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Original article

Effectiveness, safety, and cost of vancomycin and linezolid in Kuwait: A retrospective cohort study

Sarah S. Alghanem [a,*], Moetaza M. Soliman [b], Sarah Al-Manie [a], Wadha Alfouzan [c,d], Duaa Alhammadi [e], Yousif Alreshidi [e], Adnan Hajjiah [f], Rafaa Alfarhoud [f], Mai Almane [g], Mona Mataqi [h], Salma Alajmi [i], Khalifa Albenwan [c,j]

[a] Department of Pharmacy Practice, College of Pharmacy, Kuwait University, Safat 13110 Kuwait
[b] Clinical Pharmacy and Pharmacy Practice Department, Faculty of Pharmacy, Mansoura University, Egypt
[c] Department of Microbiology, College of Medicine, Kuwait University, Safat 13110 Kuwait
[d] Department of Microbiology, Al-Farwania Hospital, Kuwait Ministry of Health, Kuwait
[e] Department of Pharmacy, Mubarak Alkabeer Hospital, Kuwait Ministry of Health, Kuwait
[f] Department of Pharmacy, Ahmadi Hospital, Kuwait Oil Company, Kuwait
[g] Department of Pharmacy, Zain Hospital, Kuwait Ministry of Health, Kuwait
[h] Department of Pharmacy, Al-Adan Hospital, Kuwait Ministry of Health, Kuwait
[i] Department of Microbiology, Al-Adan Hospital, Kuwait Ministry of Health, Kuwait
[j] Department of Microbiology, Al-Amiri Hospital, Kuwait Ministry of Health, Kuwait

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ABSTRACT

Background: The effectiveness, safety, and cost of vancomycin and linezolid for managing gram-positive bacterial infections in Kuwait are unknown. This study assessed the effectiveness, safety, and cost of vancomycin, teicoplanin and linezolid for managing gram-positive bacterial infections in Kuwait.

Research design and methods: This retrospective study included adult patients who were prescribed antibiotics (vancomycin, teicoplanin, and linezolid) for the treatment of gram-positive infections at five hospitals in Kuwait. Descriptive statistics were used to assess the effectiveness and safety outcomes. A cost analysis was performed on the patients hospitalised for gram-positive infections.

Results: Among 116 patients, 42.2 % (n = 49) received glycopeptides (vancomycin [n = 45] and teicoplanin [n = 4]) or linezolid (n = 67). Clinical cure was achieved in 100 patients without significant intergroup differences (p = 0.34). Thrombocytopenia and acute kidney injury occurred in 19 and 20 patients (p = 0.82 and 0.96), respectively, and their incidence was similar with all the studied agents. The average cost per patient was USD 983.70. The estimated total direct medical costs were USD 894,570.6, the cost was highest for linezolid (USD 469,682.30) and vancomycin (USD 370,342.5), and lowest for teicoplanin (USD 20,799.9).

Conclusions: Glycopeptides and linezolid were highly effective. Linezolid was the most frequently prescribed agent; its effectiveness and safety were similar according to the antibiotic class. However, treatment with linezolid and vancomycin were associated with considerable costs.

1. Introduction

Staphylococcus aureus is the most frequently identified pathogen that causes infections in developing and Middle Eastern countries (Allegranzi et al., 2011; Alothman et al., 2020). Data from seven Middle Eastern countries, including Kuwait, show higher antimicrobial use (Alothman et al., 2020) than that in European countries (Plachouras et al., 2018). Glycopeptides are the most commonly used antimicrobials in this region (Alothman et al., 2020). Increased antimicrobial resistance (AR) complicates the global treatment of infections by limiting antibiotic therapy options,

* Corresponding author at: Department of Pharmacy Practice, College of Pharmacy at Kuwait University, PO Box 24923, Safat 13110, Kuwait.
E-mail address: sara.alghanem@ku.edu.kw (S.S. Alghanem).

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resulting in conditions that are difficult to treat. By 2050, global AR-related annual mortality and cost are estimated to reach 10 million and USD 3 trillion, respectively (O'Neill, 2016).

Glycopeptides (vancomycin and teicoplanin) and oxazolidinone (linezolid) are used to treat the infections caused by gram-positive cocci. Daptomycin and ceftaroline were registered in Kuwait in 2018 and 2019, respectively; however, their use was restricted upon a special request from a central medical store. The bioequivalence of glycopeptides (Cavalcanti et al., 2010) and linezolid has been reported in patients with methicillin-resistant *Staphylococcus aureus* (MRSA), enterococcal, and streptococcal infections (Beibei et al., 2010). Linezolid has been reported to be more effective than glycopeptides against gram-positive infections (Falagas et al., 2008) and as effective as glycopeptides against other infections (Beibei et al., 2010; Kalil et al., 2010; Walkey et al., 2011; Wang et al., 2015; Jiang et al., 2013). In Arab League countries, both *S. aureus* (95 %) and *Enterococcus faecalis* (85.7 %) are susceptible to glycopeptides (Alothman et al., 2020). Similarly, MRSA and *E. faecalis* isolates from Kuwait are susceptible to linezolid and glycopeptides (Udo and Boswihi, 2017; Udo et al., 2003).

