Comparative Cost-effectiveness of Alternative Empiric Antimicrobial Treatment Options for Suspected Enterococcal Bacteremia

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OBJECTIVES Enterococcus species are the fourth leading cause of bacteremia. Resistance rates are rising and delays in appropriate initial antimicrobial therapy have been associated with increased mortality. Empiric treatment of patients with suspected enterococcal bacteremia varies and significant cost differences exist between alternatives. The objective of this study was to determine the cost-effectiveness of various empiric treatments for patients with suspected enterococcal bacteremia.

METHODS A decision-analytic model was constructed from the hospital perspective to assess the cost-effectiveness of alternative empiric treatment options for enterococcal bacteremia, including antimicrobials active against vancomycin-resistant enterococcus (VRE). The model was populated from available literature sources and included resistance patterns, associated mortality with early versus delayed effective treatment, and the cost of treatment. Univariate sensitivity analyses tested the robustness of the model to determine the degree to which model uncertainties influenced outcomes. We also undertook a probabilistic sensitivity analysis varying parameters in 10,000 Monte Carlo simulations.

MAIN RESULTS The incremental cost-effectiveness ratio was $791 and $749/quality-adjusted-life-year utilizing empiric daptomycin and linezolid, respectively. The model also predicted an incremental cost/life saved of $11,703 by utilizing empiric daptomycin and $11,084 with linezolid utilization. Ampicillin was dominated (i.e., less effective and associated with increased costs) by both VRE-active agents and vancomycin. A probabilistic Monte Carlo sensitivity analysis showed that an agent with VRE activity had a 100% chance of being cost-effective at traditionally used willingness-to-pay thresholds. The decision-analytic model was sensitive to variations in *E. faecium* mortality and short-term postdischarge survival rates.

CONCLUSION Results of our model showed that empiric utilization of an antimicrobial with activity against VRE may be a cost-effective option for the treatment of suspected enterococcal bacteremia when compared with vancomycin or β-lactam therapy.

KEY WORDS pharmacoeconomics, enterococcal bacteremia, daptomycin, linezolid, vancomycin.
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Bloodstream infections represent nearly one-third of hospital-acquired infections and are associated with significant morbidity and mortality.[1] Approximately 10% of bloodstream infections are due to enterococcus species, making enterococcal bacteremia the fourth leading cause of bloodstream infection in North America.[2] Commonly used empiric treatment strategies include ampicillin or vancomycin, but the prevalence of vancomycin-resistant enterococcal (VRE) species is on the rise with approximately 15–30% of bloodstream isolates in North America demonstrating resistance.[3, 4] In particular, vancomycin resistance in *E. faecium* species has become a significant problem with resistance rates increasing from 40% in 1997 to 61% in 2002.[3] Furthermore, the majority of enterococcal strains that are resistant to vancomycin are also resistant to ampicillin, resulting in an increased role for antimicrobials with activity against VRE (i.e., daptomycin or linezolid) in the treatment of enterococcal infections.[5] These antimicrobial resistance patterns are particularly concerning because vancomycin resistance has been shown to increase the risk of clinical failure, prolong the length of hospitalization, and predict mortality.[4, 6–9] Bloodstream infections caused by VRE are also associated with higher median hospital costs when compared with vancomycin-sensitive enterococcal bacteremias (VSE, $42,106 vs $20,895).[10]

