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**Highlights**

- First comparative study to evaluate therapeutic drug monitoring in infective endocarditis (IE)
- Therapeutic drug monitoring (TDM) allows a reduction in amoxicillin daily doses
- Amoxicillin recommended dosages for IE seem to be too high, especially for streptococcal IE
- Individualized treatment for IE through TDM could decrease amoxicillin dose without prognosis concern

Journal Pre-proof

**Amoxicillin therapeutic drug monitoring for endocarditis: a comparative study (EISTAB)**

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**Abstract**

**Introduction.** International guidelines recommend high doses of beta-lactams for most infective endocarditis (IE). Therapeutic drug monitoring (TDM) is increasingly used to adjust the dose based on plasma concentrations, although no comparative study supports these practices. We aimed to evaluate the benefit of amoxicillin TDM during IE.

**Methods.** An observational retrospective cohort study of all adults treated with high-dose amoxicillin for enterococcal or streptococcal IE was conducted in two referral centers. We compared patients with, or without TDM. The primary outcome was mean daily amoxicillin dose.

**Results.** We enrolled 206 streptococcal (n=140, 68%) or enterococcal (n=66, 32%) IE, on native valve (n=129, 63%) or prosthetic valve (n=77, 37%). There were 154 men (75%), mean age was 70  $\pm$ 14 years, valvular surgery was performed in 81/206 (39%) patients, and in-hospital mortality was 8% (17/206). All patients in the TDM group and the vast majority of them in the other group received amoxicillin as continuous infusion. Amoxicillin TDM was performed for 114 patients (55.3%), with a mean of 4.7  $\pm$  2.3 measures per patient, a mean plasma steady-state concentration of 41.2  $\pm$  19 mg/L, most (82/114, 72%) being within the therapeutic target (20-80 mg/L). Mean amoxicillin dose was lower in patients with TDM (10.0  $\pm$  3.3 g/day vs 11.3  $\pm$  2.0 g/day in patients without TDM,  $P=0.003$ ).

**Conclusion.** Amoxicillin TDM was associated with a reduction in daily doses, with no impact on adverse events and prognosis. Individualized treatment of IE through TDM may contribute to decreased use of antibiotics.

**Keywords:** Infective endocarditis; Amoxicillin; Therapeutic drug monitoring;

Streptococcus; Enterococcus

## 1. Introduction

International guidelines recommend 100-200 mg/kg/day of amoxicillin for streptococcal/enterococcal infective endocarditis (IE) [1,2]. The rationale for these high doses stems from the heavy bacterial inoculum and concerns that antibacterial activity within vegetations may be reduced due to suboptimal diffusion, and altered bacterial metabolism [3]. However, these doses increase the risk of neurological or renal toxicity [4,5].

Over the last two decades, therapeutic drug monitoring (TDM) for  $\beta$ -lactam agents has expanded, and results are available within 24 h after sampling in an increasing number of sites. This medical progress is welcome given the heterogeneity and multiple comorbidities of patients with IE, as it contributes to more individualized-treatment [6].

$\beta$ -lactam pharmacodynamics (PD) is characterized by time-dependent killing, which implies that the most accurate predictor of therapeutic success is the fraction of time when concentrations at infected sites are above the minimal inhibitory concentration (MIC) ( $fT > MIC$ ) [7,8]. For IE, target concentrations in vegetations were set at 4-5 times the MIC throughout the dosing interval (i.e., concentrations of 100%  $fT > 4-5 \times MIC$ ) [9–12]. Although calibrated by pharmacological studies [13] and routinely performed in several centers [14,15], the benefits of  $\beta$ -lactam TDM for IE have never been investigated through a comparative study.

We took the opportunity of two close referral centers for endocarditis, with routine access to  $\beta$ -lactam TDM in one, and no on-site access to this TDM in the other, to better characterize the impact of amoxicillin TDM during IE. Our primary hypothesis was that individualized dose guided by TDM would reduce the mean daily dose with no detrimental impact on efficacy. Our secondary hypothesis was that it may prevent neurological and renal adverse events, that are supposed to be concentration-dependent.

