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Factors associated with development of nephrotoxicity in patients treated with vancomycin versus daptomycin for severe Gram-positive infections: A practice-based study

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ABSTRACT

Objectives. To evaluate nephrotoxicity development in patients treated with vancomycin (VAN) and daptomycin (DAP) for proven severe Gram-positive infections in daily practice.

Patients and methods. A practice-based, observational, retrospective study (eight Spanish hospitals) was performed including patients ≥18 years with a baseline glomerular filtration rate (GFR)>30 mL/min and/or serum creatinine level<2 mg/dL treated with DAP or VAN for >48h. Nephrotoxicity was considered as a decrease in baseline GRF to <50 mL/min or decrease of >10 mL/min from a baseline GRF<50 mL/min. Multivariate analyses were performed to determine factors associated with 1) treatment selection, 2) nephrotoxicity development, and 3) nephrotoxicity development within each antibiotic group.

Results. A total of 133 patients (62 treated with DAP, 71 with VAN) were included. Twenty-one (15.8%) developed nephrotoxicity: 4/62 (6.3%) patients with DAP and 17/71 (23.3%) with VAN (p=0.006). No differences in concomitant administration of aminoglycosides or other potential nephrotoxic drugs were found between groups. Factors associated with DAP treatment were diabetes mellitus with organ lesion (OR=7.81, 95%CI:1.39-4.35) and basal creatinine ≥0.9 mg/dL (OR=2.53, 95%CI:1.15-4.35). Factors associated with VAN treatment were stroke (OR=7.22, 95%CI:1.50-34.67), acute myocardial infarction (OR=6.59, 95%CI:1.51-28.69) and primary bacteremia (OR=5.18, 95%CI:1.03-25.99). Factors associated with nephrotoxicity (R^2=0.142; p=0.001) were creatinine clearance<80 mL/min (OR=9.22, 95%CI:1.98-30.93) and VAN treatment (OR=6.07, 95%CI:1.86-19.93). Factors associated with nephrotoxicity within patients treated with VAN (R^2=0.232; p=0.018) were congestive heart failure (OR=4.35, 95%CI:1.23-15.37), endocarditis (OR=7.63, 95%CI:1.02-57.31) and basal creatinine clearance<80 mL/min (OR=7.73, 95%CI:1.20-49.71).

Conclusions. Nephrotoxicity with VAN was significantly higher than with DAP despite poorer basal renal status in the DAP group.

Key words: Nephrotoxicity, daptomycin, vancomycin

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Factores asociados con el desarrollo de nefrotoxicidad en pacientes tratados con vancomicina frente a daptomicina en infecciones graves por grampositivos: Un estudio basado en la práctica clínica

RESUMEN

Objectivos. Evaluar el desarrollo de nefrotoxicidad en la práctica clínica diaria en pacientes con infecciones graves probadas por grampositivos, tratados con vancomicina (VAN) y daptomicina (DAP).

Pacientes y métodos. Se diseñó un estudio observacional retrospectivo, basado en la práctica clínica diaria (ocho hospitales españoles), en el que se incluyeron pacientes ≥ 18 años con una tasa basal de filtrado glomerular (GFR) > 30 mL/min y/o una creatinina sérica < 2 mg/dl para los pacientes tratados con DAP o vancomicina durante > 48 horas. La nefrotoxicidad fue considerada como una disminución del GRF basal a < 50 mL/min o una disminución de > 10 mL/min desde un GRF basal de < 50 ml/min. Se diseñaron análisis multivariantes para determinar los factores asociados con: 1) la selección del tratamiento, 2) el desarrollo de nefrotoxicidad y 3) el desarrollo de nefrotoxicidad con cada antibiótico.