Research has demonstrated that early initiation of appropriate antimicrobial therapy has the potential to improve survival in patients with enterococcal bacteremia. One study found that receipt of effective antimicrobial treatment within 48 hours significantly improved survival at 14 days (odds ratio 0.21, p=0.02) in patients with enterococcal bacteremia.[4] These results were supported by a retrospective analysis demonstrating that in patients with positive enterococcal blood cultures, mortality was significantly decreased when effective antimicrobial therapy was started early (defined as on or before the day of a positive culture result; odds ratio 0.39, confidence interval 0.19–0.78).[11] Another group utilized peptide nucleic acid fluorescent in situ hybridization (PNA FISH) technology to identify bacteria approximately 2–3 days earlier than traditional culture methods.[12] They confirmed that patients with *E. faecium* bloodstream infections received inadequate empiric antimicrobial therapy 82–87% of the time, and that initiation of effective antibiotics 2 days earlier significantly decreased mortality from 45% to 26% (p=0.04). With traditional culture methods, it may take up to 2–3 days to identify *E. faecium* and begin antiVRE antimicrobial therapy. These studies suggest that if patients receive an effective antimicrobial even 48 hours earlier, the potential exists to significantly improve survival. However, the cost associated with a course of each antibiotic is not equivalent, and VRE-active antibiotics are currently associated with a significantly higher daily cost than comparable drugs.[13] The increased morbidity, mortality, and costs associated with VRE bloodstream infections and the clinical benefit of timely therapy make early, effective treatment an important consideration.

International guidelines for the diagnosis and management of intravascular catheter–related infections provide recommendations about how to initially manage patients with suspected bacteremias.[14] Vancomycin is the recommended empiric therapy in health care settings that have an elevated prevalence of methicillin-resistant *Staphylococcus aureus*. Linezolid should not be used empirically unless institutions have a preponderance of methicillin-resistant *Staphylococcus aureus* with vancomycin minimum inhibitory concentration values above 2 μg/ml. Once enterococcal bacteremias are identified and susceptibilities return, the recommended therapies are: ampicillin for ampicillin-susceptible enterococci, vancomycin if the pathogen is resistant to ampicillin, and linezolid or daptomycin if both ampicillin and vancomycin resistance are present. In cases where VRE is the offending organism, these recommendations assume susceptibilities are known before therapy is changed, which may lead to a delay in effective therapy if the offending organism is resistant to initial therapy. Given the high risk of mortality and cost difference between alternatives, we undertook an analysis to determine the cost-effectiveness of various empiric treatment strategies in patients with suspected enterococcal bacteremia.

Methods

A decision-analytic model (DATA, TreeAge Software Inc., Williamstown, MA) was constructed from the hospital perspective to assess the cost-effectiveness of alternative empiric treatment options for suspected enterococcal bacteremia in a hypothetical cohort of adult patients in the United States. The base case outcome measures were defined as cost/life saved and as cost/quality-adjusted life year (QALY). Incremental cost-effectiveness ratios were calculated with the

following formula: (Cost Treatment Option A – Cost Treatment Option B)/(Effectiveness Treatment Option A – Effectiveness Treatment Option B). Our analysis was exempt from investigational review board review according to institutional policy. Univariate sensitivity analyses tested the robustness of the model to determine the degree to which model uncertainties influenced outcomes. We also undertook a probabilistic sensitivity analysis varying parameters in 10,000 Monte Carlo simulations.

Our model design is displayed in Figure 1. Our hypothetical patient population consisted of adult patients without documented immune-mediated hypersensitivity reactions to any class of study drugs. Patients with positive Gram stains for Gram-positive cocci in chains received either a β-lactam, vancomycin, or an antimicrobial with activity against VRE. Daptomycin and linezolid were selected as the VRE-active agents tested. We investigated the impact of varying daptomycin dosing regimens in the sensitivity and secondary analyses. Our base case assumed the availability of microbiologic rapid diagnostic testing such as matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) or PNA FISH, which allowed for species identification and prompt antimicrobial stewardship team or provider response to tailor empiric therapy. Patients ultimately determined to have streptococcal bacteremia were excluded during efficacy and mortality analyses. We accounted for the presence of streptococcal species during the empiric treatment phase by assessing the cost of treating these patients until species identification to each treatment arm. The prevalence of streptococcus and enterococcus species were varied in our sensitivity analyses according to published reports.[2] With a few exceptions, patients remained on initial therapies until susceptibilities returned. Patients started on ampicillin and vancomycin were subsequently changed to a VRE-active agent after identification of *E. faecium*. Similarly, patients started on vancomycin or a VRE-active agent were switched to ampicillin if *E. faecalis* was identified through rapid diagnostic testing. We assumed all patients were promptly changed to appropriate therapy according to international recommendations after species identification and susceptibility reporting.[14] Variation in the promptness of therapy changes and the availability of rapid diagnostic technology were investigated in our sensitivity analyses.