## 2. Patients and methods

### 2.1. Design, setting and patients

This observational retrospective study was conducted in 2 referral centers for IE in western France: Tours, where no TDM was performed during the study period (group TDM-), and Rennes where TDM was performed for all IE (group TDM +). In both centers, all patients with IE are managed by a multidisciplinary team and receive medical and surgical treatment in agreement with European guidelines [2].

Adult patients ( $\geq 18$  years) treated with  $> 7$  days of intravenous amoxicillin for streptococcal or enterococcal definite IE according to the modified Duke criteria [2] during years 2013-2018 were enrolled. During this period, amoxicillin was systematically administered through continuous intravenous infusion in Rennes and most of the time in Tours. If not, it was administered through 6 infusions per day [1,2]. Patients were identified using the national hospital discharge database. In both centers, initial dosing regimens were determined by treating physicians with possible adaptation to renal function based on the current international guidelines [1,2].

Patients under hemodialysis, extracorporeal membrane oxygenation, and those admitted for  $>7$  days in an intensive care unit were excluded because these conditions strongly interfere with antibiotic pharmacokinetics (PK) [16–18].

The study was approved by the national review board (CER-MIT n°2022-0704), and data collection was authorized (CNIL n°2205295v0). Patients were retrospectively informed of the study and could refuse to participate, but individual consent was waived in accordance with French legal standards.

### 2.2. Data collection and definitions

Data for clinical, microbiological, imaging, and pharmacological variables, as well as treatment and follow-up, were collected from medical charts through a standardized questionnaire, by 2 investigators (MD and RA).

Plasma creatinine clearance was estimated according to the eGFR equation developed by the CKD Epidemiology Collaboration (CKD-EPI) [19]. The Kidney Disease Improving Global Outcome (KDIGO) classification was used to assess renal function. Acute kidney injury (AKI) was defined as an increase in serum creatinine (SCr) by  $\geq 0.3$  mg/dL or  $\geq 1.5$  times the baseline value within 48 h [20]. Intracardiac devices were permanent pacemakers or cardioverter defibrillators. Antibacterial treatments that included gentamicin or ceftriaxone at least 5 days in association with amoxicillin were categorized as combination therapy. Neurologic side effects were defined as any neurologic symptoms attributed to amoxicillin by the physician in charge, or with no alternative cause. Relapse was defined as a new diagnosis of IE caused by the same microorganism within six months.

### *2.3. Pharmacological data*

Amoxicillin plasma concentrations were determined by a liquid chromatography method with ultraviolet detection (HPLC-UV) [21]. These concentrations corresponded to steady-state concentrations, as amoxicillin was administered through continuous infusion in the TDM+ group. The first amoxicillin plasma concentration was measured 48-72 h after start, with a target of 20-80 mg/L [13,14], in line with recent guidelines [10]. Amoxicillin plasma free concentrations (APFC) was estimated as plasma concentrations x 0.8 [10].

When available, amoxicillin MIC for the streptococcal strain responsible for IE was compared to APFC. When MIC was not available, we used the EUCAST epidemiological cutoff (ECOFF) MIC for streptococci, i.e. 2 mg/L [22].

As enterococci are beta-lactam tolerant, with a minimal bactericidal concentration (MBC) > 32 times MIC [23], we did not compare APFC to MIC for enterococcal IE.

#### 2.4. Outcomes

The primary endpoint was mean amoxicillin daily dose received throughout IE treatment course. Secondary endpoints were the number of therapeutic changes, the incidence of AKI and neurological side effects, mortality from any cause during follow-up, and relapses. Interstitial nephropathy due to amoxicillin crystalluria was reported when identified by the treating physicians as the cause of AKI in medical files.