Resultados. Se incluyeron 133 pacientes (62 tratados con DAP, 71 con vancomicina). Veintiuno (15,8%) desarrollaron nefrotoxicidad: 4/62 (6,3%) pacientes con DAP y 17/71 (23,3%) con VAN (p=0,006). No se encontraron diferencias entre los

grupos en la administración concomitante de aminoglucósidos u otros fármacos potencialmente nefrotóxicos. Los factores asociados con el tratamiento con DAP fueron diabetes mellitus con lesión orgánica (OR=7,81; IC95%:1,39-4,35) y una creatinina basal ≥0,9 mg/dL (OR=2,53; IC95%:1,15-4,35). Los factores asociados con tratamiento con VAN fueron ictus (OR=7,22; IC95%:1,50-34,67), infarto agudo de miocardio (OR=6,59; IC95%:1,51-28,69) y bacteriemia primaria (OR=5,18, IC95%:1,03-25,99). Los factores asociados con nefrotoxicidad (R^2=0,142; p=0,001) fueron aclaramiento de creatinina <80 mL/min (OR=9,22; IC95%:1,98-30,93) y tratamiento con VAN (OR=6,07; IC95%:1,86-19,93). Los factores asociados con nefrotoxicidad en los pacientes tratados con VAN (R^2=0,232; p=0,018) fueron insuficiencia cardiaca congestiva (OR=4.35; IC95%:1,23-15,37), endocarditis (OR=7,63; IC95%:1,02-57,31) y una creatinina basal <80 mL/min (OR=7,73; IC95%:1,20-49,71).

Conclusiones. La nefrotoxicidad con VAN fue significativamente más alta que la de DAP a pesar del pobre status basal renal del grupo de DAP.

Palabras clave: nefrotoxicidad, daptomicina, vancomicina

INTRODUCTION

Until recent years, vancomycin (VAN) has been the cornerstone antibiotic for the treatment of severe methicillin-resistant *Staphylococcus* spp. infections. However, the progressive loss of susceptibility of *Staphylococcus aureus* to VAN has led to the use in daily practice of doses higher than those approved by the Food and Drug Administration (1g/12h) to maintain its effectiveness [1-7]. Particularly, high-dose treatments targeting a serum trough concentration of 15-20 mg/L has been recommended in several guidelines [8-14]. This increasing dosage of VAN has been significantly associated with the development of renal failure in several studies [7,15-19]. The incidence of nephrotoxicity related with VAN treatment varies greatly due to the different baseline characteristics of the populations evaluated and the different dosing regimens. Available data suggests its association with concomitant administration of nephrotoxic agents, high serum trough levels, and prolonged duration of therapy [15,20,21]. This is important since small increases in serum creatinine of hospitalized patients are associated with increased mortality, hospital stay and health costs [22-24].

Alternative compounds such as daptomycin (DAP) and linezolid, specific agents against Gram-positive infections, have demonstrated to be less nephrotoxic than VAN (as comparator drug at 1g/12h) [25,26]. However, no comparative study has specifically evaluated nephrotoxicity as primary end-point between DAP and VAN.

The aim of the present study was to evaluate nephrotoxicity development in patients treated with VAN and DAP for severe Gram-positive infections, and factors associated with it, in daily practice.

MATERIALS AND METHODS

Study design and population. A practice-based, observational, retrospective study was conducted to evaluate nephrotoxicity in patients admitted to eight Spanish hospitals with proven Gram-positive cocci infections that had been treated with DAP or VAN according to clinical practice. The study protocol was approved by the Ethical Review Board of Hospital Central de la Defensa Gomez Ulla, Madrid, Spain.

Clinical records of antibiotic-treated patients discharged from Internal Medicine Departments of participating hospitals, at least six months prior to study approval, were reviewed and studied if they were patients ≥18 years of age that had received parenteral DAP or VAN treatment for >48 h, and had a baseline glomerular filtration rate (GFR)>30 mL/min and/or a serum creatinine level <2 mg/dL. Transplant recipients, patients presenting neutropenia (<1000 neutrophils/mm^3), AIDS (≤ 200 CD4/mm^3), and concomitant disease or infection that in opinion the investigator might confound the results of the study were not considered. Medical records were reviewed for demographic, clinical (concomitant antibiotic treatment, length of treatment, outcome…), microbiological and analytical data.

Study definitions. Nephrotoxicity was defined as a decrease in baseline GRF to <50 mL/min or a decrease of >10 mL/min from a baseline GRF <50 mL/min. Clinical response was considered as resolution or improvement of baseline signs/symptoms. Clinical failure was defined as death, persistence or worsening of baseline signs/symptoms, emergence of new signs/symptoms, or requirement of additional antibiotics different from those empirically prescribed. Microbiological response was considered as eradication (negative cultures after treatment) or absence of post-treatment cultures due to favourable clinical response. Patients were assessed at the end of parenteral treatment and until hospital discharge or death. Standard definitions for sepsis, severe sepsis or septic shock were employed [27].