The model was populated from available literature sources and included antimicrobial resistance reports, mortality rates associated with early versus delayed effective antimicrobial therapy, and associated costs of enterococcal bacteremia treatment (Table 1). The attributable inpatient cost of enterococcal bacteremia treatment was obtained from a previously published analysis and adjusted for inflation to 2013 dollars using the consumer price index.[10, 15] We excluded pharmacy costs and assessed the incremental treatment cost to patients with either VRE or VSE bacteremias. Although one study has reported a nonsignificant increased length of stay of 1 day after implementation of rapid diag-

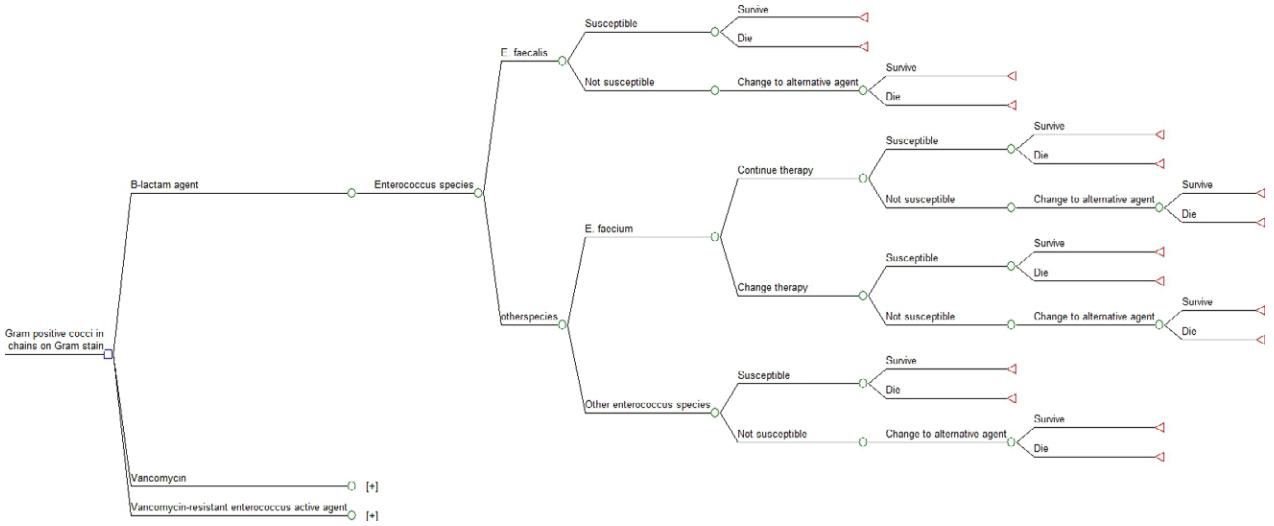

Figure 1. Decision tree comparing empiric treatment strategies in patients with suspected enterococcal bacteremias.