#### 2.5. Statistical Analysis

Quantitative variables were expressed as means and standard deviation, qualitative variables as frequencies and percentages. Missing data were excluded from the denominators. Qualitative variables were compared using Pearson Chi<sup>2</sup> test and Fisher exact test, as appropriate and quantitative variables with the Wilcoxon rank sum test. Significance was set at  $P < 0.05$ .

A multivariate analysis was performed using linear regression. We included variables identified in the literature, and those with a  $P < 0.2$  on univariate analysis. Comparisons of groups for survival were based on the use of time-to-event methods, including Kaplan–Meier estimation, log-rank test and proportional hazard regression models. Statistical analyses were performed using R 4.1.2, package survival.

### 3. Results



### 3.1. Demographics and baseline characteristics

During the study period, 206 streptococcal (n=140, 68%) or enterococcal (n=66, 32%) IE have been treated with intravenous amoxicillin in participating sites; 114 (55.3%) underwent TDM, and 92 (44.7%) did not (Figure 1).

Table 1 summarizes baseline characteristics, and IE treatment. Mean age was 70 +/- 14 years, and most patients were men (154/206, 75%). IE occurred on prosthetic valves in 77 (37%) cases, and on intracardiac devices in 28 (14%). Aortic valve was involved in 136 (66%) cases.

Among streptococci isolates, 117/140 (83%) had MICs  $\leq$  0.25 mg/L, and 9 (6.4%) between 0.25 and 2 mg/L, with a maximal MIC of 1 mg/L (n=2). For 14 isolates (10%), MICs were not available (Supplementary Table 1).

Patients were treated with a mean duration of 35 days of intravenous amoxicillin. Most enterococcal IE received a combination (62/66, 94%), with ceftriaxone (n=38, 58%) or gentamicin (n=34, 52%). For streptococcal IE, amoxicillin was associated with gentamicin in 54 cases (38%). The initial amoxicillin daily dose was 11 +/- 2.7 g. Valvular surgery was performed in 81 (39%) cases, after a mean time of 12 +/- 11 days following antibacterial treatment initiation.

Baseline characteristics were similar in both groups, except for higher proportion of streptococcal IE in the TDM+ group: 87/114 (76%) vs. 53/92 (58%),  $P=0.004$ . The combination treatment for enterococcal IE also differed, with a large predominance of gentamicin in the TDM+ group: 60/64 (94%), vs. 28/52 (54%) in the TDM- group ( $P<0.001$ ).

### 3.2. Therapeutic drug monitoring

In the TDM+ group, 536 amoxicillin plasma concentrations were determined, with a mean of 4.7 +/- 2.3 measures per patient (Table 1). Mean steady-state plasma concentration was 41.2

+/- 19 mg/L, including 72% (82/114) within the therapeutic target (20-80 mg/l). Overdosing (concentration >80 mg/L) was documented in 12/114 (10%) patients, and led to a dose reduction in 11. Underdosing (concentration <20 mg/L) was observed in 23/114 (20%) patients leading to a dose increase in 20, followed by a control within the therapeutic target for all. The 3 patients with no dose change had streptococcal IE with very low amoxicillin MIC and high APFC/MIC ratios (ie, 80, 329 and 450). For streptococcal IE (n=87), all APFC/MIC ratios were >4, 100% of the time.

### 3.3. Outcomes

Mean amoxicillin daily dose was lower in the TDM+ group (10.0 +/- 3.3 g/day vs. 11.3 +/- 2.0,  $P=0.003$ ), Table 2. After linear regression, this result remained significant, with a mean amoxicillin daily dose in the TDM+ group 0.9 g lower than in the TDM- group (95%CI -1.6 to -0.3 g,  $P=0.004$ ), Table 3.

