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CLINICAL THERAPEUTICS

Prospective Cohort Study of the Tolerability of Prosthetic Joint Infection Empirical Antimicrobial Therapy

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ABSTRACT The empirical use of vancomycin in combination with a broad-spectrum beta-lactam is currently recommended after the initial surgery of prosthetic joint infection (PJI). However, the tolerability of such high-dose intravenous regimens is poorly known. Adult patients receiving an empirical antimicrobial therapy (EAT) for a PJI were enrolled in a prospective cohort study (2011 to 2016). EAT-related adverse events (AE) were described according to the common terminology criteria for AE (CTCAE), and their determinants were assessed by logistic regression and Kaplan-Meier curve analysis. The EAT of the 333 included patients (median age, 69.8 years; interquartile range [IQR], 59.3 to 79.1 years) mostly relies on vancomycin (n = 229, 68.8%), piperacillin-tazobactam (n = 131, 39.3%), and/or third-generation cephalosporins (n = 50, 15%). Forty-two patients (12.6%) experienced an EAT-related AE. Ten (20.4%) AE were severe (CTCAE grade ≥ 3). The use of vancomycin (odds ratio [OR], 6.9; 95%CI, 2.1 to 22.9), piperacillin-tazobactam (OR, 3.7; 95%CI, 1.8 to 7.2), or the combination of both (OR, 4.1; 95%CI, 2.1 to 8.2) were the only AE predictors. Acute kidney injury (AKI) was the most common AE (n = 25; 51.0% of AE) and was also associated with the use of the vancomycin and piperacillin-tazobactam combination (OR, 6.7; 95%CI, 2.6 to 17.3). A vancomycin plasma overexposure was noted in nine (37.5%) of the vancomycin-related AKIs only. Other vancomycin-based therapies were significantly less at risk for AE and AKI. The EAT of PJI is associated with an important rate of AE, linked with the use of the vancomycin and the piperacillin-tazobactam combination. These results corroborate recent findings suggesting a synergic toxicity of these drugs in comparison to vancomycin-cefepime, which remains to be evaluated in PJI. (This study has been registered at ClinicalTrials.gov under identifier NCT03010293.)

KEYWORDS adverse events, empirical antimicrobial therapy, piperacillin-tazobactam, prosthetic joint infection, tolerability, vancomycin

Awaiting the culture results of microbiological samples obtained during the initial surgical management of prosthetic joint infection (PJI), the empirical antimicrobial therapy (EAT) must target the most frequently implicated pathogens, including methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*, coagulase-

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negative staphylococci, streptococci, and Gram-negative bacilli (1–7). Consequently, current guidelines recommend the use of vancomycin in combination with a broad-spectrum betalactams (i.e., piperacillin-tazobactam or a third-generation cephalosporins [3rdGC]) (8). Antimicrobial therapy of bone and joint infections has been associated with a high rate of adverse events (AE), mostly occurring in the first weeks of treatment (9). Nevertheless, the tolerability of the high-dose intravenous empirical combination therapies has never been specifically evaluated. We describe here the AE observed during EAT of PJI and their determinants.