Most studies and review articles from the Middle East and Kuwait have described pathogen distribution and antibiotic susceptibility; however, the clinical outcomes of gram-positive infections have not yet been assessed (Al-Khawaja et al., 2021; Al-Mousa et al., 2016; Alfouzan et al., 2021; Alhumaid et al., 2021; Rosenthal et al., 2020). Most studies focused on hospital-acquired infections (HAIs), with only a few studies addressing community-acquired infections (CAIs) (Alothman et al., 2020). Therefore, it is essential to investigate the outcomes of current treatment practices and the economic burden of antimicrobials in Kuwait. A better understanding of the treatment patterns, effectiveness, safety profile, and cost of available antimicrobials would help in designing targeted multifaceted interventions. Accordingly, this study aimed to assess the effectiveness of glycopeptides (vancomycin and teicoplanin) and linezolid, incidence of their toxicity, and the cost of treating patients with suspected or proven gram-positive coccal (Staphylococcus, Streptococcus, and Enterococcus) infections in Kuwait.

2. Materials and methods

2.1. Study design and patient population

Data were collected from one *para*-governmental hospital and four public hospitals in Kuwait between August 2019 and March 2020. This study was approved by the Human Research Ethics Committee of the Kuwait Ministry of Health (Number 1055/2019) and the Health Sciences Centre Ethical Committee of Kuwait University. Informed consent was optional owing to the retrospective nature of the study.

All patients aged $\geq$ 18 years who were prescribed glycopeptides or linezolid for at least 7 or 14 days as empirical therapy or based on culture results were identified from inpatient pharmacy prescriptions. We excluded the patients who were using prophylactic anti-MRSA therapy with haematological disease or primary thrombocytopenia from leukaemia, myelodysplasia, aplastic anaemia, or tumours. Those with a pre-treatment abnormal platelet count ($<100 \times 10^9$/L or $> 400 \times 10^9$/L) or abnormal liver function test results or who received platelet transfusion(s) concurrently with linezolid or glycopeptide therapy were also excluded. Patients with chronic kidney disease (CKD) or those on dialysis at the initiation of glycopeptide or linezolid therapy were excluded from the study. Patients with monopathogenic gram-negative bacteria or fungal infections were also excluded.

Data were collected retrospectively by reviewing the patient's electronic medical and paper records. At baseline and during therapy, data were collected regarding patient characteristics, glycopeptides (teicoplanin and vancomycin), linezolid therapy type and duration, blood biochemistry, microbiological culture results, and signs and symptoms of infection. Sepsis or septic shock was diagnosed using Sepsis 3 criteria (Singer et al., 2016). Further details are presented in Table S1.

2.2. Clinical outcomes

2.2.1. Primary outcomes: Effectiveness and safety

The primary outcomes included effectiveness, defined as clinical cure at therapy completion – day 7 or 14 of start of therapy-, and safety, defined as the occurrence of side effects (including nephrotoxicity and thrombocytopenia). Clinical cure was defined as the resolution or improvement of all signs and symptoms of infection, body temperature < 37.8 °C, WBC < 12000 per microliter, hemodynamically stable, and no need for vasopressor support or other antibiotics, in the absence of death.

Nephrotoxicity was assessed using the combined Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (RIFLE) Kidney Injury Network (AKIN) criteria (Disease, 2012). Thrombocytopenia was defined as a platelet count $< 100 \times 10^9$/L or a 50 % decrease from the baseline platelet count. The time taken to develop thrombocytopenia was recorded.

2.2.2. Secondary outcomes

Secondary outcomes included 30-day all-cause mortality, microbiological cure, the incidence of acute kidney injury (AKI) requiring dialysis, the incidence of lactic acidosis (serum pH < 7.25 or serum lactate level > 4 mmol/L), and length of hospital stay (from the first day of initiating glycopeptide or linezolid therapy until hospital discharge). The patients who were discharged before 30 days were followed up using the hospital's electronic system.

2.3. Statistical analysis

Descriptive analyses were used to report the demographic and treatment details. Non-normally distributed continuous variables are reported as the median and interquartile range (IQR). Categorical variables are described as counts (percentages). The statistical significance of the differences between patients who received glycopeptides and linezolid was tested using the Mann–Whitney test, Kruskal–Wallis test, or chi-square test, as appropriate. Kaplan–Meier estimators were employed to assess the incidence and time-to-event of 30-day mortality and thrombocytopenia. The log-rank test was used to test the statistical significance of the differences between survival functions. Patients were censored on the date of the event or the last follow-up. Statistical significance was set at $p \leq 0.05$. Stata/SE version 17.0 (Stata Corporation LLC, College Station, TX, USA) was used for all statistical analyses.

2.4. Economic outcome

The total average direct medical costs associated with glycopeptides and linezolid therapy were estimated.

2.4.1. Cost analysis

The Kuwaiti healthcare perspective was also considered. Direct medical costs, including those pertaining to hospital stays, medications, and microbiological and laboratory tests, were estimated. The length of hospital stay was determined based on the length

of therapy with study-related agents. The unit of analysis was a hospitalised patient who was administered a glycopeptide or linezolid agent, regardless of treatment intention (empirical or directed) and duration. Comparison of the cost between hospitalized patients on different anti-MRSA agents were not conducted due to the small sample size and different patient characteristics. All estimates were adjusted according to 2021 costs using the annual healthcare inflation rate.