Dose changes were more frequent in the TDM+ group: 146 modifications (for 76 patients, 67%) vs 16 (and 11 patients, 12%) in the TDM- group ( $P<0.001$ ), Table 2. These modifications occurred for the 35 patients described in the previous section with under- (23) or over dosing (12), and also for 41 others with dosages within the therapeutic range.

There was no difference in the incidence of AKI (23% in the TDM+ group vs. 30% in the TDM- group,  $P=0.6$ ), with a trend towards lower incidence of crystal nephropathy in the TDM+ group: 2/114 (2%) vs. 7/92 (8%),  $P=0.09$ . Encephalopathy was rare in both groups, approximately 5%.

In-hospital mortality was similar between the two groups, but one year-mortality was lower in the TDM+ group on univariate analysis: 16/114 (14%) vs 23/92 (25%),  $P=0.046$ ), but this was no longer significant on the survival analysis (Supplementary Figure 1).

#### 4. Discussion

This first comparative study found that amoxicillin TDM during the treatment of streptococcal and enterococcal IE was associated with a decrease of 0.9 g/d in the mean dose of amoxicillin. Despite a broad predefined therapeutic target (20-80 mg/L), TDM allowed early dose adjustment in one third of patients, because of under- (20%) or over- (10%) dosing of amoxicillin on first determination of plasma concentration. The individualization of doses through routine TDM was not associated with other outcomes, but the incidence of AKI, particularly amoxicillin-induced crystal nephropathy tended to be lower in patients with TDM.

Although amoxicillin tolerability is particularly good, even at doses >10 times higher than doses initially approved by medicine agencies (i.e., 1-1.5 g/day), dose-related side effects may occur with very high concentrations. The advent of TDM provides a valuable tool to adjust the dose, and reach the PK target for each individual patient. The benefit of precision medicine may be particularly high in IE, one of the most difficult-to-treat infectious diseases, as sub-optimal doses are at high-risk of treatment failure. In addition, IE disproportionately affects elderly patients with comorbidities, a population for whom amoxicillin plasma concentrations may be difficult to predict due to the combination of impaired renal clearance, hypoproteinemia, altered liver metabolism, and hyper- or hypovolemia.

We used a broad therapeutic target, in line with previous studies [13,14], with a lower limit of steady-state concentrations set at 20 mg/L, which may still be unnecessarily high: Indeed, such a target ensures that plasma concentrations will be >100 MICs throughout treatment course for most streptococcal isolates, as 117/126 isolates (93%) had MICs <0.25 mg/L in our study, as in other contemporary studies [24]. In Rennes, where TDM has been used since a long time, initial doses have already been decreased, as highlighted by the lower, although non-significantly different, initial amoxicillin dose than in Tours (10.7 vs 11.5,

$P=0.06$ ). However, even with this initial lower dose, TDM allows a supplementary dose reduction during the antibiotic course ( $-0.7\text{g/d}$ ,  $P=0.008$ ). Of note, therapeutic targets were reached despite these reductions. This outlines that application of current guidelines leads to excessive amoxicillin doses in a majority of patients with streptococcal IE. This is probably different for enterococcal IE where Amoxicillin PK target is more difficult to determine as enterococci are amoxicillin-tolerant. A combination with another antibiotic is required to achieve a bactericidal effect but gentamicin and ceftriaxone, the two antibiotic-companion used, have the same possible side effects than amoxicillin (i.e., renal and neurological respectively). Even with such regimens, enterococcal IE are associated with increased risk of relapses [25]. TDM is probably very useful to better individualize the optimal dosage of amoxicillin in enterococcal IE, avoiding both underdosing, that could lead to a higher probability of relapse, and overdosing, with its higher risk of toxicity. Of note, underdosing was detected and corrected in a relatively high proportion of patients (5/24, 21%) with enterococcal IE in the TDM+ group, but our study was unfortunately underpowered to demonstrate this hypothetical benefit.