RESULTS

Included population. Between 2011 and 2016, 567 patients were followed up for a PJI in our reference center; 234 of these patients were excluded because they received a targeted antimicrobial therapy at the outset, based on preliminary microbiological documentation. The 333 included patients who mostly had a hip ($n = 178$; 53.5%) or knee ($n = 142$; 42.6%) PJI mainly occurring within the year following the implantation (65.0%). All but two patients benefited from an initial surgical management, consisting in joint lavage, debridement, and implant retention or partial exchange ($n = 149$; 45.2%), one-stage ($n = 21$; 6.4%) or two-stage ($n = 115$; 34.8%) exchange, definitive device removal ($n = 24$; 7.3%), or amputation ($n = 3$; 0.9%). Vancomycin was by far the most prescribed molecule ($n = 229$; 68.8%), while piperacillin-tazobactam and 3rdGC were used in 131 (39.3%) and 50 (15.0%) of the cases, respectively. Other molecules used mostly included aminoglycosides ($n = 72$; 21.6%), fluoroquinolones ($n = 52$; 15.6%), and clindamycin ($n = 49$; 14.7%). The main combination therapies used were represented by vancomycin-piperacillin-tazobactam and vancomycin-3rdGC in 123 (36.9%) and 33 (9.9%) patients, respectively, as recommended in the current guidelines of the Infectious Disease Society of America (10). Among the 167 patients (50.2%) who did not receive one of these recommended regimens, 102 (61.1%) were managed before the publication of any recommendation for PJI management, and 32 (19.2%) received a antistaphylococcal penicillin-based regimen immediately after surgery because of very acute clinical presentations leading the prescriber to suspect *S. aureus* infections. Baseline characteristics and EAT of the 333 included patients are described in Table 1.

Description and determinants of EAT-related AE. Forty-two (12.6%) patients experienced at least one AE during EAT (Table 2), after a median treatment duration of 8 (IQR, 5 to 13) days. Seven patients presented at least two AE. Ten (20.4%) AE were considered severe. A lengthening in the hospitalization course or hospital readmission was necessary for 10 (25%) patients. A treatment discontinuation and switch was proposed in 38 (95.0%) cases; in other cases, corresponding to slight elevation of creatinine plasma levels associated with vancomycin overexposure, a simple dose adjustment was performed. All AE had a favorable outcome after treatment interruption or adjustment.

The baseline characteristics, the type of PJI, and the initial surgical management of patients with AE were comparable to those without AE. As stated in Table 1, patients experiencing AE more frequently received vancomycin ($n = 39$, 92.9% versus $n = 190$, 65.3%; $P = 0.002$), piperacillin-tazobactam ($n = 28$, 66.7% versus $n = 103$, 35.4%; $P < 10^{-3}$), and the combination of both ($n = 28$, 66.7% versus $n = 95$, 32.6%; $P < 10^{-3}$) in comparison to patients without AE. These three parameters were highlighted as the only determinants of the occurrence of EAT-related AE in univariate analysis, with odd ratios (ORs) of 6.9 (95% confidence interval [95%CI], 2.1 to 22.9), 3.7 (95%CI, 1.8 to 7.2), and 4.1 (95%CI, 2.1 to 8.2), respectively. Since these factors strongly interacted, no multivariate analysis was performed. Kaplan-Meier curve analysis confirmed that the probability of AE occurrence was higher in patients receiving vancomycin in combination with piperacillin-tazobactam compared to other vancomycin-based therapies ($P = 0.014$) and to vancomycin-free regimens ($P < 10^{-3}$; Fig. 1A).

As described in Table 2, acute kidney injury (AKI) was the most frequently observed AE (51.0%), occurring in 25 (7.5%) patients, all receiving vancomycin. Again, piperacillin-

TABLE 1 Description of included patients and comparison of patients with or without empirical antimicrobial therapy-related adverse events and acute renal failure[a]