2.4.2. Cost data source

Medication costs were determined using Kuwait Central Medical Stores (CMS). Information about the cost of the hospital stay was obtained from a book published by the Kuwaiti MOH (Ministry of Health, 2017). The book named "Cost analysis and performance evaluation for government health services" provides information about the average cost of inpatient stays for all public hospitals in Kuwait. The last version of the book for 2016–2017 was used for the current study. Public hospitals have different costs per hospital night owing to the variability in the number of working staff and the quality of services and medical devices. This book provides information about the average expenses per hospital night in the intensive care units (ICUs) and wards for each public hospital. The estimated average cost considers various cost elements, including staff salaries, drugs, laboratory tests, radiology, food, and other consumables. The unit costs of microbiological culture, vancomycin and platelet monitoring, and serum creatinine are unavailable from the Ministry of Health in Kuwait. Thus, they were calculated according to a previous study conducted in the USA (Bounthavong et al., 2011) using the lowest 25 % limit of the average unit cost. This was done to account for the inflation in healthcare costs in the United States compared with that in Kuwait.

Data on glycopeptide or linezolid dosage and therapy duration were obtained as described in Section 2.1. Linezolid was given as an intravenous (IV) infusion at a dose of 600 mg twice daily. Vancomycin is available as a 500 mg reconstitution powder for IV infusions. The vancomycin dose was 15 mg/kg, and it was administered every 12 h. Teicoplanin was available in 200 mg vials. It was administered at a loading dose of 6–12 mg/kg every 12 h for 3–5 d, followed by a maintenance dose of 6–12 mg/kg once daily. Based on clinical standards in Kuwait, clinical experts suggested that vancomycin trough testing be performed once every three days. Platelet monitoring was performed once every three days for all drugs. The microbiological culture was performed once, and serum creatinine (SCr) levels were measured on days 1, 2, and 7 to monitor therapy. Teicoplanin levels have recently been measured in Kuwait. However, teicoplanin levels were not monitored at the time of data collection. Therefore, teicoplanin levels was excluded from the cost analysis. Table S2 summarises the study-associated item costs.

2.4.3. Cost calculation

A bottom-up approach was used to estimate the average total direct medical costs for hospitalised patients receiving glycopeptide or linezolid therapy. The mean cost per unit was calculated, and the costs of all units were summed to obtain the total cost.

3. Results

3.1. Descriptive statistics

3.1.1. Patient characteristics

A total of 116 patients were included in this analysis. Baseline demographic characteristics according to glycopeptide or linezolid therapy type are shown in Table 1. Of the 116 patients, 46 (42.2 %) received glycopeptides (vancomycin [n = 45] and teicoplanin [n = 4]), and 67 (57.8 %) received linezolid. At glycopeptide or linezolid therapy initiation, 73 participants (62.9 %) were in medical units and 43 (37.1 %) were in intensive care units (ICUs). Hospital acquired infections accounted for 73 cases (62.9 %). According to the Sepsis-3 criteria, 41 (35.3 %) participants were diagnosed with sepsis or septic shock. The most frequent comorbidities were hypertension (n = 59; 50.9 %) and diabetes mellitus (n = 52; 44.8 %). Table S3 shows the baseline clinical characteristics of the patients, which were similar between the glycopeptide and linezolid groups. The most frequent infection sites necessitating glycopeptide or linezolid therapy were respiratory infections (n = 67, 57.8 %), followed by skin and soft tissue infections (SSTIs) (n = 20, 17.2 %) and bloodstream infections (BSIs) (n = 10, 8.6 %). Linezolid was prescribed more often than glycopeptides for respiratory infections (n = 47, 70.1 %; p = 0.01; Table S4). By contrast, linezolid and glycopeptides were equally prescribed for SSTIs (n = 10, 50 %). Glycopeptides were prescribed more often than linezolid for BSIs (n = 6, 60.0 %) and other infections (n = 13, 68.4 %), including urinary tract and intra-abdominal infections and CNS or endocarditis.

3.1.2. Glycopeptide and linezolid therapies

Of all the patients, 83 (71.6 %) were prescribed glycopeptides and linezolid therapies empirically and 33 (28.4 %) were prescribed glycopeptide or linezolid therapy as directed therapy. Empiric therapy was continued following culture results in 57 (68.7 %) patients (Table 1). The median duration of therapy was 7.5 days (IQR: 5–9 days; Fig. 1). Glycopeptide and linezolid therapies were well tolerated, except in one patient who developed a vancomycin infusion reaction after receiving vancomycin.

3.1.3. Culture results and pathogens

The culture results and pathogens in total and per agent are shown in Table 2. Of the 110 cultures, 61 (55.5 %) showed microbial growth, with 34 (55.7 %) showing mono-pathogen growth and 27 (44.3 %) showing polymicrobial growth. Gram-positive pathogens accounted for 47 positive cultures (coagulase-positive bacteria, n = 31; MRSA, n = 26; and methicillin-sensitive *S. aureus* [MSSA], n = 5). Five coagulase-negative staphylococci cultures were considered true infections. The other gram-positive pathogens included six enterococcal strains (*E. faecalis*, n = 3; *E. faecium*, n = 3) and eight streptococcal infections. The other positive cultures had 17 g-negative infections and nine fungal infections and were considered polymicrobial infections with gram-positive pathogens. Table S5 shows antibiotic resistance profiles according to pathogen type. All the pathogens were susceptible to vancomycin, teicoplanin, and linezolid.