The renal toxicity of amoxicillin, especially crystal nephropathy, is mostly described with high doses, and several studies suggested that amoxicillin TDM could prevent AKI [26,27]. Although the incidence of AKI and crystal nephropathy was lower in the TDM+ group as compared to the TDM- group (respectively, 23% vs. 30% and 2% vs 8%), these differences didn't reach statistical significance in our study, probably underpowered for this endpoint. Neurological side effects may also be dose-related, but they have been mostly reported with very high overdosing, especially when renal function has not been accounted for in the calculation of amoxicillin doses [5].

Our study is the first comparative study evaluating routine amoxicillin TDM in patients with IE, but it has several limitations. First, it was retrospective, which could lead to

potential biases and confounding factors. However, there were few missing data, and our findings are consistent with others [13]. Second, it was a bicentric study, with a possible center effect. However, both sites are referral centers, where patients are managed according to international guidelines. Hence, our findings may probably be extrapolated to other sites with similar practices. More importantly, all patients benefited from routine TDM over the study period in Rennes, while this was not available in Tours, thus avoiding indication bias, which is the most persistent bias in observational studies [28]. Third, our results are only valid for streptococcal and enterococcal IE and cannot be extrapolated to other bacteria. For methicillin-susceptible staphylococcal IE, the variety of beta-lactam agents recommended as first-line treatment (i.e., cloxacillin, oxacillin, cefazolin, and nafcillin [1,2]), would complicate the documentation of TDM benefit, although such study would be most welcome given the emergence of *Staphylococcus aureus* as the primary pathogen in recent cohorts of IE. Forth, we did not include patients with conditions interfering with antibiotics pharmacokinetic (i.e. under hemodialysis, extracorporeal membrane oxygenation, or hospitalized in an intensive care unit for >7 days). Those patients might benefit more than others from TDM and specific studies are needed to address the interest of TDM in these specific situations. Fifth, despite a relatively large numbers of patients, our sample size is small, especially when comparing the subgroups separately for streptococcal and enterococcal infections.

## 5. Conclusions

This study advocates for systematic use of amoxicillin TDM for streptococcal and enterococcal IE, to better adjust the doses to each individual patient. Its use could lead to a more individualized approach for each patient with two main lines: dose reduction for streptococcal endocarditis and close monitoring of high amoxicillin dosage for enterococcal

endocarditis. Further comparative studies, ideally with randomization, would be requested to confirm these findings.

### **Declarations**

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**Competing Interests:** No conflicts of interest

**Ethical Approval:** Not required

**Sequence Information:** Not applicable

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- **Access data:** Matthieu Revest, Marie Dorel and Robin Albert have full access to the data. Matthieu Revest is the guarantor for the data. These data are available from Matthieu Revest, should the manuscript be accepted for publication
- **Contribution:** Matthieu Revest, Marie Dorel, Audrey Le Bot and Adrien Lemaigen contributed to the study conception and design. Material preparation and data collection were performed by Marie Dorel and Robin Albert. Data analysis were performed by Marie Dorel, Audrey Le Bot, Leila Caillault and Matthieu Revest. Statistical analysis was performed by Leila Caillault. Sébastien Lalanne and Marie-Clémence Verdier performed the pharmacological analysis. The first draft of the manuscript was written by Marie Dorel. Audrey Le Bot, Pierre Tattevin and Matthieu Revest corrected the manuscript. All authors read and approved the final manuscript.