Parameter or therapy	Descriptive analysis[b]					Determinants for AE (univariate analysis)		Determinants for AKI (univariate analysis)	
	Total population (n = 333)	AE (n = 42)	P*	AKI (n = 25)	P†	OR (95%CI)	P	OR (95%CI)	P
Demographics and comorbidities									
Sex, no. male	168 (50.5%)	26 (61.9%)	0.137	16 (64.0%)	0.307	1.705 (0.878–3.312)	0.115	1.643 (0.722–3.737)	0.236
Mean age, yrs	69.8 (59.3–79.1)	68.1 (60.3–73.9)	0.217	70.9 (64.4–74.1)	0.936	0.992 (0.975–1.009)	0.343	1.008 (0.982–1.036)	0.538
Mean BMI, kg/m^2 (range)	28.0 (24.7–33.0)	28.8 (25.1–31.7)	0.583	29.8 (25.1–31.6)	0.433	1.005 (0.951–1.062)	0.850	1.017 (0.952–1.088)	0.612
Obesity, BMI > 30 kg/m^2	89 (39.4%)	18 (45.0%)	0.477	12 (50.0%)	0.194	1.325 (0.665–2.641)	0.424	1.801 (0.781–4.154)	0.168
ASA score	2 (2–3)	2 (2–3)	0.692	3 (2–3)	0.208	0.914 (0.591–1.414)	0.687	1.461 (0.842–2.534)	0.177
ASA score > 2	143 (43.5%)	17 (40.5%)	0.740	13 (52.0%)	0.538	0.869 (0.450–1.679)	0.676	1.346 (0.604–3.004)	0.467
Empirical antimicrobial therapy									
Glycopeptide	262 (78.7%)	39 (92.9%)		25 (100%)					
Vancomycin	229 (68.8%)	39 (92.9%)	$<10^{-3}$	25 (100%)	$<10^{-3}$	6.911 (2.084–22.917)	0.002	NC	NC
Vancomycin trough concn (mg/liter)	NA	NA	NC	23.5 (13.6–35.8)	NC	NC	NC	NC	NC
Vancomycin overexposure (>30 mg/liter)	NA	NA	NC	8 (33.3%)	NC	NC	NC	NC	NC
Teicoplanin	33 (9.9%)	0 (0%)	0.013	0 (0%)	0.091	NC	NC	NC	NC
Daptomycin	4 (1.2%)	0 (0%)	1.000	0 (0%)	1.000	NC	NC	NC	NC
Beta-lactam									
PT	131 (39.3%)	28 (66.7%)	$<10^{-3}$	20 (80.0%)	$<10^{-3}$	3.650 (1.840–7.242)	$<10^{-3}$	5.988 (2.334–15.362)	$<10^{-3}$
3rdGC	50 (15.0%)	5 (11.9%)	0.650	2 (8.0%)	0.395	0.739 (0.275–1.981)	0.547	0.441 (0.101–1.928)	0.277
ASP	30 (9.0%)	2 (4.8%)	0.399	0 (0%)	0.149	0.470 (0.108–2.048)	0.314	NC	NC
Carbapenem	8 (2.4%)	1 (2.4%)	1.000	0 (0%)	1.000	0.990 (0.119–8.250)	0.992	NC	NC
Aminoglycoside	72 (21.6%)	6 (14.3%)	0.315	4 (16.0%)	0.470	0.568 (0.229–1.407)	0.222	0.626 (0.208–1.878)	0.403
Plus glycopeptide	46 (13.8%)	4 (9.5%)	0.480	4 (16.0%)	0.771	0.624 (0.212–1.839)	0.393	1.126 (0.369–3.429)	0.835
Others									
Clindamycin	49 (14.7%)	2 (4.8%)	0.061	1 (4.0%)	0.147	0.260 (0.061–1.111)	0.260	0.217 (0.029–1.641)	0.139
Pristinamycin	21 (6.3%)	1 (2.4%)	0.493	0 (0%)	0.392	0.330 (0.043–2.529)	0.286	NC	NC
Fluoroquinolone	52 (15.6%)	2 (4.8%)	0.040	1 (4.0%)	0.398	0.241 (0.056–1.030)	0.055	0.420 (0.096–1.834)	0.249
Rifampin	10 (3.0%)	2 (4.8%)	0.366	1 (4.0%)	0.567	1.769 (0.363–8.626)	0.481	1.302 (0.159–10.698)	0.806
Main combinations									
Vancomycin + PT	123 (36.9%)	28 (66.7%)	$<10^{-3}$	20 (80.0%)	$<10^{-3}$	4.126 (2.076–8.200)	$<10^{-3}$	6.733 (2.622–17.294)	$<10^{-3}$
Vancomycin + 3rdGC	33 (9.9%)	5 (11.9%)	0.586	2 (8.0%)	1.000	1.269 (0.461–3.492)	0.644	0.728 (0.164–3.231)	0.677

