future pharmacology

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Real-World Data Study on Risk Factors Associated with Acute Kidney Damage in Patients Treated with Anti-MRSA Antibiotics

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Abstract: The objective was to evaluate the incidence of nephrotoxicity related to vancomycin and other anti-MRSA antibiotics (linezolid and daptomycin). Patients receiving any of these drugs between July 2014 and December 2020 at a tertiary hospital were included. Renal failure was evaluated using the acute renal injury (AKIN) system. Univariate analysis was conducted on the 5806 patients who were included. Among them, 1023 patients (17.62%) developed renal failure. The renal damage incidence was 14.74% (496/3365) for vancomycin, 19.13% (367/1918) for linezolid, and 30.59% (160/523) for daptomycin. Patients with lower basal glomerular filtration had a higher risk of AKIN. In the vancomycin group, the risk factors were high creatinine and urea serum basal values, duration of treatment (DOT), body mass index (BMI), ICU stay, age, and low CKDEPI and albumin levels. In the linezolid group, AKIN was linked to high creatinine and urea levels, BMI, age, and ICU stay and to low CKDEPI levels; for daptomycin, AKIN was associated with low CKDEPI and albumin levels and a long DOT. Patients with AKIN showed higher mortality rates. Vancomycin-associated nephrotoxicity remains a great concern. However, linezolid and daptomycin could also cause nephrotoxicity. Bearing in mind risk factors that may prompt nephrotoxicity in hospitalized patients taking anti-staphylococcal antibiotics will result in better pharmacotherapeutic management.

Keywords: vancomycin; linezolid; daptomycin; renal failure; risk factors; MRSA; antibiotics

Citation: Maray, I.; Álvarez-Asteinza, C.; Macía-Rivas, L.; Fernández-Laguna, C.L.; Alaguero-Calero, M.; Valledor, P.; Fernández, J. Real-World Data Study on Risk Factors Associated with Acute Kidney Damage in Patients Treated with Anti-MRSA Antibiotics. *Future Pharmacol.* **2024**, *4*, 30–40. https://doi.org/10.3390/futurepharmacol4010004

Academic Editor: Fabrizio Schifano

Received: 29 November 2023
Revised: 16 December 2023
Accepted: 4 January 2024
Published: 9 January 2024

1. Introduction

Staphylococcus aureus is a Gram-positive bacterium that can cause a wide variety of diseases, including infections related to the skin and soft tissues, respiratory system, bones, joints, and endovascular system. Drug-resistant strains, especially methicillin-resistant *S. aureus* (MRSA), have experienced strong epidemiologic growth, becoming a significant cause of hospital- and community-acquired infections. In 2020, MRSA represented over 17% of all the *S. aureus* infections in Europe, though there has been a decreasing trend compared with the number of infections in Europe in the period 2016–2020 [1].

Some studies have reported that between 19 and 25% of patients colonized with MRSA develop infection, mostly bacteremia, followed by pneumonia and cellulitis [2]. Moreover, MRSA infections are associated with a 50% greater likelihood of mortality than methicillin-susceptible *S. aureus* infections in intensive care units (ICUs) and as such, optimizing its treatment is a matter of considerable importance [3].

Vancomycin, a glycopeptide, has been the keystone for treating MRSA infections over the years. The inclusion, in the last few decades, of other anti-staphylococcals, such as

linezolid (an oxazolidinone) and daptomycin (a lipopeptide), has increased the therapeutic arsenal against MRSA [4].

Even though vancomycin has been the mainstay of MRSA treatment for decades, increased nephrotoxicity remains the most common adverse event after vancomycin administration, with a 2.45-fold increased risk (95% CI = 1.69–3.55) compared with that for treatment with non-glycopeptide antibiotics, according to a meta-analysis that only included randomized controlled trials and cohort studies [5]. Vancomycin is mostly eliminated through the kidneys, with its presence in urine thought to result from a combination of active tubular secretion and glomerular filtration [6]. The mechanism of vancomycin-associated nephrotoxicity (VAN) is unknown for certain, but it is thought to be due to the induction of oxidative stress, complement activation following inflammatory injury, and mitochondrial damage, leading to acute tubular injury [7]. Renal damage due to this drug may also be attributed to acute tubulointerstitial nephritis [8]. Moreover, drug-induced obstructive tubular cast formation has recently been proposed as a mechanism of vancomycin-related kidney injury [9].

