9
Dobutamine		1 (1%)	3 (3%)	4 (2%)	
Norepinephrine		16 (20%)	20 (18 %)	36 (19%)	
None		62 (79%)	87 (78%)	149 (78%)	
Biology upon admission					
Urea, mmol/L (med, IQR)	3	6.5 [4.5;11.1]	10.1 [6.0;15.3]	8.6 [5.1;13.0]	**0.001**
Sodium, mmol/L (med, IQR)	1	138 [134;140]	138 [135;143]	138 [134;141]	0.1
Creatinine, mmol/L (med, IQR)	3	86 [64;128]	107 [69;170]	98 [67;167]	0.09
Glycemia, mmol/L (med, IQR)	48	8.3 [6.5;10.8]	8.4 [6.6;11.8]	8.4 [6.6;11.7]	0.6
Bilirubin, µmol/L (med, IQR)	53	9.5 [7.0;15.5]	12.0 [8.0;18.5]	11.0 [7.0;17.0]	**0.04**
Prothrombin time, % (med, IQR)	79	70 [53;83]	70 [53;80]	70 [53;80]	0.6

WBC, G/L (med, IQR)	0	12.2 [6.9;16.1]	12.7 [8.0;16.6]	12.4 [7.9;16.4]	0.7
Hemoglobin, g/dL (med, IQR)	9	11 [8.8;13.4]	11.1 [9.1;13.2]	11.1 [8.9;13.3]	0.7
Platelet, G/L (med, IQR)	9	213 [152;282]	203 [139;271]	205 [142;277]	0.6
Hyponatremia <135mmol/L	1	23 (29%)	27 (25%)	50 (27%)	0.5
Hypernatremia > 145mmol/L	1	4 (5%)	17 (16%)	21 (11%)	**0.03**
Hypoglycemia < 3mmol/L	48	1 (2%)	1 (1%)	2 (1%)	>0.99
Hyperglycemia > 10 mmol/L	48	18 (31%)	30 (36%)	48 (34%)	0.5
Hypercapnia > 45mmHg	14	21 (29%)	19 (18%)	40 (23%)	0.1

COPD: chronic obstructive pulmonary disease; BMI: body mass index; AKI: acute kidney injury; RRT: renal replacement therapy; FiO2: fraction of inspired oxygen; PaO2: arterial partial pressure of oxygen; PaCO2: arterial partial pressure of carbon dioxide; SaO2: arterial saturation of oxygen; WBC: white blood cells; TP: prothrombin time;

Table 2. Treatments and evolution

Label	NA	No encephalopathy N= 79	Encephalopathy N= 111	Total N= 190	P value
Time to first sedation discontinuation, days (med ,IQR)	0	2 [1;3]	2 [1;5]	2 [1;4]	0.049
Sedation at inclusion					
Propofol		26 (34%)	29 (27%)	55 (30%)	0.3
Midazolam		43 (56%)	71 (65%)	114 (61%)	0.2
Sufentanil		54 (70%)	82 (75%)	136 (73%)	0.4
Dexmedetomidine		0 (0%)	1 (1%)	1 (1%)	> 0.99
Antibiotics and dosing					
Overdosing 2 days before sedative withdrawal[#]					
At least 8 times above BP*	50	12 (22%)	19 (22%)	31 (22%)	0.9
At least 10 times above BP*	50	8 (15%)	16 (19%)	24 (17%)	0.5
Antibiotics with published neurotoxic thresholds	77	6 (13%)	18 (28%)	24 (21%)	0.05
Overdosing at any time before sedative withdrawal[#]					
At least 8 times above BP*	43	14 (24%)	25 (28%)	39 (27%)	0.6
At least 10 times above BP*	43	10 (17%)	19 (21%)	29 (20%)	0.5
Antibiotics with published neurotoxic thresholds	71	7 (14%)	22 (32%)	29 (24%)	**0.02**
Neurological explorations					
Tomodensitometry	0	23 (29.1%)	65 (58.6%)	88 (46.3%)	**0.0001**
Magnetic resonance imaging	0	7 (8.9%)	24 (21.6%)	31 (16.3%)	**0.02**
Electro-encephalogram	0	13 (16.5%)	52 (46.8%)	65 (34.2%)	**<0.0001**
None	0	54 (68.4%)	39 (35.1%)	93 (48.9%)	**<0.0001**
Epilepsy on EEG	126	0 (0%)	2 (3.8%)	2 (3.1%)	>0.99
TDM/MRI results					
Ischemic stroke	96	3 (12.0%)	19 (27.5%)	22 (23.4%)	0.1
Hemorrhagic stoke	96	1 (4.0%)	9 (13.0%)	10 (10.6%)	0.3
Tumor or mass	96	2 (8.0%)	3 (4.3%)	5 (5.3%)	0.6
Sequellae or leucopathy	106	3 (13.6%)	17 (27.4%)	20 (23.8%)	0.2
Outcomes					
Extubation success	0	73 (92.4%)	75 (67.6%)	148 (77.9%)	**0.0001**
Tracheotomy	0	1 (1%)	6 (5%)	7 (4%)	0.2
Ventilation duration, (med ,IQR)	2	3 [2, 7]	9 [5, 19]	7 [3, 13]	**<0.0001**
ICU length of stay (med, IQR)	0	6 [3;11]	10 [4;20]	8 [3;14]	**0.01**
Death	0	6 (8%)	35 (32%)	41 (22%)	**0.0001**