3.2. Primary outcomes

Of 116 patients, 100 (86.2 %) showed clinical improvement in signs and symptoms of all infections (Table 3), without significant differences between agents (p = 0.34). The sub-analysis of those who continued therapy even when culture results were negative showed that the clinical cure rate remained unchanged (86.9 %), with no difference between the glycopeptide and linezolid groups (p = 0.43). There was no difference in the cure rate between patients with gram-positive microbes as mono pathogens and those with polymicrobial (gram-positive and negative) infection; 85.3 % versus 88.9 %, respectively, p = 0.68. A total of 19 (16.4 %) patients developed thrombocytopenia (Table 3) after a median of 7 days (IQR: 4–9 days), with no significant difference according to the antibiotic type (p = 0.82). The Kaplan–Meier survival estimates of thrombocytopenia did not differ significantly according to the antibiotic type (log-rank test, p = 0.58) (Fig. 2-A). Regarding AKI analysis, 20 (17.2 %)

Table 1
Baseline patients' characteristics and details of glycopeptides and linezolid therapies.

Age, median year (IQR)	Glycopeptides (n = 49) 57 (42, 69)		Linezolid (n = 67) 60 (41, 79)		Total (n = 116) 58 (41, 76)		P value * 0.55
Gender							
Male	28	(57.1)	49	(73.1)	77	(66.4)	0.13
Female	20	(40.8)	18	(26.9)	38	(32.8)	
Missing	1	(2.0)	0	(0.0)	1	(0.9)	
Nationality							
Kuwait	20	(40.8)	35	(52.2)	55	(47.4)	0.22
Non-Kuwait	29	(59.2)	32	(47.8)	61	(52.6)	
Site of Care							
Intensive care unit	16	(32.7)	27	(40.3)	43	(37.1)	0.40
Medical or surgical unit	33	(67.3)	40	(59.7)	73	(62.9)	
Type of infection							
Community acquired	16	(32.7)	27	(40.3)	43	(37.1)	0.23
Hospital acquired	33	(67.3)	40	(59.7)	73	(62.9)	
Infection severity							
Diagnosis of sepsis or septic shock	14	(28.6)	27	(40.3)	41	(35.3)	0.19
Comorbidities							
Hypertension	20	(40.8)	39	(58.2)	59	(50.9)	0.06
Diabetes Mellitus	20	(40.8)	32	(47.8)	52	(44.8)	0.46
Dyslipidemia	4	(8.2)	5	(7.5)	9	(7.8)	0.89
Cardiovascular disease	10	(20.4)	14	(20.9)	24	(20.7)	0.95
Seizures	3	(6.1)	5	(7.5)	8	(6.9)	0.78
Type of therapy							
Empirical	38	(77.6)	45	(67.2)	83	(71.6)	0.22
Directed	11	(22.4)	22	(32.8)	33	(28.4)	
Decision for empirical therapy (n = 83)							
Continue	30	(78.9)	27	(60.0)	57	(68.7)	0.10
Stop	6	(15.8)	12	(26.7)	18	(21.7)	
Switch	1	(2.6)	0	(0.0)	1	(1.2)	
Missing	1	(2.6)	6	(13.3)	7	(8.4)	

Values are n (%) or otherwise specified. *P values are based on Mann-Whitney test for age and duration of therapy and on x^2 test for other variables.

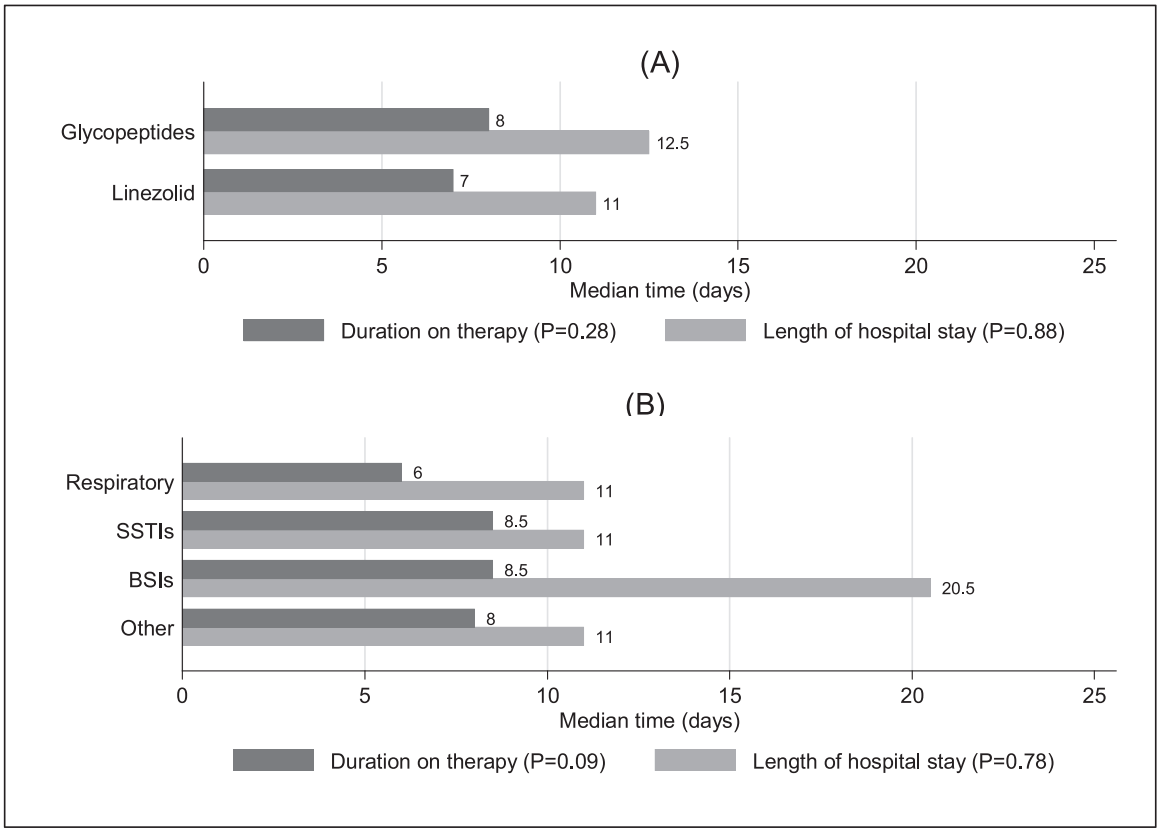

Fig. 1. The median duration on glycopeptides and linezolid therapies and length of hospital stays by type of glycopeptides and linezolid therapies (A) and site of infection (B). SSTIs: skin and soft tissue infections, and BSIs: bloodstream infections.