The treatment of MRSA infections with other anti-staphylococcal drugs is often stimulated by the fear of causing kidney damage with vancomycin, especially in at-risk patients. However, although linezolid and daptomycin are not commonly linked to nephrotoxicity, some clinical trials have reported renal injury as an adverse event in relation to both, ranging from 4 to 8% for linezolid [10,11] and from 1 to 7% for daptomycin [12,13].

On the other hand, daptomycin is known for its rare side effect of increasing creatine kinase levels; the underlying mechanism is not completely known, but it has been hypothesized that it may occur because daptomycin can cause pore-like formations on rhabdomyocytes that are mixed with cellular membrane lipids, leading to cellular depolarization and lysis [12]. According to published research, this increase in creatine kinase levels may cause rhabdomyolysis and acute renal failure [13,14].

Even though vancomycin is thought to be more nephrotoxic than other anti-staphylococcal antibiotics, studies are contradictory because some prospective studies and meta-analyses have not found vancomycin to induce higher rates of renal failure than linezolid [15,16].

An evaluation of a total of 2,042,801 reports (including 20,138 renal damage reports) in the US Food and Drug Administration's Adverse Event Reporting System found significant renal injury reporting associations (RORs) not only with vancomycin (15.28, CI 95%: 13.82–16.90) but also with daptomycin (6.07, CI 95%: 4.61–7.99) and linezolid (3.48, CI 95%: 2.54–4.77). Though results from pharmacovigilance-reporting databases must be interpreted with caution owing to their limitations, these findings show that no antibiotic is exempt from causing side effects [17].

Risk factors for VAN have been studied previously, although not all risks have been fully elucidated. Most studies have reported low renal clearance to be a predisposing factor. Also, many studies have linked this adverse effect to the duration of treatment (DOT), high vancomycin trough levels, concomitant administration of nephrotoxic drugs, and prolonged length of ICU stays. The body mass index (BMI), urea levels, and advanced age have also been reported as risk factors in some studies, while low concentrations of albumin have been found to be correlated with VAN in only a few studies [18–21].

Because nephrotoxicity associated with linezolid and daptomycin is rare, there is a lack of studies analyzing the risk factors that lead to this adverse event.

Real-world data (RWD) are data that are commonly collected from a wide range of sources about the health status of a patient and/or about the provision of healthcare. Normally, variables from a large pool of data are extracted and studied to create new knowledge. Information from RWD is being used more often to guide clinical practice, using information from patients and conditions that clinical trials do not access [22].

In line with all the above, the aim of this study was to evaluate the incidence of nephrotoxicity related to vancomycin and other anti-MRSA antibiotics (linezolid and daptomycin) in a large real-world population and to clarify the risk factors that may prompt its appearance.

2. Materials and Methods

2.1. Database and Data Collection

This study was carried out following the anonymization of clinical data obtained from electronic clinical records at a tertiary hospital in northern Spain (Hospital Universitario Central de Asturias) and subsequent addition to a database in accordance with data protection requirements. Ethical approval for the study was given by the regional ethics committee (CEImPA 2021.209), and an exemption from informed consent was granted by the committee.

All the patients who received vancomycin, linezolid, or daptomycin between July 2014 and December 2020 were included in the study. The following exclusion criteria were applied: patients with an antibiotic treatment of fewer than four days, baseline creatinine serum values over 4 mg/dL, patients under 18 years old, and subjects with no data for creatinine serum values around the time for starting the antibiotic treatment (within the last 48 h prior to the beginning of the antibiotic treatment). A creatine serum value over 4 mg/dL was chosen as a cutoff because patients with higher creatine serum values are classified as having renal failure according to the acute renal injury (AKIN) classification.