Statistical analysis. Differences between treatments were assessed by t test or U-Mann-Whitney non-parametric tests (continuous variables) or by Chi square/Fish exact tests (discrete variables). Significance level was established at $p \leq 0.05$. Several stepwise logistic regression multivariate analyses were conducted in order to determine: 1) factors associated with treatment selection, 2) factors associated with development of nephrotoxicity, 3) factors associated with development of nephrotoxicity among patients treated with VAN, and 4) factors associated with development of nephrotoxicity among patients treated with DAP. All variables showing differences in bivariate analyses ($p < 0.1$) were considered for inclusion in the models. In addition, based on the well-known nephrotoxicity of aminoglycosides, concomitant administration of these drugs was introduced in the model as independent variable. All statistical calculations were computed using SAS system version 9.2® for Windows®

RESULTS

A total of 133 patients were included, 62 patients treated with DAP and 71 patients with VAN. The median (range) total daily dose for DAP was 390 mg (500 mg-700 mg), and for VAN, doses were 1-2g/12h, with 76.1% patients having received 2g/12h. Treatment duration [median (interquartile range)] was significantly higher for DAP [15 (8-28.5) days] than for VAN [10 (6-15) days] (p=0.002). Overall, nephrotoxicity occurred in 21 out of 133 (15.8%) patients: 4 out of 62 (6.3%) patients treated with DAP and 17 out of 71 (23.3%) with VAN (p=0.006). Median (interquartile range) time to nephrotoxicity was 9.5 (2.8-29.8) days with DAP and 7.0 (4.0-18.5) days with VAN (p=0.893).

Table 1 shows microorganisms isolated and concomitant antibiotics. Drugs other than antibiotics with potential nephrotoxicity (furosemide, salicylic acid, non-steroidal anti-inflammatory drugs...) were administered to 15 out of 133 (11.3%) patients, without differences between antibiotic groups and between patients developing or not nephrotoxicity. Methicillin-resistant *S. aureus* (MRSA) accounted for 29.3% of all isolates. The percentage of the different species isolated did not show differences between groups. With respect to concomitant antibiotics during DAP or VAN treatment, β-lactams administration was more frequent among patients not developing nephrotoxicity, with cephalosporins more frequently used among patients receiving VAN (vs. DAP).

Tables 2 and 3 show characteristics of patients, comorbidities, and type and severity of infections distributing patients by antibiotic treatment and development of nephrotoxicity or not, respectively. More than 65% patients were ≥65 years old, without differences between antibiotic groups but being significantly higher the percentage of patients from this age group among those developing nephrotoxicity. Up to 31.6% patients had a Charlson index ≥3; median (interquartile range) index value for the study population was 2 (0-3), without differences between antibiotic groups or patients developing nephrotoxicity or not. Patients with sepsis/severe sepsis/septic shock represented 88.7% of the study population (118 out of 133 patients), without differences between groups.

In bivariate analysis (table 2), acute myocardial infarction and stroke (as comorbidities) and primary bacteremia (type of infection) were significantly more frequent among patients treated with VAN than among those with DAP, whereas hypertension, basal creatinine and endocarditis were more frequent