Table 1. Decision-Analytic Model Variables

Variable	Base Case Value	Range	Distribution	Parameters Mean (SD)
Costs				
Ampicillin 2000 mg q 6 hrs[a,13]	$27	$10–50	Normal	2.7
Vancomycin 1000 mg twice/day[a,13]	$8	$4–50	Normal	1
Daptomycin 420 mg/day[a,13]	$254	$100–1000	Normal	51
Linezolid 600 mg IV twice/day[a,13]	$241	N/A	N/A	N/A
Attributable cost (excluding pharmacy costs)[10, 15]				
Vancomycin-resistant enterococcus	$50,627	$40,502–60,752	Normal	5063
Vancomycin-susceptible enterococcus	$25,827	$20,622–30,922	Normal	2583
Incremental hospital cost [a,10, 15]				
Vancomycin-resistant enterococcus	$3468	$2468–4468	Normal	347
Vancomycin-susceptible enterococcus	$2583	$1583–3583	Normal	258
Increased length of stay if not susceptible (days)[12]	0	1–6	Normal	1
Days until species identified	2	1–5	Normal	1
Days until susceptibilities return	4	1–14	Normal	1
Years survival[12, 17]	27	0.1–50	Normal	2.7
Probabilities				
Gram positive cocci in chains identified as enterococcal species[2]	0.5	0.3–0.7	Beta	
E. faecalis				
Prevalence[1]	0.35	0.1–0.9	Beta	0.035
Ampicillin susceptible[21]	1	0.8–1	Beta	0.01
Vancomycin susceptible[21]	0.96	0.8–1	Beta	0.096
Daptomycin susceptible[21]	1	0.8–1	Beta	0.01
30-day mortality when organism susceptible to empiric therapy[12]	0.1	0–0.2	Beta	.01
30-day mortality when organism nonsusceptible to empiric therapy[12]	0.13	0.03–0.23	Beta	0.013
E. faecium				
Prevalence[1]	0.51	0.1–0.9	Beta	0.051
Ampicillin susceptible[21]	0.054	0–0.2	Beta	0.005
Vancomycin susceptible[21]	0.283	0.08–0.48	Beta	0.028
Daptomycin susceptible[21]	0.997	0.8–1	Beta	0.099
30-day mortality when organism susceptible to empiric therapy[12]	0.26	0.06–0.46	Beta	0.026
30-day mortality when organism nonsusceptible to empiric therapy[12]	0.45	0.25–0.65	Beta	0.045
Other enterococcal species				
Prevalence[1]	0.14	0.4–0.24	Beta	0.014
Ampicillin susceptible[22]	0.86	0.66–1	Beta	0.086
Vancomycin susceptible[22]	0.86	0.66–1	Beta	0.086
Daptomycin susceptible[22]	1	0.8–1	Beta	0.01
30-day mortality when organism susceptible to empiric therapy[12]	0.1	0–0.2	Beta	0.01
30-day mortality when organism nonsusceptible to empiric therapy[12]	0.13	0.03–0.23	Beta	0.13
Utilities				
QALY[12]	0.8	0.5–1	N/A	
Discount rate	3%	0–6%	N/A	

[a]Daily cost.
SD = standard deviation; IV = intravenous; N/A = not applicable; QALY = quality-adjusted life year

nostic testing despite reporting an improved time to appropriate antimicrobial therapy,[12] we chose not to increase the anticipated length of stay in the base case scenario when susceptible empiric therapy was correctly chosen. We instead chose to analyze the incremental cost of both increased and decreased lengths of stay in our sensitivity analyses by assigning an incremental cost/day for increased or decreased stay corresponding to identification as a VRE or VSE infection.[10] Indirect costs associated with drug preparation, administration, and monitoring were assumed to be fixed and not included in our model.

Survival rates associated with early versus delayed treatment were obtained from the pub-

lished report discussed previously.[12] Initiation of effective empiric enterococcal treatment resulted in improved survival in all enterococcal species with the largest benefit observed in patients with *E. faecium*. Survival differences were not reported in patients with enterococcal species other than *faecalis* and *faecium*. For enterococcal species, we assumed a survival difference equivalent to patients with *E. faecalis* and analyzed potential variations in mortality rates in our sensitivity analyses.