The following variables were studied: demographics; BMI; DOTs of vancomycin, linezolid, and daptomycin (measured in days and as a categorical variable, i.e., $\leq$10 days or >10 days); ICU stay (measured as a categorical variable, i.e., ICU stay or no stay); white blood cell count (WBC); neutrophil count; and urea, creatinine, and albumin serum values. The analytical values measured the closest to the antibiotic start date were selected (a maximum of 48 h before starting the therapy) using structured query language (MySQL version 8.0). Creatinine clearance was calculated according to the CKDEPI formula [23]. Renal damage during the antibiotic treatment was assessed using the AKIN grading system, taking into account that the highest creatinine value during the antibiotic treatment, AKIN I, represents an increase in the serum creatinine level of $\geq$0.3 mg/dL or from 150 to 200% compared with that of the baseline; AKIN II, an increase in the serum creatinine level from 200 to 300% above that of the baseline; and AKIN III, an increase in the serum creatinine level of >300% above that of the baseline or over 4 mg/dL. All the AKIN grades were considered as an indication of renal injury. Mortality rates were obtained from the regional health card database.

A univariate analysis between the groups of patients receiving each of the three antibiotics was performed to determine if patients treated with each antibiotic could be compared.

2.2. Statistical Analysis

The study population was summarized using descriptive statistics to provide an overview of the study. A total of two groups were created for each antibiotic, based on AKIN criteria: patients with renal failure and patients without renal failure. The normality was calculated using a Shapiro–Wilk test. The mean and standard deviation were used to represent regularly distributed continuous data, whereas the median and interquartile range were used to represent non-normally distributed continuous variables. Frequencies and percentages were used to represent categorical variables.

A Student's *t* test was used to assess continuous variables with a normal distribution for the univariate analysis. Using a Mann–Whitney U test, continuous variables with non-normal distributions were examined. Fisher's exact test was used to assess categorical variables.

R software (version 4.0.1) was used for all the statistical analyses. It was assumed that a *p*-value of 0.05 or less indicated statistical significance.

3. Results

A total of 5806 patients who received antibiotic treatment with either vancomycin (3365), linezolid (1918), or daptomycin (523) for at least four days; had a basal creatine serum value below 4 mg/dL; and were over 18 years old were included in the study. Of them, 1023 (17.62%) developed renal failure during the therapy.

Table 1 shows the baseline characteristics of the patients who were treated in the three treatment groups. It can be observed that the characteristics of the patients differed substantially among the three treatment groups. The analysis showed that patients who received vancomycin therapy had the highest basal CKDEPI and albumin levels and had the lowest creatinine and urea levels, WBC, neutrophil count, weight, BMI, percentage of ICU stays, and shortest ICU stays when compared with those of patients who did not receive vancomycin therapy. It is also noteworthy that this group displayed the lowest mortality rate of all the groups.

Table 1. Baseline population characteristics and statistical comparison of patients treated with daptomycin and linezolid versus vancomycin.