Table 2
Culture results and pathogens.

Mono versus multi pathogen	Glycopeptides (n = 49)		Linezolid (n = 67)		Total (n = 116)		P value *
Mono-pathogen	15	(30.6)	19	(28.4)	34	(29.3)	0.41
Multi-pathogen	8	(16.3)	19	(28.4)	27	(23.3)	
No growth	24	(49.0)	25	(37.3)	49	(42.2)	
No culture was done	2	(4.1)	4	(6.0)	6	(5.2)	
Isolated pathogen							
Coagulase positive	8	(16.3)	23	(34.3)	31	(26.7)	0.03
MRSA	5	(10.2)	21	(31.3)	26	(22.4)	0.01
MSSA	3	(6.1)	2	(3.0)	5	(4.3)	0.41
Coagulase negative	2	(4.1)	3	(4.5)	5	(4.3)	0.92
Enterococci	3	(6.1)	3	(4.5)	6	(5.2)	0.69
Others (Streptococci)	5	(10.2)	3	(4.5)	8	(6.9)	0.23
Gram positive	17	(34.7)	30	(44.8)	47	(40.5)	0.28
Gram negative	5	(10.2)	12	(17.9)	17	(14.7)	0.25
Fungi	1	(2.0)	8	(11.9)	9	(7.8)	0.05

Key: Values are n (%). *P values are based on x^2 test. MRSA: Methicillin-resistant *Staphylococcus aureus*, and MSSA: methicillin-susceptible *Staphylococcus aureus*.

Table 3
Primary and secondary outcomes of glycopeptides and linezolid therapies and according to the site of infection.

Primary and secondary outcomes of anti-MRSA therapies											
	Glycopeptides (n = 49)				**Linezolid (n = 67)**		**Total (n = 116)**			**P value ***	
Primary outcomes											
Clinical cure at end of therapy	44		(89.8)		56	(83.6)	100	(86.2)		0.34	
Thrombocytopenia	7		(14.3)		12	(17.9)	19	(16.4)		0.82	
Acute kidney injury	9		(18.4)		11	(16.4)	20	(17.2)		0.96	
Secondary outcomes											
Microbiological cure (n = 48)	15		(88.2)		26	(83.9)	41	(85.4)		0.68	
Incidence of AKI needing dialysis	2		(4.1)		2	(3.0)	4	(3.4)		0.46	
Lactic acidosis	0		(0.0)		2	(3.0)	2	(1.7)		0.22	
30-days mortality	3		(6.1)		10	(14.9)	13	(11.2)		0.14	
Hospital discharge	30		(61.2)		36	(55.4)	66	(57.9)		0.53	
Primary and secondary outcomes according to the site of infection											
	Respiratory infections (n = 67)		**Skin & soft tissue infections (n = 20)**		**Bloodstream infection (n = 10)**		**Other* (n = 19)**	**Total (n = 116)**		**P value †**	
Primary outcomes											
Clinical cure at end of therapy	54	(80.6)	19	(95.0)	9	(90.0)	18	(94.7)	100	(86.2)	0.23
Thrombocytopenia	10	(14.9)	3	(15.0)	5	(50.0)	1	(5.3)	19	(16.4)	0.02
Acute kidney injury	12	(17.9)	2	(10.0)	1	(10.0)	5	(26.3)	20	(17.2)	0.37
Secondary outcomes											
Microbiological cure (n = 48)	25	(83.3)	8	(88.9)	3	(75.0)	5	(100.0)	41	(85.4)	0.71
Incidence of AKI needing dialysis	3	(4.5)	0	(0.0)	1	(10.0)	0	(0.0)	4	(3.4)	0.62
Lactic acidosis	1	(1.5)	0	(0.0)	0	(0.0)	1	(5.3)	2	(1.7)	0.58
30 days mortality	12	(17.9)	0	(0.0)	1	(10.0)	0	(0.0)	13	(11.2)	0.047
Hospital discharge	34	(52.3)	16	(80.0)	4	(40.0)	12	(63.2)	66	(57.9)	0.095

Results are n (%) or otherwise specified. *Other sites of infections include urinary tract infection, central nervous system infections, intra-abdominal infection, endocarditis and others. *P values are based on x^2 test.
† P values are based on K-Wallis test for duration of therapy and on x^2 test for other variable.

developed AKI. The incidence of AKI did not differ significantly according to antibiotic type (p = 0.96). Four (3.4 %) patients developed AKI and required renal replacement therapy. Patients with SSTIs had the highest clinical cure percentage (95.0 %), whereas those with respiratory infections had the lowest (80.6 %, p = 0.23; Table 3). Furthermore, patients with BSIs were significantly more likely to develop thrombocytopenia than those with infections at other sites (p = 0.02; Fig. 2-B). The incidence of AKI did not differ according to the site of infection (p = 0.37; Table 3).