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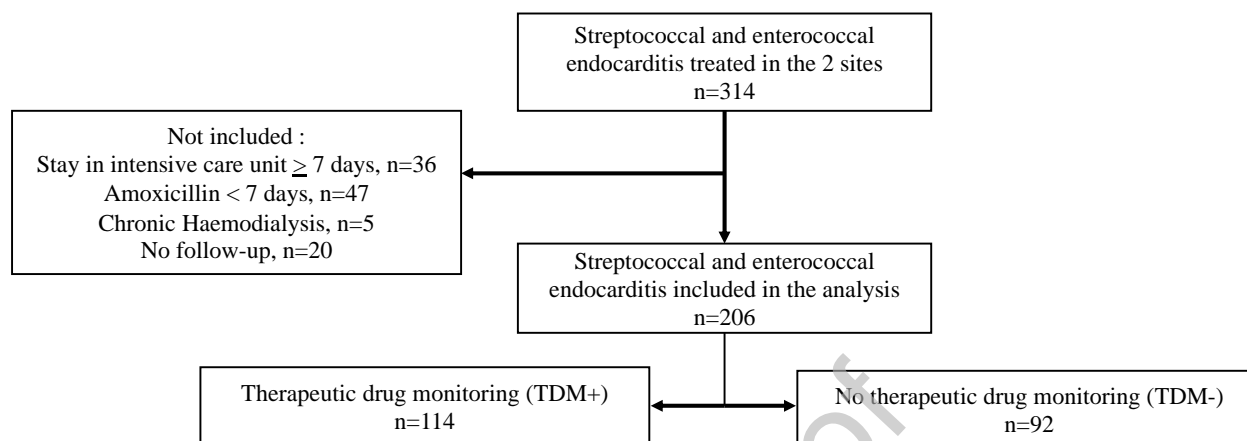
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**Figure 1.** Flow diagram of patient enrollment**Table 1.** Baseline characteristics and treatment of 206 cases of endocarditis with or without amoxicillin therapeutic drug monitoring (TDM).

Characteristic	Both groups (N= 206)	TDM + (n=114)	TDM - (n=92)	P Value <sup>1</sup>
<b>Demographic features and comorbidities</b>				
Age, years	70 (14)	69 ± 14	70 ± 14	0.85
Gender, male	154 (75)	87 (76)	67 (73)	0.57
Charlson comorbidity index	2.7 ± 2.5	2.7 ± 2.5	3.1 ± 2.5	0.27
Weight, kg	75 ± 17	75 ± 16	75 ± 19	0.76
Kidney failure	63 (31)	36 (32)	27 (29)	0.73
Creatinine clearance, ml/mn/1.73 m <sup>2</sup>	73 ± 27	73 ± 28	73 ± 26	0.90
Cirrhosis	15 (7)	7 (6)	8 (9)	0.48
<b>Clinical features</b>				
Prosthetic valve	77 (37)	44 (39)	33 (36)	0.69
Intracardiac device	28 (14)	16 (14)	12 (13)	0.84
Endocarditis location				

Aortic valve	136 (66)	79 (69)	57 (62)	0.27
Mitral valve	85 (41)	42 (37)	43 (47)	0.15
Right-sided	11 (5)	4 (3)	7 (8)	0.22
Multiple valves	36 (17)	20 (18)	16 (17)	0.98
Osteoarticular infection	48 (23)	23 (20)	25 (27)	0.24
Cerebral emboli	49 (24)	25 (22)	24 (26)	0.49
<b>Microbiology</b>				
<i>Streptococcus</i> sp	140 (68)	87 (76)	53 (58)	0.004
Oral streptococci	59 (42)	34 (39)	25 (47)	0.30
<i>Streptococcus gallolyticus</i>	41 (29)	30 (34)	11 (21)	0.08
Other Streptococci	40 (29)	23 (26)	17 (32)	0.50
<i>Enterococcus</i> sp	66 (32)	27 (24)	39 (42)	0.004
<i>Enterococcus faecalis</i>	64 (97)	26 (96)	38 (97)	0.90
<i>Enterococcus durans</i>	2 (3)	1 (4)	1 (3)	0.91
Duration of bacteremia, days	6 ± 9	7 ± 11	5 ± 6	0.16
Positive valve culture if surgery	27 (34)	16 (36)	11 (31)	0.70
<b>Treatment</b>				
Duration of intravenous antibiotic, days	35 ± 11	36 ± 9	34 ± 12	0.59
Duration of intravenous amoxicillin, days	33 ± 12	35 ± 9	31 ± 14	0.06
Initial amoxicillin daily dose, g	11 ± 2.7	10.7 ± 3.0	11.5 ± 2.2	0.06
Single-drug (amoxicillin)	90 (44)	50 (44)	40 (43)	0.96
Combination	116 (56)	64 (56)	52 (57)	0.96
With ceftriaxone	38 (33)	9 (14)	29 (56)	<0.001
With gentamicin	88 (76)	60 (94)	28 (54)	<0.001
Suppressive antibacterial treatment	4 (2)	3 (3)	1 (1)	0.63
Amoxicillin concentrations determination	N.A	4.7 ± 2.3	0	N.A
Valve surgery	81 (39)	46 (40)	35 (38)	0.74
Time from amoxicillin start to surgery, days	12 ± 11	10 ± 7	14 ± 14	0.60