	Vancomycin	**Linezolid**	**Daptomycin**		
	Total Population *n* = 3365	**Total Population *n* = 1918**	**Total Population *n* = 523**	***p* (Vancomycin vs. Linezolid)**	***p* (Vancomycin vs. Daptomycin)**
Creatinine Level (mg/dL)	0.79 (0.60–1.05)	1.02 (0.67–1.74)	1.30 (0.89–2.17)	**<0.001**	**<0.001**
CKDEPI Level (mL/min/1.73 m²)	89.57 (66.01–106.31)	69.71 (35.60–98.66)	47.97 (28.38–81.87)	**<0.001**	**<0.001**
DOT (Days)	8.00 (6.00–12.00)	7.00 (5.00–11.00)	9.00 (6.00–15.00)	**<0.001**	**<0.001**
DOT (Stratified)				**0.006**	**<0.001**
4–10 Days	2343 (69.6%)	1405 (73.3%)	308 (58.9%)		
Over 10 Days	1022 (30.4%)	513 (26.7%)	215 (41.1%)		
Albumin Level (g/L)	30.00 (26.00–34.00)	27.00 (23.00–31.00)	28.00 (24.00–33.00)	**<0.001**	**<0.001**
White Blood Cell Count ($10^3/\mu L$)	9.13 (5.49–13.63)	12.49 (7.82–18.03)	10.38 (6.96–14.67)	**<0.001**	**<0.001**
Neutrophil Count ($10^3/\mu L$)	6.75 (3.55–10.93)	10.06 (5.93–15.40)	7.74 (4.87–12.46)	**<0.001**	**<0.001**
Urea Level (mg/dL)	37.00 (26.00–54.00)	56.00 (35.00–89.00)	64.00 (39.00–109.50)	**<0.001**	**<0.001**
Weight (kg)	74.80 (64.00–85.00)	75.0 (65.8–86.0)	76.00 (68.00–88.80)	**0.013**	**0.002**
BMI (kg/m^2)	26.58 (23.44–30.45)	26.82 (23.84–30.80)	27.44 (24.38–31.25)	0.146	**0.002**
Sex				**0.002**	**<0.001**
Male	2070 (61.5%)	1335 (69.6%)	358 (68.5%)		
Female	1295 (38.5%)	583 (30.4%)	165 (31.5%)		
ICU Length of Stay (Days)	14.02 (4.71–36.04)	19.21 (7.18–42.96)	14.35 (5.02–38.62)	**<0.001**	0.347
ICU Stay (Yes/No)	1046 (31.1%)	893 (46.6%)	247 (47.22%)	**<0.001**	**<0.001**
Age (Years)	65.28 (54.79–74.67)	67.04 (57.93–75.90)	68.97 (58.49–75.58)	**<0.001**	**<0.001**
Age (Stratified)				**<0.001**	**0.002**
<50 Years	546 (16.2%)	227 (11.8%)	58 (11.1%)		
≥50 Years	2819 (83.8%)	1691 (88.2%)	465 (88.9%)		
15-Day Mortality Rate	186 (5.5%)	235 (12.3%)	51 (9.8%)	**<0.001**	**<0.001**
30-Day Mortality Rate	365 (10.9%)	373 (19.4%)	85 (16.3%)	**<0.001**	**<0.001**
60-Day Mortality Rate	538 (16.0%)	481 (25.1%)	106 (20.3%)	**<0.001**	**<0.001**

CKDEPI: chronic kidney disease epidemiology collaboration (glomerular filtration rate); DOT: duration of treatment; BMI: body mass index; ICU: intensive care unit.

Basically, the three different populations included in the study were different in terms of every studied variable except for BMI and ICU Stay, as stated in Table 1.

There was a very low rate of missing data (less than 1.5%) for the serum urea levels, white blood cell counts, and neutrophil counts; a high rate of missing data for the albumin levels (40%) and BMI (25%); and no missing data for the rest of the studied variables. Because only univariate and descriptive analyses were performed, missing values either were not curated or were eliminated.

The incidences of renal damage during the antibiotic treatments were 14.74% (496 out of 3365 patients), 19.13% (367/1918), and 30.59% (160/523) for vancomycin, linezolid, and daptomycin, respectively.

Overall, patients with a lower basal CKDEPI level tended to have a higher risk for suffering from renal failure than those with a higher basal CKDEPI level. Taking a closer look at each treatment group individually, it was found that patients with higher creatinine levels, DOTs, urea levels, and BMIs, as well as lower CKDEPI and albumin levels in the vancomycin group had a greater risk of renal failure compared with participants with lower creatinine levels, DOTs, urea levels, and BMIs. As far as the linezolid group is concerned, patients with higher creatinine and urea levels, BMIs, ages, and longer ICU stays as well as lower serum CKDEPI levels exhibited a higher rate of renal failure when compared with patients who did not receive the medication. Lastly, in the daptomycin group, patients with lower CKDEPI and albumin levels and higher DOTs presented renal failure more frequently. Detailed information on all the risk factors associated with renal failure and a univariate analysis have been provided in Table 2.

Patients who presented with renal failure had a worse outcome in terms of mortality rates, especially those who were treated with linezolid or daptomycin. The 30-day mortality rates were 10.9% for patients treated with vancomycin, 16.3% for patients undergoing treatment with daptomycin, and 19.4% in patients treated with linezolid. These results were consistent with the 15-day mortality and 60-day mortality rates, and they were statistically significant ($p < 0.001$).