Table 1 **Isolated microorganisms, concomitant antibiotics and outcome**

	Total	Treatment with			Nephrotoxicity		
	(n=133)	Daptomycin (n=62)	Vancomycin (n=71)	p	YES (n=21)	NO (n=112)	p
CNS[a]	43 (32.3)	18 (29.0)	25 (35.2)	0.447	9 (42.9)	34 (30.4)	0.261
MRSA[b]	39 (29.3)	22 (35.5)	17 (23.9)	0.145	3 (14.3)	36 (32.1)	0.099
MSSA[c]	21 (15.8)	11 (17.7)	10 (14.1)	0.564	4 (19.0)	17 (15.2)	0.744
Enterococcus spp.	24 (18.0)	11 (17.7)	14 (19.7)	0.591	5 (23.8)	19 (17.0)	0.536
Other Gram-positive bacteria	9 (6.8)	2 (3.2)	7 (9.9)	0.178	1 (4.8)	8 (7.1)	1.000
Gram-negative bacteria	5 (3.8)	2 (3.2)	3 (4.2)	1.000	1 (4.8)	4 (3.6)	0.583
Concomitant antibiotics	70 (53.0)	31 (58.8)	39 (54.9)	0.367	8 (38.1)	62 (55.4)	0.146
Penicillins	9 (6.8)	3 (4.8)	6 (8.5)	0.502	0 (0.0)	9 (8.0)	0.353
Cephalosporins	15 (11.3)	3 (4.8)	12 (16.9)	0.028	2 (9.5)	13 (11.6)	1.000
Aztreonam	2 (1.5)	2 (3.2)	0 (0.0)	0.215	0 (0.0)	2 (1.8)	1.000
Carbapenem	22 (16.5)	11 (17.7)	11 (15.5)	0.727	1 (4.8)	21 (18.8)	0.198
Total β-lactams	48 (36.1)	19 (30.6)	29 (40.8)	0.221	3 (14.3)	45 (40.2)	0.043
Aminoglycosides	13 (9.8)	5 (8.1)	8 (11.3)	0.383	4 (19.0)	9 (8.0)	0.125
Quinolones	13 (9.8)	5 (8.1)	8 (11.3)	0.383	1 (4.8)	12 (10.7)	0.691
Rifampicin	9 (6.8)	6 (9.7)	3 (4.2)	0.301	2 (9.5)	7 (6.3)	0.633
Others	8 (6.0)	4 (6.5)	3 (4.2)	0.705	1 (4.8)	6 (5.4)	1.000
Clinical cure	117 (88.0)	55 (88.7)	62 (87.3)	0.806	15 (71.4)	102 (91.1)	0.011
Eradication + presumed eradication	109 (82.2)	52 (83.9)	57 (80.3)	0.591	15 (71.4)	94 (83.9)	0.171

[a]**CNS: Coagulase-negative *staphylococci*;** [b]**MRSA: Methicillin-resistant *Staphylococcus aureus*;** [c]**MSSA: Methicillin-susceptible *Staphylococcus aureus***

Table 2 **Basal data potentially influencing antibiotic selection: patient's characteristics, comorbidities (present in >9% patients), type of infection and severity. Data expressed as n (%) or mean ± SD**

	Total (n=133)	Daptomycin (n=62)	Vancomycin (n=71)	p
Males	85 (63.9)	44 (71.0)	41 (57.7)	0.113
Age	68.5 ± 15.2	67.9 ± 14.9	69.1 ± 15.4	0.656
≥65 years	87 (65.4)	40 (64.5)	47 (66.2)	0.839
Congestive heart failure	36 (27.1)	16 (25.8)	20 (28.2)	0.760
Diabetes mellitus (DM)	27 (20.3)	12 (19.4)	15 (21.1)	0.800
COPD[a]	23 (17.3)	8 (12.9)	15 (21.1)	0.211
Acute myocardial infarction	20 (15.0)	5 (8.1)	15 (21.1)	0.036
Malignancies	23 (17.3)	9 (14.5)	14 (19.7)	0.429
Dementia	17 (12.8)	5 (8.1)	12 (16.9)	0.128
Stroke	16 (12.0)	3 (4.8)	13 (18.3)	0.017
DM with organ lesion	13 (9.8)	9 (14.5)	4 (5.6)	0.085
Hypertension	12 (9.0)	9 (14.5)	3 (4.2)	0.039
Basal GFR[b] (mL/min/1.73 m^2)	63.5 ± 31.5	59.5 ± 31.2	67.2 ± 31.5	0.183
Basal GFR[b] ≤50 mL/min/1.73 m^2	49 (36.8)	26 (41.9)	23 (32.4)	0.255
Basal creatinine (mg/dL)	1.0 ± 0.4	1.1 ± 0.4	1.0 ± 0.4	0.036
Basal creatinine ≥0.9 mg/dL	71 (53.4)	40 (64.5)	31 (43.7)	0.017
Basal creatinine >1.2 mg/dL	40 (30.1)	23 (37.1)	17 (23.9)	0.099
Basal creatinine clearance (mL/min)	78.9 ± 37.4	73.8 ± 33.1	83.1 ± 40.4	0.242
Basal creatinine clearance <80 mL/min	84 (63.2)	43 (69.4)	41 (57.7)	0.166
Basal CPK[c] (U/L)	155.0 ± 363.6	134.6 ± 196.2	171.9 ± 460.2	0.666
Osteoarticular infection	31 (23.3)	19 (30.6)	12 (16.9)	0.061
Skin & Soft tissue infection	29 (21.8)	16 (25.8)	13 (18.3)	0.296
Catheter-related bacteremia	26 (19.5)	11 (17.7)	15 (21.1)	0.623
Endocarditis	17 (12.8)	12 (19.4)	5 (7.0)	0.034
Primary bacteremia	15 (11.3)	2 (3.2)	13 (18.3)	0.006
Intraabdominal infection	6 (4.5)	1 (1.6)	5 (7.0)	0.215
Respiratory infection	4 (3.0)	0 (0.0)	4 (5.6)	0.124
Urinary tract infection	7 (5.3)	2 (3.2)	5 (7.0)	0.448
Others	11 (8.3)	5 (8.1)	6 (8.5)	0.936
Sepsis	97 (72.9)	43 (69.4)	54 (76.1)	0.778
Severe sepsis	16 (12.0)	9 (14.5)	7 (9.9)	0.410
Shock	5 (3.8)	3 (4.8)	2 (2.8)	0.663