We utilized a QALY utility measure corresponding to a study that reported a 20% reduction in quality of life after a septic episode.[16] Thus, we predicted an additional year of survival would generate 0.8 QALYs. The median age of patients with enterococcal bacteremia in the earlier trial was 56 years. We therefore estimated that survivors would live 27 additional years after development of enterococcal bacteremia.[17] All utilities and costs were valued in 2013 dollars (U.S.) and discounted at a rate of 3%.[15]

Results

The results of our analyses are listed in Table 2. Using empiric vancomycin as the primary point of reference, the incremental cost-effectiveness ratio utilizing empiric daptomycin compared with alternatives was $791/QALY. Our model predicted that 14 patients would need to be treated with a VRE-active agent rather than vancomycin to save one life. The incremental cost/life saved associated with the empiric use of daptomycin in these patients was $11,703. Utilization of linezolid as the VRE-active agent resulted in an incremental cost/QALY of $749 and an incremental cost/life saved of $11,084. Ampicillin was dominated (i.e., less effective and associated with increased costs) by both daptomycin and vancomycin for cost/life saved and cost/QALY.

A probabilistic Monte Carlo sensitivity analysis showed that both VRE-active agents had a 100% chance of being cost-effective at a willingness-to-pay threshold of $100,000/QALY and at $50,000/QALY (Figure 2). Daptomycin had a 93% chance of being cost-effective at a cost/life saved threshold of $50,000 and a 99.5% chance at $100,000/life saved.

Both models proved robust to variations in nearly all model parameters at a willingness-to-pay threshold of $50,000. The models were sensitive to changes in *E. faecium* mortality rates and short-term postdischarge survival rates. Vancomycin was more cost-effective if the long-term survival was less than 4 months after development of bacteremia. Empiric use of a VRE-active agent was no longer cost-effective at our willingness-to-pay threshold when mortality due to delayed effective therapy in patients with *E. faecium* dropped from 45% to 26.2% (cost/QALY) or 30.4% (cost/life saved), while the mortality rate associated with appropriate antibiotic selection remained at 26%. Likewise, increasing *E. faecium* mortality rates without delays in therapy from 26% to 40.6% in the cost/life saved and 44.8% in our cost/QALY models, respectively, negated the advantage for a VRE-active agent when *E. faecium* mortality remained 45%. Varying the mortality rates in patients with bacteremia from other enterococcal species to reflect mortality rates similar to *E. faecium,* rather than

Table 2. Cost-effectiveness of Empiric Enterococcal Bacteremia Treatment Strategies[a]

Strategy	Cost	Incremental Cost	Effect	Incremental Effect	Incremental C/E (ICER)
Base Case (Cost/life saved)			(Survival %)	(Survival %)	
Vancomycin therapy	$35,967		74.5		
β-lactam therapy	$36,030	$63	71.9	−2.7	Dominated
VRE-active therapy					
Daptomycin	$36,775	$808	81.4	7	$11,703
Linezolid	$36,719	$765	81.4	7	$11,084
Base Case (Cost/QALY)			(QALY)	(QALY)	
Vancomycin therapy	$35,967		11		
β-lactam therapy	$36,030	$63	10.6	−0.4	Dominated
VRE-active therapy					
Daptomycin	$36,775	$808	12.1	1	$791
Linezolid	$36,719	$765	12.1	1	$749

[a]Calculations for cost-effectiveness were performed by taking the incremental cost (difference between costs of compared strategies) divided by the incremental effectiveness (difference between the effectiveness of the compared strategies).

C/E = cost/effectiveness; ICER = incremental cost-effectiveness ratio; VRE = vancomycin-resistant enterococci; QALY = quality-adjusted life year

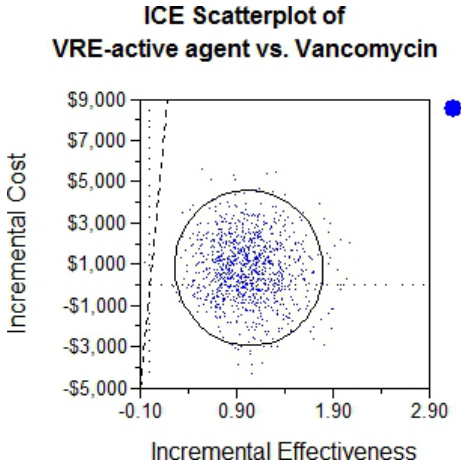

Figure 2. Incremental cost-effectiveness (ICE) scatterplot comparing a vancomycin-resistant enterococcus (VRE) active agent versus vancomycin across 10,000 simulations at a willingness-to-pay threshold of $50,000 per quality adjusted life year (QALY).