Table 2. Univariate analysis of patients undergoing antibiotic treatment with vancomycin, linezolid, or daptomycin and who developed renal failure or not.

	Vancomycin					Linezolid					Daptomycin				
	Total Population *n* = 3365	**Renal Failure *n* = 496**	**No Renal Failure *n* = 2869**	***p***	**OR**	**Total Population *n* = 1918**	**Renal Failure *n* = 367**	**No Renal Failure *n* = 1551**	***p***	**OR**	**Total Population *n*= 523**	**Renal Failure *n* = 160**	**No Renal Failure *n* = 363**	***p***	**OR**
Creatinine Level (mg/dL)	0.79 (0.60–1.05)	0.84 (0.57–1.16)	0.78 (0.60–1.02)	0.064		1.02 (0.67–1.74)	1.32 (0.87–2.14)	0.95 (0.66–1.64)	**<0.001**		1.30 (0.89–2.17)	1.47 (0.99–2.31)	1.26 (0.86–10.96)	0.075	
CKDEPI Level (mL/min/1.73 m²)	89.57 (66.01–106.31)	85.57 (57.66–105.66)	90.38 (67.70–106.34)	**<0.001**		69.71 (35.60–98.66)	53.55 (28.51–84.34)	75.02 (38.08–100.68)	**<0.001**		47.97 (28.38–81.87)	44.04 (27.25–71.74)	58.36 (28.66–85.95)	**0.04**	
DOT (Days)	8.00 (6.00–12.00)	8.00 (6.00–13.00)	8.00 (6.00–12.00)	**<0.001**		7.00 (5.00–11.00)	8.00 (5.00–12.00)	7.00 (5.00–11.00)	0.071		9.00 (6.00–15.00)	10.00 (6.00–17.00)	9.00 (6.00–14.00)	**<0.001**	
DOT (Stratified)				**<0.001**	1.357				0.131	1.22				**0.034**	1.511
4–10 Days	2343 (69.6%)	317 (64.0%)	2026 (70.6%)			1405 (73.3%)	257 (70.0%)	1148 (74.0%)			308 (58.9%)	83 (51.9%)	225 (62.0%)		
Over 10 Days	1022 (30.4%)	179 (36.0%)	843 (29.4%)			513 (26.7%)	110 (30.0%)	403 (26.0%)			215 (41.1%)	77 (48.1%)	138 (38.0%)		
Albumin Level (g/L)	30.00 (26.00–34.00)	29.00 (25.00–34.00)	30.00 (27.00–34.00)	**0.016**		27.00 (23.00–31.00)	27.00 (23.00–31.00)	27.00 (23.00–31.00)	0.124		28.00 (24.00–33.00)	26.00 (23.00–31.00)	29.00 (26.00–33.00)	**<0.001**	
White Blood Cell Count ($10^3/\mu L$)	9.13 (5.49–13.63)	8.96 (5.06–13.76)	9.19 (5.57–13.59)	0.424		12.49 (7.82–18.03)	12.44 (7.67–18.90)	12.50 (7.83–17.63)	0.547		10.38 (6.96–14.67)	11.03 (5.99–15.19)	10.28 (7.11–14.52)	0.689	
Neutrophil Count ($10^3/\mu L$)	6.75 (3.55–10.93)	6.53 (3.35–10.78)	6.80 (3.61–10.94)	0.283		10.06 (5.93–15.40)	10.57 (5.67–16.16)	9.92 (5.99–15.27)	0.454		7.74 (4.87–12.46)	7.92 (4.40–12.47)	7.72 (5.08–12.43)	0.849	
Urea Level (mg/dL)	37.00 (26.00–54.00)	40.00 (26.00–64.00)	36.00 (26.00–53.00)	**<0.001**		56.00 (35.00–89.00)	67.00 (42.00–102.25)	53.00 (33.00–86.00)	**<0.001**		64.00 (39.00–109.50)	68.00 (41.00–109.00)	63.00 (38.00–110.00)	0.38	
Weight (kg)	74.80 (64.00–85.00)	75.00 (65.00–85.00)	74.50 (64.00–85.00)	0.503		75.0 (65.8–86.0)	75.0 (68.0–86.0)	75.0 (65.0–86.0)	0.133		76.00 (68.00–88.80)	74.00 (65.45–83.40)	77.00 (69.50–90.00)	0.051	
BMI (kg/m^2)	26.58 (23.44–30.45)	27.08 (23.96–31.05)	26.47 (23.39–30.34)	**0.016**		26.82 (23.84–30.80)	27.64 (24.80–30.93)	26.56 (23.66–30.75)	**<0.001**		27.44 (24.38–31.25)	26.58 (24.35–30.03)	27.77 (24.54–31.84)	0.178	
Sex				0.842	1.021				**0.02**	0.735				0.919	1.022
Male	2070 (61.5%)	303 (61.1%)	1767 (61.6%)			1335 (69.6%)	274 (74.7%)	1061 (68.4%)			358 (68.5%)	109 (68.1%)	249 (68.6%)		
Female	1295 (38.5%)	193 (38.9%)	1102 (38.4%)			583 (30.4%)	93 (25.3%)	490 (31.6%)			165 (31.5%)	51 (31.9%)	114 (31.4%)		
ICU Length of Stay (Days)	14.02 (4.71–36.04)	16.95 (5.59–44.04)	13.30 (4.56–34.85)	**0.039**		19.21 (7.18–42.96)	19.26 (10.02–45.05)	19.04 (6.78–42.16)	0.319		14.35 (5.02–38.62)	16.37 (4.97–45.90)	14.02 (5.32–35.19)	0.468	
ICU Stay (Yes/No)	1046 (31.1%)	193 (38.9%)	868 (30.3%)	**<0.001**	1.505	893 (46.6%)	192 (52.3%)	701 (45.2%)	**0.015**	1.33	247 (47.22%)	83 (51.9%)	164 (45.2%)	0.183	1.307
Age (Years)	65.28 (54.79–74.67)	66.00 (57.79–75.05)	65.17 (54.29–74.55)	**0.037**		67.04 (57.93–75.90)	68.29 (58.97–76.21)	66.88 (57.32–75.55)	**0.049**		68.97 (58.49–75.58)	71.34 (61.79–77.96)	68.50 (57.91–75.99)	0.101	
Age (Stratified)				**<0.001**	1.655				**0.015**	1.634				0.175	1.599
<50 Years	546 (16.2%)	55 (11.1%)	517 (18.0%)			227 (11.8%)	30 (8.2%)	197 (12.7%)			58 (11.1%)	13 (8.1%)	45 (12.4%)		
≥50 Years	2819 (83.8%)	441 (88.9%)	2378 (82.0%)			1691 (88.2%)	337 (91.8%)	1354 (87.3%)			465 (88.9%)	147 (91.9%)	318 (87.6%)		