[a]Abbreviations: 3rdGC, third-generation cephalosporin; 95%CI, 95% confidence interval; AE, adverse event; AKI, acute kidney injury; ASA, American Society of Anesthesiologists; ASP, antistaphylococcal penicillin; BMI, body mass index; NA, not available; NC, not calculable; OR, odds ratio; PJI, prosthetic joint infection; PT, piperacillin-tazobactam. *, Comparison of patients with or without empirical antimicrobial therapy-related adverse events; †, comparison of patients with or without empirical antimicrobial therapy-related acute kidney injury.

[b]Values in parentheses indicate ranges unless specified as percentages.

TABLE 2 Description of 49 adverse events occurring in 42 patients during antimicrobial therapy according to CTCAE[a]

Type of adverse event (*n*)	Subtype of adverse event (*n*)	CTCAE grade (*n*)	Antimicrobial therapy (*n*)
Renal and urinary disorders (25)	Acute kidney injury (25)	Grade 1 (5) Grade 2 (17) Grade 3 (3)	Vancomycin (25) Piperacillin-tazobactam (20) Gentamicin (4) Ceftriaxone (2) Others: clindamycin, ofloxacin, metronidazole, rifampin (1 each)
Skin and subcutaneus tissue disorders (8)	Pruritus (4) Rash, maculopapular (4)	Grade 1 (4) Grade 2 (3) Grade 3 (1)	Vancomycin (7) Piperacillin-tazobactam (4) Ceftriaxone (2) Others: clindamycin, fosfomycin, gentamicin, imipenem, linezolid, metronidazole (1 each)
General disorders and administration site conditions (5)	Fever (4) Injection site reaction (1)	Grade 1 (2) Grade 2 (2) Grade 3 (1)	Vancomycin (5) Piperacillin-tazobactam (4) Pristinamycin (1)
Blood and lymphatic system disorders (4)	Febrile neutropenia (1) Other, hypereosinophilia (3)	Grade 2 (3) Grade 3 (1)	Vancomycin (3) Piperacillin-tazobactam (2) Gentamicin (2) Ceftriaxone (1) Oxacillin (1)
Immune system disorders (4)	Allergic reaction, DRESS (4)	Grade 4 (4)	Vancomycin (3) Others: ceftriaxone, cloxacillin, fosfomycin, ofloxacin, piperacillin-tazobactam (1)
Hepatobiliary disorders (2)	Cytolytic hepatitis (2)	Grade 2 (2)	Vancomycin (2) Others: gentamicin, piperacillin-tazobactam, rifampin (1 each)
Gastrointestinal disorders (1)	Vomiting (1)	Grade 2 (1)	Gentamicin, oxacillin, rifampin (1)

[a]Common Terminology Criteria for Adverse Events (CTCAE, National Cancer Institute, 2003).

tazobactam (OR, 6.0; 95%CI, 2.3 to 15.4), and especially its combination with vancomycin (OR, 6.7; 95%CI, 2.6 to 17.3), was significantly associated with the occurrence of AKI (Table 1, Fig. 1B). Interestingly, a vancomycin overexposure (i.e., a plasma trough concentration of >30 mg/liter) was observed in only 9 (37.5%) of the vancomycin-related AKIs.