[a]COPD: Chronic obstructive pulmonary disease; [b]GFR: Glomerular filtration rate; [c]CPK: Creatine phosphokinase

among patients treated with DAP. In the multivariate analysis for treatment selection (R^2=0.209; p<0.001), factors associated with DAP treatment were diabetes mellitus (DM) with organ lesion (OR=7.81, 95%CI: 1.39-4.35) and basal creatinine ≥0.9 mg/dL (OR=2.53, 95%CI: 1.15-4.35) while factors associated with VAN treatment were stroke (OR=7.22, 95%CI: 1.50-34.67), acute myocardial infarction (OR=6.59, 95%CI: 1.51-28.69) and primary bacteremia (OR=5.18, 95%CI: 1.03-25.99).

Basal creatinine values were significantly higher and creatinine clearance lower among patients developing nephrotoxicity during treatment (table 3), with higher percentage of patients with congestive heart failure. On the contrary, the percentage of patients with malignancies was higher among patients not developing nephrotoxicity. In the multivariate analysis (R^2=0.142; p=0.001), factors associated with nephrotoxicity were basal creatinine clearance <80 mL/min (OR=9.22, 95%CI: 1.98-30.93) and treatment with VAN (OR=6.07, 95%CI: 1.86-19.93).

Table 4 shows basal data potentially influencing development of nephrotoxicity for patients treated with VAN. In the bivariate analysis, patients developing nephrotoxicity were significantly older and presented more frequently congestive heart failure, higher values of basal creatinine and lower values of basal creatinine clearance. In the multivariate analysis (R^2=0.232; p=0.018), factors associated with nephrotoxicity were congestive heart failure (OR=4.35, 95%CI: 1.23-15.37), endocarditis (OR=7.63, 95%CI: 1.02-57.31) and basal creatinine clearance <80 mL/min (OR=7.73, 95%CI: 1.20-49.71).

Table 5 shows basal data potentially influencing development of nephrotoxicity for patients treated with DAP. All patients developing nephrotoxicity presented a basal GFR ≤50 mL/min/1.73 m^2. In the multivariate analysis (R^2=0.080; p=0.029) only DM with organ lesion (OR=16.00, 95%CI: 1.25-204.11) was associated with nephrotoxicity.

No differences in outcome were found between antibiotics (88.7% for DAP vs. 87.3% for VAN), but the percentage of clinical cure among patients developing nephrotoxicity was significant lower (71.4% vs. 91.1% for patients without nephrotoxicity, p=0.011). Eradication or presumed eradication was obtained in 82.2% patients without differences between groups.