Table 2. *Cont.*

	Vancomycin					Linezolid					Daptomycin				
	Total Population *n* = 3365	**Renal Failure *n* = 496**	**No Renal Failure *n* = 2869**	***p***	**OR**	**Total Population *n* = 1918**	**Renal Failure *n* = 367**	**No Renal Failure *n* = 1551**	***p***	**OR**	**Total Population *n*= 523**	**Renal Failure *n* = 160**	**No Renal Failure *n* = 363**	***p***	**OR**
15-Day Mortality Rate	186 (5.5%)	59 (11.9%)	127 (4.43%)	**<0.001**	2.914	235 (12.3%)	98 (26.7%)	137 (8.8%)	**<0.001**	3.757	51 (9.8%)	25 (15.6%)	26 (7.2%)	**<0.001**	2.396
30-Day Mortality Rate	365 (10.9%)	107 (21.6%)	258 (8.99%)	**<0.001**	2.783	373 (19.4%)	138 (37.6%)	235 (15.2%)	**<0.001**	3.372	85 (16.3%)	42 (26.3%)	43 (11.9%)	**<0.001**	2.643
60-Day Mortality Rate	538 (16.0%)	139 (28.0%)	399 (13.9%)	**<0.001**	2.41	481 (25.1%)	162 (44.1%)	319 (20.6%)	**<0.001**	3.05	106 (20.3%)	56 (35.0%)	50 (13.8%)	**<0.001**	3.362

CKDEPI: chronic kidney disease epidemiology collaboration (glomerular filtration rate); DOT: duration of treatment; BMI: body mass index; ICU: intensive care unit.