DISCUSSION

PJI can be devastating and difficult-to-treat infections, for which the inevitable initial surgical procedure largely determines the outcome by reducing the microbiological inoculum (11) and allowing deep tissue sampling for bacteriological analysis in order to drive at best the subsequent antimicrobial therapy. Awaiting the final results of the microbiological cultures (i.e., 15 days), the postoperative EAT must be broad enough to target the most frequently involved pathogens, while avoiding potential toxicities for the patient. Current guidelines recommend the use of an anti-Gram-positive agent such as vancomycin in combination with a broad-spectrum beta-lactam such as 3rdGC or piperacillin-tazobactam at high doses to permit bone tissue penetration (8, 10). The tolerability of such high-dose intravenous combination therapies has never been evaluated. However, the occurrence of AE (i) most often leads to a treatment switch for a possibly less appropriate option, which can worsen patient prognosis, and (ii) is frequently associated with a lengthening in hospital stay or readmission, which may result in a significant increase in the overall cost of care. In other clinical settings, the use of prolonged high-dose intravenous and/or combined antimicrobials has been associated with high toxicity rates (12). In a previous study evaluating the global tolerability of antimicrobial therapy during bone and joint infection with methicillin-susceptible *S. aureus*, our group pinpointed a rate of severe AE of 15%, mostly occurring in the first weeks of treatment (9), which is consistent with the findings of a meta-analysis reporting incidence rates of 16.1 and 7.7% for mild and moderate-to-severe AE,

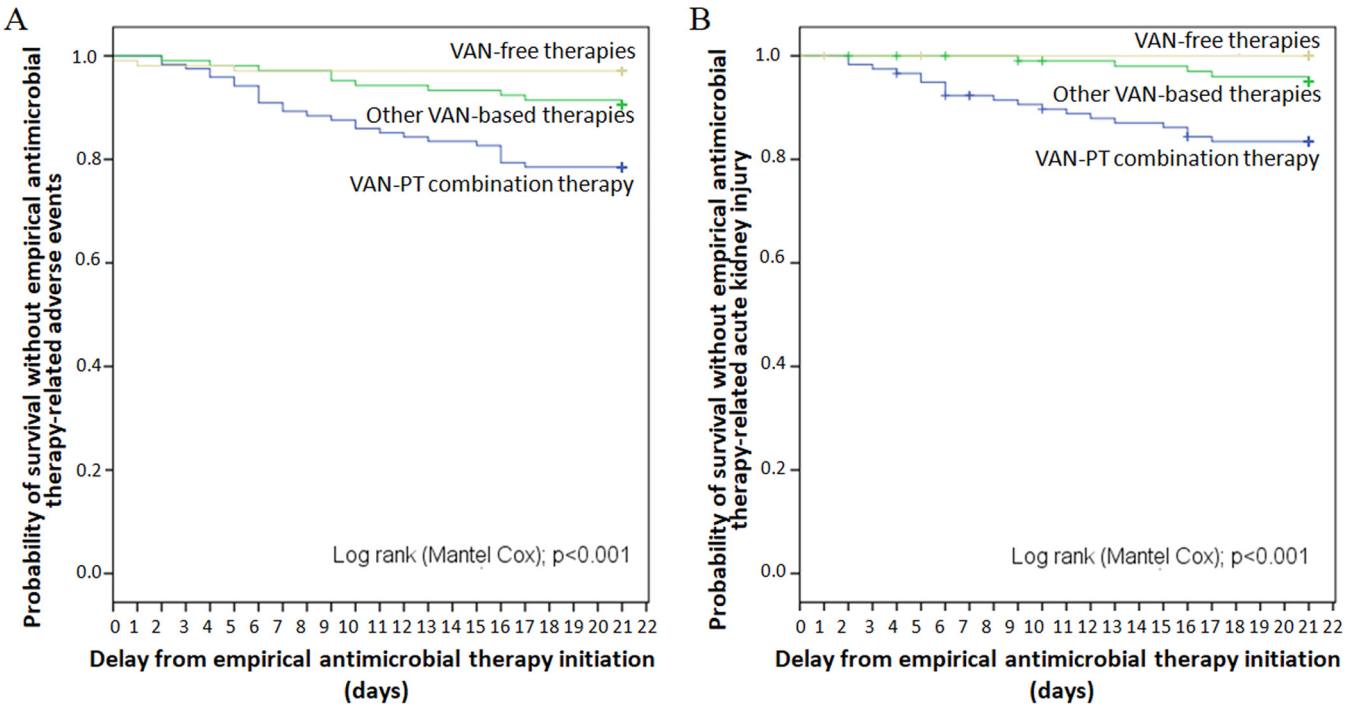

FIG 1 Kaplan Meier curve showing the probability of survival without empirical antimicrobial antibiotic therapy-related adverse events (A) and acute kidney injury (B). PT, piperacillin-tazobactam; VAN, vancomycin.