3.3. Secondary outcomes

Thirteen patients (11.2 %) died within 30 days of starting glycopeptide or linezolid therapy (median survival time: 14 days, IQR: 8–21 days). The Kaplan–Meier survival estimates of 30-day mortality are shown in Fig. 2-C and 2-D. Survival did not differ significantly according to antibiotic type (log-rank test, p = 0.14, Fig. 2-C). According to the site of infection, patients with SSTIs and other infections were less likely to die (p = 0.05, Fig. 2-D). In the clinical cure analysis, 48 patients had microbiological follow-up culture results, with confirmed microbiological cure in 41 (85.4 %), without significant differences between agents (p = 0.68). Lactic acidosis occurred in 2 (1.7 %) patients treated mainly with linezolid. Of all the patients, 66 (57.9 %) were discharged from the hospital. The median (IQR) length of hospital stay was 11 (8.0–27.5) days, which did not differ between the groups treated with glycopeptide and linezolid (p = 0.88, Fig. 1-A). Similarly, the microbiological cure and hospital discharge percentages

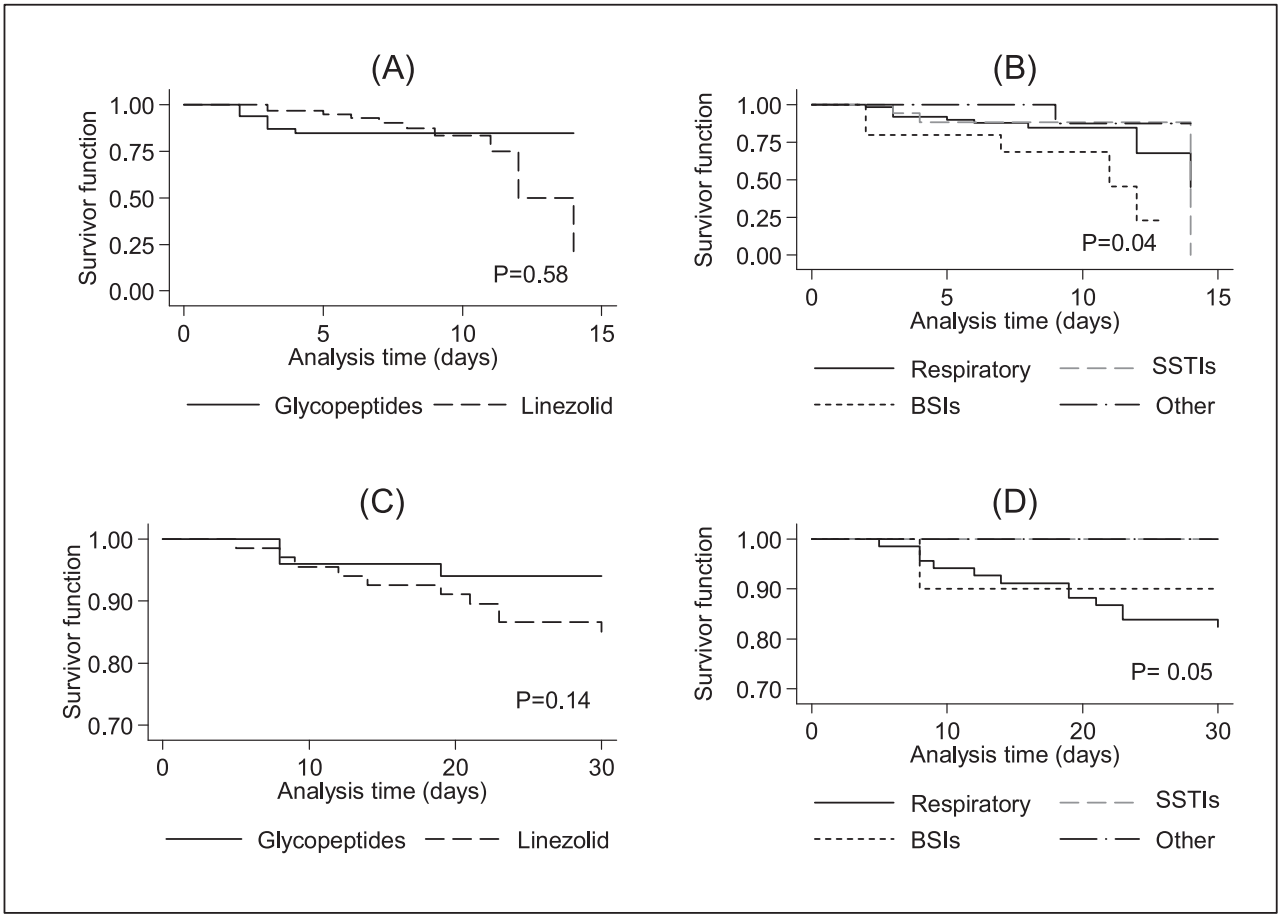

Fig. 2. Kaplan-Meier survival estimates of developing thrombocytopenia by type of glycopeptides and linezolid therapies (A), developing thrombocytopenia by site of infection (B), 30-day mortality by type of therapy (C), and 30-day mortality by site of infection (D). SSTIs: skin and soft tissue infections, and BSIs: bloodstream infections.

did not vary according to the infection site (p = 0.71, and p = 0.95, respectively; Table 3).