Quantitative variables are expressed as the mean  $\pm$  standard deviation, and qualitative variables are expressed by numbers (%)

Abbreviations: TDM: therapeutic drug monitoring

Kidney failure: creatinine clearance (CKD EPI)  $< 60$  ml/min/1.73 m<sup>2</sup> at antibiotic start

<sup>1</sup> Wilcoxon rank sum test; Pearson's chi-squared test; Fisher's exact test

**Table 2.** Outcomes of 206 episodes of infective endocarditis with or without amoxicillin therapeutic drug monitoring (TDM).

Characteristic	Both groups (N= 206)	TDM + (n=114)	TDM - (n=92)	P Value <sup>1</sup>
<b>Primary endpoint</b>				
Average amoxicillin daily dose, g	10.6 $\pm$ 2.8	10.0 $\pm$ 3.3	11.3 $\pm$ 2.0	0.003
<b>Secondary endpoint</b>				
At least one dose change	87 (42)	76 (67)	11 (12)	< 0.001
Acute kidney injury	54 (26)	26 (23)	28 (30)	0.22
Crystalluria	9 (4)	2 (2)	7 (8)	0.09
Encephalopathy	12 (6)	7 (6)	5 (5)	0.83
<b>Mortality</b>				
In-hospital	17 (8)	7 (6)	10 (11)	0.22
One-year	39 (19)	16 (14)	23 (25)	0.046
Relapse	5 (2)	2 (2)	3 (3)	0.70

Quantitative variables are expressed as the mean  $\pm$  standard deviation, and qualitative variables are expressed by numbers (%)

Abbreviations: TDM, therapeutic drug monitoring

<sup>1</sup> Wilcoxon rank sum test; Fisher's exact test; Pearson's chi-squared test

**Table 3.** Factors associated with mean amoxicillin daily dose (results expressed in g)

Characteristic	Coefficient <sup>a</sup> (95% CI)	P Value
<b>TDM +</b>	<b>-0.95 (-1.6 to -0.30)</b>	<b>0.004</b>
Bacterium (reference: <i>Streptococcus</i> sp.)	-0.32 (-1.01 to 0.36)	0.35
Creatinine clearance <sup>b</sup> , ml/min/1.73 m <sup>2</sup>	0.05 (0.04 to 0.06)	<0.001
Initial amoxicillin daily dose <sup>b</sup> , mg/kg/d	0.02 (0.01 to 0.03)	<0.001
Duration of amoxicillin iv, days	-0.01 (-0.03 to 0.02)	0.67
Duration of bacteremia <sup>b</sup> , days	-0.00 (-0.03 to 0.03)	0.96

Abbreviations: TDM: therapeutic drug monitoring, mg/kg/d: milligrams per kilogram per day, iv: intravenous

<sup>a</sup> Coefficient of the multivariate linear regression between average amoxicillin daily dose and potential explanatory factors

<sup>b</sup> Continuous variable.