respectively (13). Older series even reported higher AE rates during the parenteral treatment phase, reaching 50% (14, 15). However, to our knowledge, the present study is the first to specifically assess the tolerability of the empirical broad-spectrum treatment in PJI, highlighting a high AE rate (12.6%), 20% of which were severe. According to current guidelines, the combination of vancomycin with piperacillin-tazobactam was the most frequently used. However, an increasing number of studies warns against the synergic nephrotoxicity of this combination (16–18). We confirm here its high toxicity rate, with a 4-fold increased risk for developing AE in comparison to patients receiving other empirical regimens—including other vancomycin-based combinations—mainly related to a rise in AKI occurrence. Mechanism is still not well elucidated, but two hypotheses have been suggested (16). The first is the association of a vancomycin-induced cellular necrosis with an acute interstitial nephritis caused by piperacillin-tazobactam. The second is that piperacillin-tazobactam might decrease the clearance of vancomycin, leading to a plasma overexposure. Our results advocate the first option since a vancomycin plasma overexposure was found in only one-third of patients developing an AKI. In addition, the hypothesis of a physicochemical interaction between the two molecules is supported by the incompatibility observed when the two drugs are administered simultaneously, with a risk of formation of precipitates in the infusion lines (19, 20). It can be assumed that these precipitates may form in the renal tubules in certain conditions, leading to renal obstruction. Such obstructive mechanism has recently been experimentally proven (21). In that case, interindividual variability regarding protein binding of vancomycin may be one of the determinants of toxicity. Indeed, a weak protein binding is associated with a higher urinary clearance of vancomycin, and the resulting high urinary concentration may increase the risk of tubular precipitation and of renal failure (22, 23). Even if not already specifically evaluated in PJI, an interesting alternative could be the vancomycin-cefepime combination, which showed a more acceptable tolerability in recent studies (24, 25). However, a pitfall of this regimen is an incomplete coverage of anaerobes, which can require the addition of metronidazole in some particular cases. In the future, daptomycin, which has a significantly better safety profile than vancomycin, or linezolid, which can be

taken orally, could be good anti-Gram-positive antimicrobial agent alternatives (26, 27). Of note, an important set of patients included in our study received aminoglycosides. However, aminoglycoside use and their combination with vancomycin were not associated with an increased risk of AE, and more specifically of AKI, in contrast to previous published findings (28).

Some limitations of our study should be addressed. First of all, the heterogeneity of patients and of their EAT prevent us from providing a more accurate case-control study, but the prospective comparison of conventional EAT with new options such as vancomycin-cefepime combination is ongoing. Unfortunately, the role of some confounding factors could not be addressed. In particular, no precise information about underlying comorbidities (including baseline renal function), severity of illness (including admission in intensive care unit), or other medications associated with antimicrobials was available, even though polymedication is a well-known risk factor for drug-related toxicity (29). These factors might also have influenced the choice of empirical antimicrobial therapy in the included patients, even if the similar characteristics of the two main used empirical combination therapies make this hypothesis unlikely. Another unevaluated point was the impact of the way of administration of vancomycin, although the lowest toxicity risk of continuous versus discontinuous infusions is still debated (30). This information was not available for all patients, and as a uncontrolled and observational study, the administration route could have change for some patients during the treatment course. Finally, the relationship between vancomycin plasma concentration and toxicity should be interpreted with caution. Indeed, as the data regarding AE were retrospectively collected, it is not possible to be certain that plasma for vancomycin trough concentrations was sampled before the onset of renal failure. An overexposure may therefore be the consequence—and not the cause—of the acute kidney injury. Moreover, the threshold chosen to define vancomycin overexposure (30 mg/liter) is high, since it is well known that the risk of vancomycin-induced renal toxicity increases gradually as early as 15 mg/liter in discontinuous administration (31–34). However, the poor bone penetration of vancomycin requires targeting plasma trough concentrations between 20 and 25 mg/liter in the specific setting of bone and joint infections (35, 36).