Table 3 **Basal data potentially influencing development of nephrotoxicity: patient's characteristics, comorbidities (present in >9% patients), type of infection and severity. Data expressed as n (%) or mean ± SD**

	Nephrotoxicity			
	Total (n=133)	YES (n=21)	NO (n=112)	p
Males	85 (63.9)	10 (47.6)	75 (67.0)	0.090
Age	68.5 ± 15.2	75.9 ± 8.3	67.2 ± 15.8	0.001
≥65 years	87 (65.4)	19 (90.5)	68 (60.7)	0.009
Congestive heart failure	36 (27.1)	10 (47.6)	26 (23.2)	0.021
Diabetes mellitus (DM)	27 (20.3)	5 (23.8)	22 (19.6)	0.768
COPD[a]	23 (17.3)	5 (23.8)	18 (16.1)	0.363
Acute myocardial infarction	20 (15.0)	4 (19.0)	16 (14.3)	0.522
Malignancies	23 (17.3)	1 (4.8)	22 (19.6)	0.039
Dementia	17 (12.8)	3 (14.3)	14 (12.5)	0.733
Stroke	16 (12.0)	5 (23.8)	11 (9.8)	0.134
DM with organ lesion	13 (9.8)	4 (19.0)	9 (8.0)	0.126
Hypertension	12 (9.0)	1 (4.8)	11 (9.8)	0.690
Basal GFR[b] (mL/min/1.73 m^2)	63.5 ± 31.5	63.9 ± 32.4	61.2 ± 25.8	0.738
Basal GFR[b] ≤50 mL/min/1.73 m^2	49 (36.8)	8 (38.1)	41 (36.6)	0.896
Basal creatinine (mg/dL)	1.0 ± 0.4	1.0 ± 0.4	1.2 ± 0.4	0.085
Basal creatinine ≥0.9 mg/dL	71 (53.4)	16 (76.2)	55 (49.1)	0.022
Basal creatinine >1.2 mg/dL	40 (30.1)	13 (61.9)	27 (24.1)	<0.001
Basal creatinine clearance (mL/min)	78.9 ± 37.4	83.0 ± 38.9	52.7 ± 19.9	<0.001
Basal creatinine clearance <80 mL/min	84 (63.2)	19 (90.5)	65 (58.0)	0.005
Basal CPK[c] (U/L)	155.0 ± 363.6	165.0 ± 395.9	104.1 ± 82.5	0.599
Osteoarticular infection	31 (23.3)	5 (23.8)	26 (23.2)	1.000
Skin & Soft tissue infection	29 (21.8)	4 (19.0)	25 (22.3)	1.000
Catheter-related bacteremia	26 (19.5)	2 (9.5)	24 (21.4)	0.367
Endocarditis	17 (12.8)	5 (23.8)	12 (10.7)	0.146
Primary bacteremia	15 (11.3)	1 (4.8)	14 (12.5)	0.464
Intraabdominal infection	6 (4.5)	1 (4.8)	5 (4.5)	1.000
Respiratory infection	4 (3.0)	1 (4.8)	3 (2.7)	0.501
Urinary tract infection	7 (5.3)	2 (9.5)	5 (4.5)	0.305
Others	11 (8.3)	1 (4.8)	10 (8.9)	1.000
Sepsis	97 (72.9)	15 (71.4)	82 (73.2)	0.865
Severe sepsis	16 (12.0)	4 (19.0)	12 (10.7)	0.281
Shock	5 (3.8)	1 (4.8)	10 (8.9)	1.000

[a]COPD: Chronic obstructive pulmonary disease; [b]GFR: Glomerular filtration rate; [c]CPK: Creatine phosphokinase

DISCUSSION

The present study, to our knowledge the first comparative study assessing VAN- and DAP- induced nephrotoxicity in the treatment of Gram-positive infections in the uncontrolled setting of daily medical practice, showed significantly higher nephrotoxicity among patients treated with VAN than with DAP, not attributable to previous conditions or concomitant treatment with other potential nephrotoxic drugs.