3.4. Cost analysis

The cost analysis included 116 patients. The total average direct medical cost of all hospitalised patients using the study agents was USD 894,570.6, with patients in the medical wards accounting for 53.86 % of the total direct medical costs. The total average direct medical cost was highest for linezolid (USD 469,682.30) and vancomycin (USD 370,342.5) and lowest for teicoplanin (USD 20,799.9). The average direct medical cost per patient per night was USD 983.70. The mean costs per night in the ICU, medical ward, and surgical ward were USD 1,184.77, 743.82, and 925.31, respectively; the average total costs per patient in the ICU, medical ward, and surgical ward were USD 8,095.86, 6,815.85, and 6,014.42, respectively. The average direct medical cost per patient was USD 7,711.80, and the average direct medical cost per patient per night was USD 983.70. Antibiotics against gram-positive bacteria accounted for only 5.93 % of the average total price. The total cost of linezolid during the study period was USD 48,654.94. The total expenses of vancomycin and teicoplanin were USD 2,379.86 and 1,479.00, respectively. The cost of laboratory tests, including vancomycin trough, platelet monitoring, microbiological culture, and SCr measurement, had a share of 1.13 % of the total costs. The total medication cost for glycopeptide or linezolid empirical therapy was USD 34,634.89, accounting for 65.26 % of the total costs of a glycopeptide or linezolid drug. The overall direct medical expenses according to cost components are presented in Table S6. Table 4 presents the total estimated costs based on the infection site.

Table 4
Overall cost by site of infection.

Site of infection	Average cost per patient ($)	Total average cost* ($)
Respiratory	7,685.57	514,932.07
Bacteremia	8,194.89	81,948.93
SSTIs	6,595.84	131,916.94
Other infections	8,724.87	165,772.66
Total direct medical costs	–	894,570.6

SSTIs: Skin and soft tissue infections.
* All costs were adjusted for 2021 US dollars ($).

4. Discussion

We assessed the real-life usage patterns and associated clinical outcomes of glycopeptides and linezolid in the treatment of gram-positive coccal infections in Kuwait. The study revealed high effectiveness in clinical cure, with the highest effectiveness against SSTIs. Linezolid was the most frequently prescribed drug, followed by vancomycin. The antibiotic type was not associated with a clinical cure. This finding is consistent with the results of six *meta*-analyses that linezolid is as effective as glycopeptides are against

gram-positive infections in patients with SSTIs, pneumonia, or bacteraemia (Beibei et al., 2010; Kalil et al., 2010; Walkey et al., 2011; Wang et al., 2015; Jiang et al., 2013; Kato et al., 2021). However, a *meta*-analysis of 12 randomised controlled trials found that linezolid was more effective than glycopeptides against gram-positive infections in patients with SSTIs, pneumonia, or bacteraemia (Falagas et al., 2008), possibly because of the inclusion of lactams, which are unsuitable for managing staphylococcal infections, with glycopeptides in the comparator arm. The superiority of linezolid over glycopeptides in treating SSTIs was confirmed in a Cochrane review (Yue et al., 2016). The microbiological cure was documented in 85.4 % of patients without significant inter-agent differences. These results are consistent with those of *meta*-analyses that showed no significant differences between the linezolid and glycopeptide groups in the microbiological eradication of nosocomial pneumonia, including MRSA pneumonia (Kalil et al., 2010; Walkey et al., 2011; Wang et al., 2015). However, microbiological eradication was better with linezolid in a few *meta*-analyses of gram-positive infections in patients with SSTIs, pneumonia, or bacteraemia (Beibei et al., 2010; Falagas et al., 2008; Jiang et al., 2013; Kato et al., 2021). In two *meta*-analyses, linezolid was associated with better eradication of *S. aureus* but not MRSA strains or enterococcal species (Beibei et al., 2010; Falagas et al., 2008).

In the present study, thrombocytopenia occurred in 16.4 % of patients, and the median duration to onset was seven days, which emphasises the need for thrombocytopenia evaluation within seven days of therapy. The incidence was similar among patients who received glycopeptides and linezolid. An essential finding of this study was that patients with BSIs were more likely to develop thrombocytopenia than those with infections at other sites or in both treatment arms. However, the small BSI sample size (n = 10) was insufficient to reach any conclusions. Further studies are required to confirm these findings. Some studies have found an increased incidence of thrombocytopenia in patients treated with linezolid (Beibei et al., 2010; Falagas et al., 2008; Kalil et al., 2010), although the difference was significant in only one study (Kalil et al., 2010) and not in two (Beibei et al., 2010; Falagas et al., 2008). Three published *meta*-analyses (Walkey et al., 2011; Wang et al., 2015; Kato et al., 2021) did not find any difference in the risk of thrombocytopenia between the vancomycin and linezolid groups, possibly because of the duration of therapy. Linezolid causes mild, reversible, and time-dependent myelosuppression, mainly if the treatment lasts > 14 days (Kuter and Tillotson, 2001). In this study, approximately 60 % of the patients who received linezolid developed thrombocytopenia after seven days. This result is consistent with the results of other studies (Walkey et al., 2011; Kato et al., 2021), wherein a therapy duration of < 7 days was insufficient for linezolid to cause thrombocytopenia.

Acute kidney injury occurred in 17.2 % of patients. The incidence of AKI did not differ according to the study agent but was higher than that previously reported (1.14 %) (Beibei et al., 2010). These findings are similar to those of Kalil *et al.* (Kalil et al., 2010) and Kato *et al.* (Kato et al., 2021). Other studies have shown a significantly increased incidence of nephrotoxicity with glycopeptides, mainly in vancomycin-treated patients, compared to that with linezolid administration (Beibei et al., 2010; Wang et al., 2015; Jiang et al., 2013).