In conclusion, EAT of PJI is associated with a high rate of AE, and especially AKI, for which the primary determinant appears to be the use of the currently recommended combination of vancomycin and piperacillin-tazobactam. This risk must be considered in the empirical period treatment, with a close monitoring of patients, and alternatives should specifically be evaluated in patients with PJI, including vancomycin-cefepime (with or without metronidazole) combination therapy.

MATERIALS AND METHODS

Ethical statements. This study (ClinicalTrials.gov registration number NCT03010293) received the approval of the French South-East Ethics Committee (reference QH20/2014). All patients received written information about the study. No written informed consent was required for inclusion.

Inclusion criteria and data collection. All adult patients with PJI followed up in our reference center for the management of complex bone and joint infection between 2011 and 2016 were enrolled in a prospective cohort study referencing baseline characteristics of patients, PJI type, and management. Patients with previous microbiological documentation were excluded since they were not considered empirically treated. AE occurring during initial treatment phase were prospectively registered and more precisely characterized retrospectively. For each patient, data were collected from medical records and biological software in an anonymous standardized case report form.

Definition. PJI diagnosis was based upon the usual clinical, radiological, and microbiological criteria (1, 10). The antimicrobial therapy was considered empirical in the absence of previous microbiological documentation. Antimicrobials were prescribed according to current guidelines. In particular, vancomycin was administered intravenously by discontinuous (every 12 h) or continuous infusions at an initial dose of 20 to 30 mg/kg/day, with subsequent adaptation according to twice-a-week monitoring of plasma trough concentrations (therapeutic target, 20 to 25 mg/liter). A vancomycin plasma trough concentration exceeding 30 mg/liter was considered an overexposure. Piperacillin-tazobactam was prescribed at the dose of 4 g/8 h. In patients with intravenous combination therapy, the antimicrobials were not administered simultaneously. AE occurring during the first 3 weeks of treatment were considered related to the EAT. The imputability of the antimicrobial agents in AE occurrence was left to the judgment of the clinician, with the help of a pharmacovigilance specialist in doubtful cases. All AE

were defined and classified according to the Common terminology criteria for AE (CTCAE, National Cancer Institute, 2003) and were considered severe if the CTCAE grade was ≥3. In particular, acute kidney injury was defined as a serum creatinine level (routinely evaluated 2 to 3 times a week) exceeding 0.3 mg/dl or increasing >1.5-fold above the baseline.

Statistical analysis. Descriptive statistics were used to estimate the frequencies of the study variables, described as effectives (%) for dichotomous values and medians (interquartile range [IQR]) for continuous values. For the percentage calculation of each variable, the number of missing values was excluded from the denominator. Nonparametric statistical methods were used to compare the study groups (Fisher exact test or Mann-Whitney U test, as appropriate). Kaplan-Meier curves were compared between the groups using the log-rank test. Logistic regression analysis was used to determine the risk factors for EAT-related AE among the following variables: demographics and baseline patient characteristics (sex, age, body mass index [BMI] and American Society of Anesthesiologists [ASA] score), empirically used molecules (mainly glycopeptides, daptomycine, betalactams and aminoglycosides), and main combination therapies (vancomycin-piperacillin-tazobactam and vancomycin-3rdGC). A P value of <0.05 was considered significant. All analyses were performed using SPSS software version 17.0 (SPSS, Chicago, IL).

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