In the literature, high daily doses of VAN providing serum trough levels of 15-20 mg/L, which are recommended when the MIC for MRSA is >1 mg/L, have been independently associated with an increased risk of nephrotoxicity [7,15-19]. A recent retrospective multicenter study with VAN trough levels of 17 mg/L concluded that rates of acute kidney injury were significantly lower in the DAP group in the treatment of bloodstream infections [28]. Two clinical trials, compared DAP with VAN at the dose of 1 g every 12 h [25,29]. Arbeit et al. in a study analysing patients with complicated skin and skin soft tissue infections did not document significant statistical differences between both antibiotics (DAP 2.2% vs VAN 2.7%; p >0.05) [29]. On the contrary, Fowler et al. in a randomized controlled trial that evaluated DAP versus standard therapy (VAN or antistaphylococcal penicillin ± gentamicin) in patients with *S. aureus* bacteremia and endocarditis reported higher rates of nephrotoxicity with VAN (18.1% vs 6.7% with DAP; p= 0.009) [25]. However, the incidence of renal impairment was similar among patients who received gentamicin and VAN (20.4%) and patients who received gentamicin and an antistaphylococcal penicillin (18.6%) [25]. Thus, as reported, the presence of other nephrotoxic factors such as aminoglycosides and a great variety of comorbidities confound the VAN-induced nephrotoxicity [20]. For these reasons, the present study was carried out to assess factors associated with treatment selection in daily practice and development of nephrotoxicity in a non-selected population with different comorbidities. Although the retrospective nature of the study represents a limitation, the lack of differences between groups in the administration of potential nephrotoxic drugs as aminogly-

Table 4 **Basal data potentially influencing development of nephrotoxicity for patients treated with vancomycin: patient's characteristics, comorbidities (present in >9% patients), type of infection and severity. Data expressed as n (%) or mean ± SD**

	Nephrotoxicity		
	YES (n=17)	NO (n=54)	p
Males	8 (47.1)	33 (61.1)	0.306
Age	75.8 ± 8.0	67.0 ± 16.6	0.004
≥65 years	15 (88.2)	32 (59.3)	0.039
Congestive heart failure	10 (58.8)	10 (18.5)	0.004
Diabetes mellitus (DM)	3 (17.6)	12 (22.2)	1.000
COPD[a]	4 (23.5)	11 (20.4)	0.745
Acute myocardial infarction	4 (23.5)	11 (20.4)	0.745
Malignancies	1 (5.9)	13 (24.1)	0.162
Dementia	3 (17.6)	9 (16.7)	1.000
Stroke	5 (29.4)	8 (14.8)	0.278
DM with organ lesion	2 (11.8)	2 (3.7)	0.241
Hypertension	0 (0.0)	3 (5.6)	1.000
Basal GFR[b] (mL/min/1.73 m^2)	66.3 ± 25.5	67.4 ± 33.2	0.910
Basal GFR[b] ≤50 mL/min/1.73 m^2	5 (29.4)	18 (33.3)	0.763
Basal creatinine (mg/dL)	1.1 ± 0.4	0.9 ± 0.3	0.100
Basal creatinine ≥0.9 mg/dL	12 (70.6)	19 (35.2)	0.010
Basal creatinine >1.2 mg/dL	7 (41.2)	7 (13.0)	0.030
Basal creatinine clearance (mL/min)	54.1 ± 22.4	89.7 ± 40.8	0.003
Basal creatinine clearance <80 mL/min	15 (88.2)	26 (48.1)	0.035
Basal CPK[c] (U/L)	104.1 ± 82.5	200.9 ± 547.9	0.549
Osteoarticular infection	4 (23.5)	8 (14.8)	0.463
Skin & Soft tissue infection	3 (17.6)	10 (18.5)	1.000
Catheter-related bacteremia	2 (11.8)	13 (24.1)	0.496
Endocarditis	3 (17.6)	2 (3.7)	0.085
Primary bacteremia	1 (5.9)	12 (22.2)	0.167
Intraabdominal infection	1 (5.9)	4 (7.4)	1.000
Respiratory infection	1 (5.9)	3 (5.6)	1.000
Urinary tract infection	2 (11.8)	3 (5.6)	0.587
Others	1 (5.9)	5 (9.3)	1.000
Sepsis	12 (70.6)	42 (77.8)	0.532
Severe sepsis	3 (17.6)	4 (7.4)	0.346
Shock	1 (5.9)	1 (1.9)	0.424

[a]COPD: Chronic obstructive pulmonary disease; [b]GFR: Glomerular filtration rate; [c]CPK: Creatine phosphokinase

cosides and in responsible microorganisms, as well as the presence of different comorbidities, strength the value of the present practice-based analysis.

The study population can be clearly considered elderly (65.4% were ≥65 years old) with comorbidities (31.6% patients had a Charlson index ≥3) and with moderate-severe infections (88.7% patients presenting sepsis/severe sepsis/septic shock). One important study finding was that osteoarticular infections accounted for 23.3% infections, with higher percentage among patients treated with DAP (30.6% vs. 16.9% for VAN; p=0.061), with no approved indication. However, two previous studies specifically assessed DAP treatment in this type of infections, one retrospective cohort study showing similar efficacy and safety than VAN [30], and one prospective study in combination with rifampicin [31].