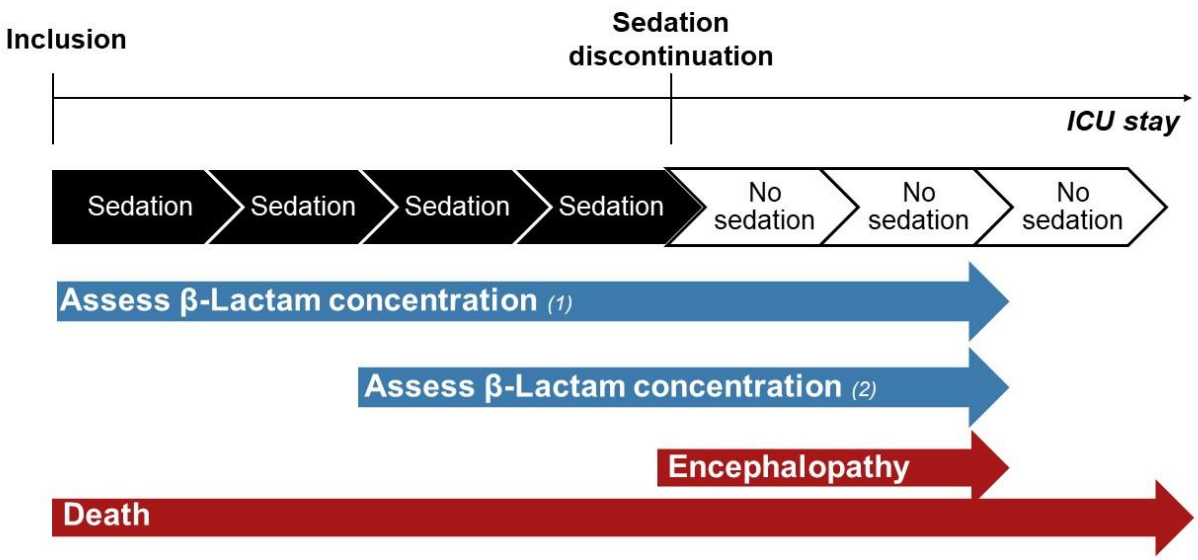
¤ (Meropenem, Piperacillin, Cefepime); [#] Overdosing at any time before sedative withdrawal, and up to 48 hours after, or overdosing 48 hours before, and up to 48 hours after sedative withdrawal (Figure 1); * threshold value for overdosing for oxacillin and cefazolin are > 50mg/L and > 80mg/L, respectively; FiO2: fraction of inspired oxygen; PaO2: arterial partial pressure of oxygen; PaCO2: arterial partial pressure of carbon dioxide; SaO2: arterial saturation of oxygen; WBC: white blood cells; ICU: intensive care unit**;** BP : breakpoint according to the European Committee on Antimicrobial Susceptibility Testing

Table 3. Univariate and multivariate analysis of factors associated with encephalopathy