E. faecalis, did not have an impact on the results. No other variable within our predefined sensitivity ranges had the potential to impact the results of the model. This included the QALY utility measure utilized, drug acquisition costs, susceptibility reporting times, variations in length of stay, or hospitalization cost.

Utilizing increased dosing regimens of daptomycin had minimal impact on economic burden. The incremental cost/QALY and incremental cost/life saved by utilizing 8 mg/kg of daptomycin versus 6 mg/kg in a 70-kg patient was $1061 and $15,747, respectively. Utilization of 10 mg/kg daptomycin dosing in the same 70-kg patient provided similar results ($1334/QALY and $19,744/life saved). We also investigated the impact of increased doses in obese patients through a wide range on VRE-active agent cost in our sensitivity analyses. No variation in patient weight, up to and including a 277-kg patient dosed at 6 mg/kg, had the potential to impact results based on our willingness-to-pay thresholds.

Empiric utilization of a VRE-active agent (i.e., daptomycin or linezolid) remained cost-effective when we analyzed scenarios without the benefit of rapid diagnostic testing technology or prompt deescalation. When the initial treatment choice was continued until susceptibilities returned, use of daptomycin remained cost-effective ($1433/QALY and $21,369/life saved). Likewise, empiric utilization of daptomycin proved cost-effective when rapid diagnostic testing was not present and deescalation from daptomycin to vancomycin when VSE was identified did not occur ($1788/QALY and $26,464/life saved).

Discussion

Results of our analysis demonstrate that empiric utilization of an antimicrobial with activity against VRE followed by prompt deescalation once susceptibilities return is cost-effective in patients with suspected enterococcal bacteremia. When compared with utilization of vancomycin or a β-lactam antimicrobial, our model predicted that effective empiric coverage against VRE improves overall survival, as well as patients' quality of life, at a cost well below traditional willingness-to-pay thresholds.

Our analysis has several limitations that decision makers should consider before implementing widespread empiric use of VRE-active agents in this patient population. First, we did not predict future consequences of increased VRE-active agent utilization. Many institutions reserve agents with VRE activity in order to extend the effective life of these agents. Resistance and collateral damage would likely be accelerated with widespread use. Predicting the economic or clinical consequences of future resistance patterns would be difficult to quantify and beyond the scope of this analysis. We hope further studies shed more light on this going forward. The role of antimicrobial conservation should remain an important consideration for decision and policy makers when developing treatment guidelines and algorithms based on this evidence.

Another limitation is that we did not incorporate costs of adverse events associated with use of either treatment regimen. The clinical and financial impact of adverse reactions such as nephrotoxicity, creatinine-kinase elevations, or immune-mediated reactions would have affected each arm differently. The short empiric therapy timeframe of our analysis would lessen exposure, which may decrease, though not eliminate, incidence of adverse events and associated costs between alternatives. In addition, we are unaware of studies reporting adverse event rates for treatment alternatives during the time between the beginning of empiric therapy and the return of susceptibilities. Including accurate adverse event estimates would therefore prove very difficult and beyond the scope of our analysis.