4. Discussion

Nephrotoxicity is a major adverse event that can lead to higher mortality rates and should be avoided in any way possible. It is estimated that around 20% of acute kidney damage is caused by medication, rising to 60% in the elderly [24]. Acute kidney injuries occur in 5–7% of hospitalized patients and in those admitted to ICUs, this figure increases to 30–60% [25,26]. Moreover, acute kidney damage in hospitalized patients is associated with a high mortality rate [27].

According to the results of this study, the VAN frequency was around 15%. In most published studies, the incidence of mumps has been reported to range from 10 to 20% [6,20–23], and the above number falls within the expected range. In contrast, nephrotoxicity was reported in an unusually high number of patients receiving linezolid or daptomycin, with 19% and 31% of the patients experiencing it, respectively, for patients who received these drugs. This finding should also be considered in light of the fact that the average incidence of nephrotoxicity among hospitalized patients is below 7% [25], thereby highlighting the fact that these drugs (perhaps in combination with underlying pathologies) can also cause acute kidney damage.

When analyzing the three groups, it is important to highlight that the baseline patient characteristics were significantly different, thereby making comparisons of the incidence of nephrotoxicity for each of the three antibiotics unreliable, and hypotheses can only be made but not confirmed. Specifically, when comparing the patients treated with linezolid and daptomycin with those treated with vancomycin, the median creatinine and urea serum values were higher and the CKDEPI levels were lower in the former patients. Impaired renal function at the therapy baseline is a well-known risk factor for acute kidney damage [28] and could be a factor in explaining why patients treated with vancomycin showed lower rates of nephrotoxicity. The serum concentration of albumin was also higher in the vancomycin group. The vancomycin–albumin binding rate is highly variable, with a mean rate of 55% [29]. The daptomycin–albumin binding rate is high (90%), while linezolid binding to albumin in healthy subjects is around 30%, increasing to 60% in critically ill patients [30,31]. This suggests that because all three drugs bind to albumin to some extent, a reduction in albumin levels might contribute to an elevation in the free portion of the drug. This, in turn, could result in higher concentrations of the drug and, consequently, an escalation in adverse events. Furthermore, it has been demonstrated that albumin plays a protective role in nephrotoxicity and is a mortality predictor [32]. Patients undergoing daptomycin and linezolid therapies exhibited higher weights and BMIs. Prior research has established a connection between obesity and acute kidney damage, heightening the susceptibility of these patients to nephrotoxicity [33]. Patients who were admitted to the ICU exhibited a higher incidence of acute kidney damage compared with those who were not admitted [20,21]. In this study, linezolid and daptomycin were used in critically ill patients at higher rates than vancomycin, which could explain why acute kidney damage was more likely in patients who received the former drugs. Moreover, age is also a risk factor for acute kidney damage, and patients who received linezolid and daptomycin were, on average, older than those undergoing vancomycin treatment.

The above arguments could explain why the patients treated with linezolid and daptomycin displayed higher incidences of acute kidney damage than those treated with vancomycin. There is a great fear of VAN among medical staff and, therefore, a fragile patient (elderly, impaired renal function, ICU patient, etc.) is less likely to receive vancomycin, fearing that vancomycin could cause renal failure in these patients. As a result, the use of linezolid and daptomycin is increased in those patients who are most inclined to develop renal failure. This could also explain why the mortality rate is doubled in patients receiving linezolid or daptomycin because apparently, at our hospital, as can be observed in the analysis of the three different groups of patients, vancomycin is reserved for healthier patients.