Variable	Univariate		Multivariate	
	OR	**P value**	**OR**	**P value**
Overdosing at any time before sedative withdrawal (8BP) *	1.23 [0.6;2.7]	0.6	0.8 [0.3;1.8]	0.5
Age	1.1 [1.;1.1]	**0.0001**	1 [1;1.1]	**0.01**
Hypertension	2.3 [1.3;4.2]	**0.01**	1.7 [0.7;3.9]	0.2
Serotonin Reuptake Inhibitor	0.2 [0.03;0.8]	**0.04**	0.2 [0;1.8]	0.2
Sedation duration	1.2 [1.02;1.3]	**0.03**	1.2 [1;1.4]	**0.02**
SOFA score	1.2 [1.1;1.3]	**0.0002**	1.1 [1;1.3]	**0.04**
Urea, mmol/L ¤	1.1 [1;1.1]	**0.01**		
Acute kidney injury	2 [1.1;3.6]	**0.02**		
Bilirubin, µmol/L	1 [1;1.1]	**0.03**		
Hypernatremia > 145mmol/L	3.4 [1.2;12.3]	**0.03**	3.7 [1;18.2]	0.07
Urea on the day of sedation withdrawal¤	1.1 [1;1.1]	**0.001**		
Creatinine on the day of sedation withdrawal¤	1 [1;1]	**0.03**		

***** Threshold value for overdosing for oxacillin > 50mg/L and cefazolin > 80mg/L ¤ not in the multivariate because of collinearity with SOFA score (for Urea), and acute kidney injury (for urea and creatinine on the day of sedation withdrawal); BP : breakpoint according to the European Committee on Antimicrobial Susceptibility Testing