Of importance, basal creatinine ≥0.9 mg/dL and DM with organ lesion were factors associated with DAP treatment, suggesting that this antibiotic was majority chosen for patients with suspicion of possible future nephrotoxicity. Regardless this fact, development of nephrotoxicity was associated with basal creatinine clearance <80 mL/min and treatment with VAN. Therefore, the present study showed that nephrotoxicity with VAN was significantly higher than with DAP despite the poorer basal renal status in the DAP group and absence of differences in aminoglycosides use as concomitant antibiotic. The role of comorbidities could be assessed within the VAN group, nephrotoxicity being associated with congestive heart failure and endocarditis while within the DAP group it was associated with DM with organ lesion, although the small number of patients developing nephrotoxicity in this group weakens the data.

In conclusion, the present practice-based study showed that among hospitalized elderly population with Gram-positive severe infections, treatment selection was associated with comorbidities and basal values of creatinine, and nephrotoxicity was associated with VAN treatment and not to other concomitant antibiotics.

Table 5 **Basal data potentially influencing development of nephrotoxicity for patients treated with daptomycin: patient's characteristics, comorbidities (present in >9% patients), type of infection and severity. Data expressed as n (%) or mean ± SD**

	Nephrotoxicity		
	YES (n=4)	NO (n=58)	p
Males	2 (50.0)	42 (72.4)	0.573
Age	76.0 ± 10.8	67.3 ± 15.1	0.209
≥65 years	4 (100)	36 (62.1)	0.287
Congestive heart failure	0 (0.0)	16 (27.6)	0.565
Diabetes mellitus (DM)	2 (50.0)	10 (17.2)	0.166
COPD[a]	1 (25.0)	7 (12.0)	0.433
Acute myocardial infarction	0 (0.0)	5 (8.6)	1.000
Malignancies	0 (0.0)	9 (15.5)	1.000
Dementia	0 (0.0)	5 (8.6)	1.000
Stroke	0 (0.0)	3 (5.2)	1.000
DM with organ lesion	2 (50.0)	7 (12.1)	0.097
Hypertension	1 (25.0)	8 (13.8)	0.475
Basal GFR[b] (mL/min/1.73 m^2)	37.0 ± 7.0	60.7 ± 31.6	0.085
Basal GFR[b] ≤50 mL/min/1.73 m^2	4 (100)	23 (39.7)	0.031
Basal creatinine (mg/dL)	1.5 ± 0.4	1.1 ± 0.4	0.061
Basal creatinine ≥0.9 mg/dL	4 (100)	36 (62.1)	0.287
Basal creatinine >1.2 mg/dL	3 (75.0)	20 (34.5)	0.139
Basal creatinine clearance (mL/min)	48.4 ± 11.7	75.8 ± 33.4	0.170
Basal creatinine clearance <80 mL/min	4 (100)	39 (67.2)	0.302
Basal CPK[c] (U/L)	186.2 ± 240.2	134.6 ± 199.2	1.000
Osteoarticular infection	1 (25.0)	18 (31.0)	1.000
Skin & Soft tissue infection	1 (25.0)	15 (25.9)	1.000
Catheter-related bacteremia	0 (0.0)	11 (19.0)	1.000
Endocarditis	2 (50.0)	10 (17.2)	0.166
Primary bacteremia	0 (0.0)	2 (3.4)	1.000
Intraabdominal infection	0 (0.0)	1 (1.7)	1.000
Respiratory infection	0 (0.0)	0 (0.0)	-
Urinary tract infection	0 (0.0)	2 (3.4)	1.000
Others	0 (0.0)	5 (8.6)	1.000
Sepsis	3 (75.0)	40 (69.0)	1.000
Severe sepsis	1 (25.0)	8 (13.8)	0.475
Shock	0 (0.0)	3 (5.2)	1.000

[a]COPD: Chronic obstructive pulmonary disease; [b]GFR: Glomerular filtration rate; [c]CPK: Creatine phosphokinase

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CONFLICT OF INTERESTS

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