Integration of rapid diagnostic testing (MALDI-TOF or PNA FISH) with antimicrobial stewardship team intervention or provider ability to tailor therapy on species identification may not be a reality in most health systems at this time. As mentioned previously, our base case focused on the time from identification of

species on Gram stain until susceptibilities were reported and deescalation occurred. Assuming availability of this technology in our base case biased results against vancomycin or ampicillin since there was less exposure to the costly VRE-active agents. However, we accounted for variations in time to species and susceptibility identification in our sensitivity analyses by investigating results with and without the availability of rapid diagnostic testing. Empiric utilization of VRE-active agents remained cost effective in institutions under both scenarios. Likewise, we were also able to investigate whether deescalation through good antimicrobial stewardship practices was essential to maintain results. Our model predicted that continuing a VRE-active agent for a 2-week treatment course without deescalation was also cost-effective. Although we advocate for deescalation when appropriate and caution that extending the treatment duration in this secondary analysis compounds several of the model's preexisting limitations, these secondary results provide further information for decision makers without antimicrobial stewardship programs or mechanisms at their institution to ensure consistent deescalation.

Patients with prolonged intensive care unit admission, neutropenia, or liver transplantation with VRE colonization may be at higher risk for the development of VRE bacteremia based on surveillance cultures or prior colonization.[18–20] We did not analyze scenarios where empiric initial therapy could be guided by these risk factors. However, the higher likelihood of developing a VRE versus VSE bacteremia in these populations would strengthen the efficacy projections and further improve the cost-effectiveness of empiric utilization of a VRE-active agent. Our model predicted that even institutions with lower rates of VRE or higher rates of *E. faecalis* would benefit from empiric utilization of an agent with VRE activity. Daptomycin remained the preferred empiric antimicrobial at a willingness-to-pay threshold of $50,000/QALY when the prevalence of *E. faecalis* was set to an intentionally high 90%. When *E. faecium* isolates were analyzed individually, a VRE-active agent was cost-effective only when vancomycin susceptibility was greater than 99%.

Finally, our model is based on published studies and microbiologic incidence and susceptibility reports. We were unable to incorporate very recent national enterococcal species prevalence or susceptibility estimates. Further, individual institution or regional streptococcal and enterococcal prevalence and susceptibility data may vary. We intentionally set wide sensitivity ranges, and our univariate and probabilistic sensitivity analyses confirm results across a range of likely susceptibility and prevalence scenarios. Similarly, although a number of studies have demonstrated that early initiation of appropriate antimicrobial therapy has the potential to improve survival in patients with enterococcal bacteremia, the efficacy data used in our analysis were primarily pulled from one analysis.[4, 11, 12] If we are to believe that early effective therapy does not improve survival, then the cost of using empiric VRE-active therapy to the institution and society may be considerable. The estimated increased cost by utilizing a VRE-active agent until the organism strain is identified is approximately $800/patient. This cost could rise depending on factors such as the dosing regimens, patient-specific factors, and whether VRE-active therapy is not promptly deescalated once the organism is identified or susceptibilities return. Depending on the incidence of suspected enterococcal bacteremia, this additional cost could drive up health care costs considerably, which is a particular concern in today's cost-conscious health care environment. Results of our analysis suggest that if there is even the slightest mortality benefit from timely effective antimicrobial selection, then selection of an agent with activity against VRE combined with prompt deescalation saves lives and improves patients' quality of life at a minimal cost. As with all economic modeling, real-world results are needed to validate or refute results of our analysis.

To our knowledge, this is the first analysis investigating the cost-effectiveness of empiric antimicrobial selection in patients with suspected enterococcal bacteremia. Our results showed that empiric utilization of an antimicrobial with activity against VRE may be a cost-effective option for the treatment of suspected enterococcal bacteremia when compared with vancomycin or ampicillin. Results of our analysis provide prescribers, antimicrobial stewardship teams, and other decision makers with additional information when considering empiric antimicrobial therapy for the treatment of patients with suspected enterococcal bacteremia.

Conclusion

Empiric utilization of an antimicrobial with activity against VRE may be a cost-effective option for the treatment of suspected enterococcal

bacteremia when compared with vancomycin or a β-lactam antimicrobial.

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