VAN risk factors in this study include low renal clearance at the baseline, longer DOTs, being older, low concentrations of serum albumin, high serum urea levels, higher BMIs,

and admission to ICUs, particularly for patients with prolonged stays. Vancomycin is mainly eliminated by the kidneys, so impaired renal function might increase the toxicity of this drug. Moreover, as mentioned before, vancomycin binds to albumin, so a decrease in albumin levels can raise the vancomycin concentration in the blood. Critically ill patients often suffer from septic shock, and receiving high amounts of fluids and other nephrotoxic drugs as a result of this increases the possibility of renal damage. Vancomycin has been linked to increased toxicity in obese patients and longer DOTs [20–23].

There is currently no information available on the risk factors that may contribute to the occurrence of acute kidney injury in patients receiving linezolid and daptomycin. A number of factors were found to increase the risk of nephrotoxicity in this study, including high levels of creatinine and serum urea, age, body mass index, and the male gender. In addition, low CKDEPI levels, ICU admission, and extended lengths of stay in this ward increased the likelihood of nephrotoxicity. Regarding the patients treated with daptomycin, renal damage was associated with low CKDEPI and albumin levels and with longer DOTs. Both daptomycin and linezolid are eliminated by the kidneys, so impaired renal function can lead to higher toxicity [34,35]. As mentioned above, ICU patients are more likely to suffer from acute kidney damage, as are the elderly. As occurs in patients treated with vancomycin, low serum albumin levels are also a risk factor for kidney damage in patients treated with daptomycin. There is a good reason for this: daptomycin binds strongly to albumin, which is a protein in the blood, and patients with low serum levels of albumin have a higher concentration of daptomycin in the blood, which can result in more severe side effects [32].

In this study, some relevant variables, like sites of infection or microorganisms, could not be obtained owing to the nature of the study and the availability of that information. Designing further studies including these variables could increase the accuracy of the results presented herein. As this is an observational study utilizing RWD and given its methodological limitations arising from data collection in a non-controlled environment, conclusions should be validated through additional clinical trials and further studies.

5. Conclusions

The incidence of VAN remains a significant concern among physicians. However, opting for alternative antibiotics to treat MRSA infections (or other microorganisms) is not risk free, and patients on these drugs may also develop AKIN. This may be attributed to the treatment itself, underlying medical conditions, or a combination of both factors. Despite the fact that the current study has a sufficiently large sample size to be able to draw certain conclusions, it is important to note that this is an observational study, which should therefore be properly validated before drawing any final conclusions as the confounders varying over time and the heterogeneity of the studied population may lead to bias in this study. Despite these limitations, the results strongly suggest that the renal function should be closely monitored not only for patients undergoing vancomycin therapy but also for those receiving linezolid and daptomycin, especially in populations presenting the risk factors mentioned above and in those who are severely ill.

Real-world data are a powerful tool that can be used to help to understand the side effects and effectiveness of drugs in populations that are normally not represented in clinical trials and shed light on matters that are often not investigated.

Understanding the risk factors that can lead to nephrotoxicity in hospitalized patients receiving anti-staphylococcal antibiotics is crucial for clinicians. This knowledge can aid in making informed therapeutic decisions, improving pharmacotherapeutic management, and potentially reducing mortality rates, which tend to be elevated in patients experiencing renal failure during anti-MRSA treatments.

Author Contributions: Conceptualization, I.M., J.F. and M.A.-C.; methodology, I.M., P.V. and J.F.; software, I.M. and P.V.; validation, P.V. and M.A.-C.; formal analysis, P.V.; investigation, L.M.-R. and C.L.F.-L.; resources, C.Á.-A.; data curation, I.M.; writing—original draft preparation, I.M. and C.Á.-A.;

writing—review and editing, I.M. and J.F.; supervision, J.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee "Comité de Ética en la Investigación con Medicamentos del Principado de Asturias" (protocol code CEImPA 2021.209, approved in March 2021).

Informed Consent Statement: An exemption from informed consent was granted by the institutional ethics committee.

Data Availability Statement: Data can be made available upon request.

Conflicts of Interest: JF and PV are founders of the company Pragmatech AI Solutions, which provides artificial intelligence solutions in healthcare. The company had no role in the design of the study; in the collection, analyses, or interpretation of the data; in the writing of the manuscript; or in the decision to publish the results. The other authors do not have any conflicts of interest regarding this work.

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