Figure 1. Time-line of the study



(1) Overdosing at any time before sedative withdrawal, and up to 48 hours after

(2) Overdosing 48 hours before, and up to 48 hours after sedative withdrawal

Figure 2. Flow chart of patients included

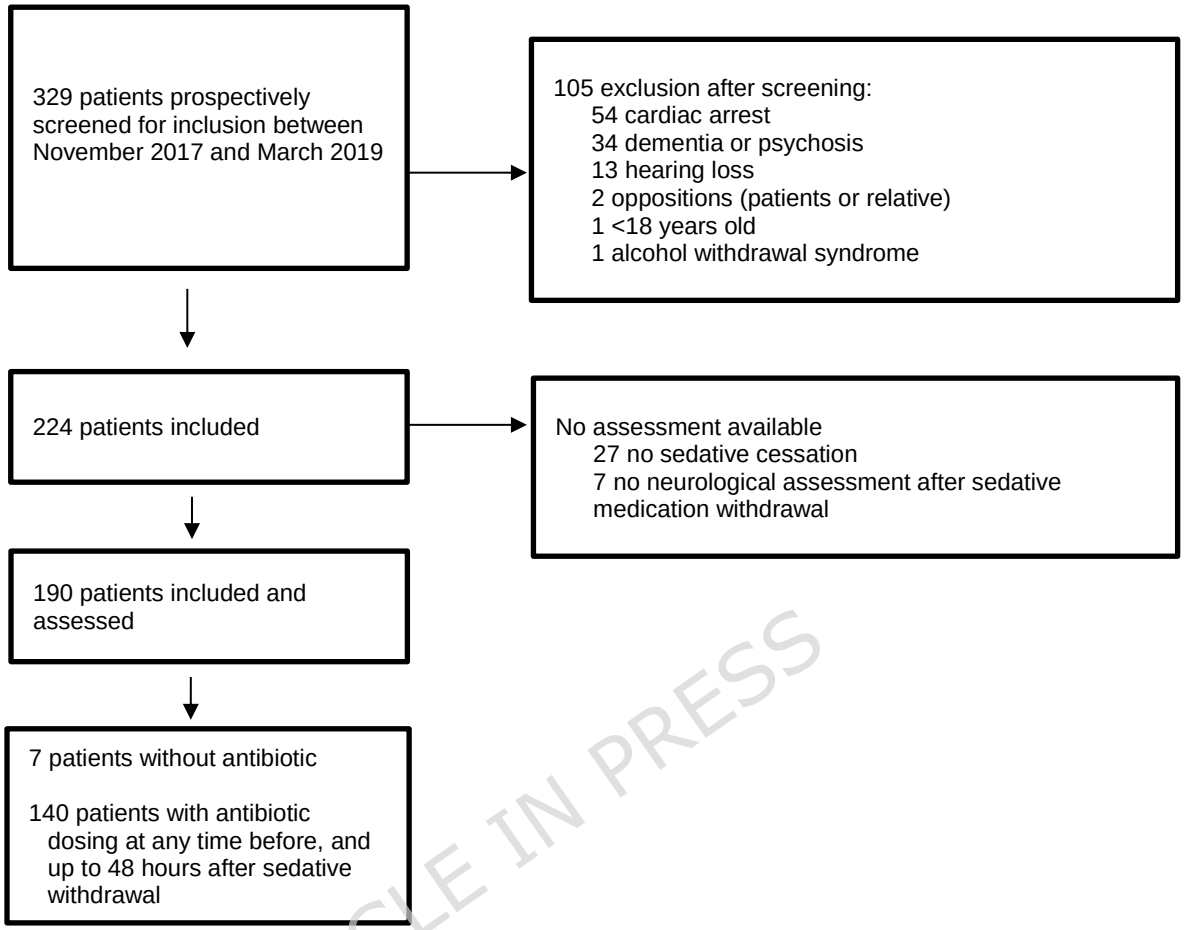
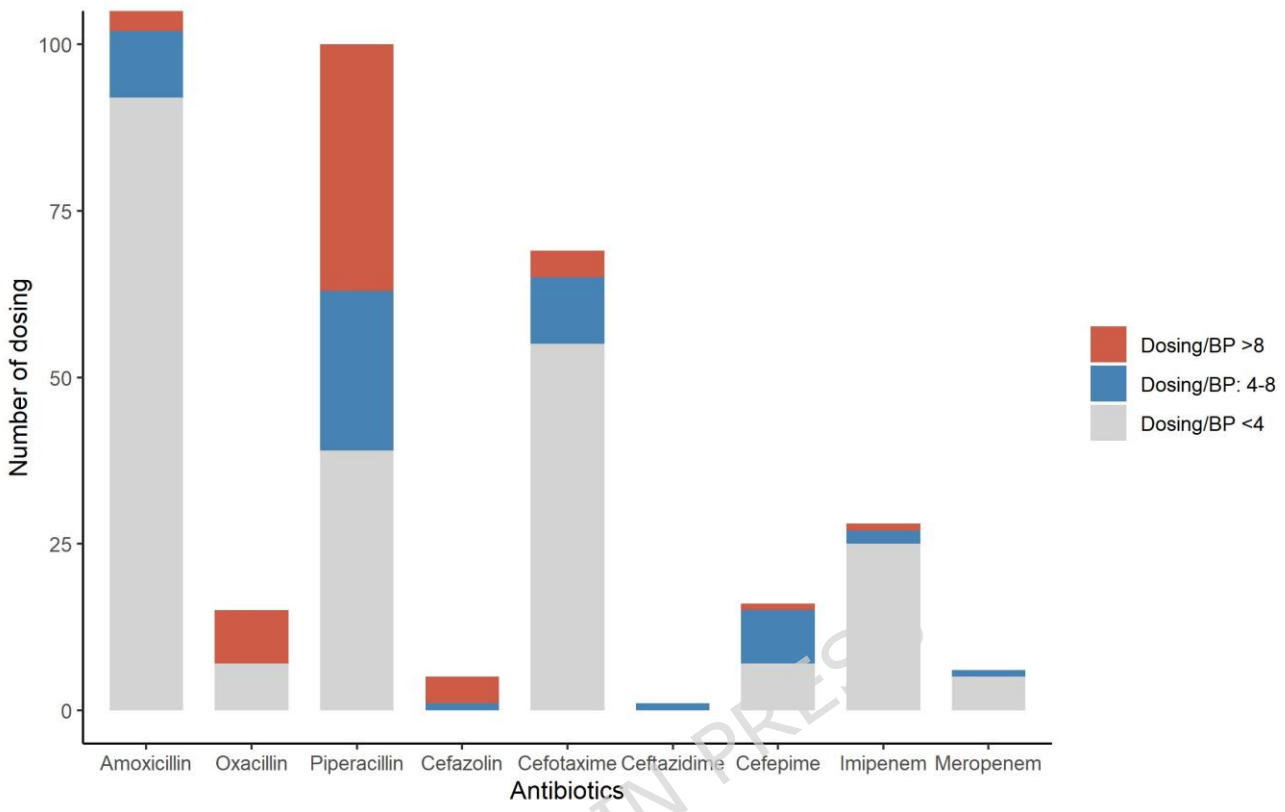


Figure 3. β-Lactams dosing available before and 48 hours after sedation discontinuation



BP: breakpoint according to the European Committee on Antimicrobial Susceptibility Testing

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