This is the first study to quantify the total average direct medical costs among patients receiving glycopeptides and linezolid therapies in Kuwait. Previous studies have estimated the economic impact of MRSA as a burden of infection (Köck et al., 2010; Lee et al., 2013; Valiquette et al., 2014; Zhen et al., 2020) and the cost-effectiveness of linezolid for MRSA pneumonia (De Cock et al., 2009); however, none of these studies were conducted in Kuwait or the Middle East. Patients in medical wards had the highest total cost, followed by those in the ICU and surgical wards. Empirical treatment constituted more than two-thirds of glycopeptide or linezolid therapy; 48 patients without culture growth continued therapy for 7.4 days on an average, with an estimated average medication cost of approximately USD 17,626.19. Knowing that empirical treatment should be administered for only a few days until culture results become available, its extended use wastes resources. Linezolid (IV) was used in approximately half of the patients and incurred the highest cost among the studied agents, even when compared with that of vancomycin, considering the need for concentration measurement. Based on the findings of the current study, linezolid should not be used routinely for suspected gram-positive cocci infections, particularly MRSA, because of its presumed superior effectiveness. The incidence of multidrug-resistant gram-positive coccal infections is increasing. Recent outbreaks of linezolid-resistant *S. aureus* and linezolid resistance in vancomycin-resistant enterococci have been shown to correlate with the increased use of linezolid (Falagas et al., 2008; Olearo et al., 2021). Due to its added cost, linezolid should be limited to specific patient populations or targeted therapy for difficult-to-treat infections. Linezolid is more cost-effective than vancomycin for treating MRSA pneumonia despite linezolid having an approximately ten times higher cost than vancomycin (De Cock et al., 2009). Our results and those of a *meta*-analysis by Walkey *et al.* (Walkey et al., 2011) call for a re-evaluation and cost-effectiveness analysis, given the lack of significant differences in clinical cure or mortality rates between these agents. The Kuwait Ministry of Health should establish guidelines for using glycopeptides and oxazolidinones based on their effectiveness, safety, and cost.

Our findings provide helpful baseline quantitative data for assessing current glycopeptide or linezolid prescription patterns, which can be utilised by hospital authorities to design targeted multifaceted interventions in the future. This is the first study to describe the pattern of glycopeptides and linezolid therapy use, quantify the total average direct medical costs in Kuwait, and provide a basis for comparative studies in the Middle East, North America, and worldwide.

4.1. Strengths and limitations

The strengths of this study include the exclusion of patients with underlying haematological abnormalities or lower baseline values to eliminate bias and confounding factors. The current percentage may be a true reflection of thrombocytopenia caused by the investigated agents. Teicoplanin, approved only by the European Medicines Agency, is not approved by the US Food and Drug Administration; thus, few studies have been conducted on its safety. This is the first study to evaluate the cost of a glycopeptide or linezolid therapy in Kuwait.

The limitations of this study include its small sample size, partly due to the COVID-19 pandemic. Prospective studies are needed to confirm the findings. Repeat cultures were performed in a few patients. This may have resulted in an overestimation of the microbiological cure. Information about antibiotic use in the past six months was not available. Pathogen-specific analyses were not conducted because of the small number of confirmed gram-positive cultures per pathogen. Serum vancomycin concentration data were excluded to allow consistency with the data of other agents, including linezolid and teicoplanin, which also require therapeutic drug monitoring (Pea, 2020; Rao et al., 2020) but are not currently performed in Kuwait. The estimated total cost may not reflect the actual costs of the study agents in Kuwaiti public hospitals. Only the direct medical costs were considered. Laboratory test costs may have been overestimated because they were

based on a study conducted in the USA (Bounthavong et al., 2011), and healthcare costs in Kuwait may differ from those in the USA. The lower 25 % limit estimate was used in the current analysis to overcome this limitation. Finally, patients were admitted to the ICU, medical ward, or surgical ward for reasons other than suspected or confirmed infections. Therefore, the average cost per hospital stay used in the analysis may not represent the cost of using the study agents.

4.2. Conclusion

No superiority of glycopeptides and linezolid was observed for gram-positive infections regarding clinical cure, microbiological eradication, or mortality. The high early incidence of thrombocytopenia highlights the need for early disease monitoring. The overall direct medical cost for hospitalised patients using glycopeptide or linezolid therapies is estimated to be more than USD 894,570.6. Guided use of glycopeptides or linezolid based on evidence of cost-effectiveness is needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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This work has not been previously presented as an abstract at a conference or similar.

Ethics approval statement

Ethical clearance for this study was obtained from the Human Research Ethics committee of the Ministry of Health, Kuwait (Ethics approval number: 1055/2019).

Author contributions

All authors met the ICMJE authorship criteria and have read and approved the final version of the manuscript. Sarah S Alghanem, Moetaza M. Soliman, Sarah Al-Manie, and Wadha Alfouzan contributed to the study conception and design. Material preparation and data collection were performed by Wadha Alfouzan, Duaa Alhammadi, Yousif Alreshidi, Adnan Hajjiah, Rafaa Alfarhoud, Mai Almane, Mona Mataqi, Salma Alajmi, and Khalifa Albenwan. Data analysis was performed by Sarah S Alghanem and Moetaza M. Soliman. Cost analysis was conducted by Sarah Al-Manie. The first draft of the manuscript was written by Sarah S Alghanem, Moetaza M. Soliman, and Sarah Al-Manie. All the authors critically reviewed the submitted version of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2023.101813.

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