Exploratory Cost-Effectiveness Analysis for Treatment of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections: Are Daptomycin and Linezolid Favored over Vancomycin and Other Antibiotics?

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Background

- There is a lack of high quality, head-to-head comparative studies for initial treatment of methicillin-resistant *Staphylococcus aureus* bloodstream infections (MRSAB).[1]
  - Limited to non-inferiority randomized-controlled trials and observational studies.
  - Most available evidence for vancomycin and daptomycin.
- Vancomycin is most commonly used and a low-cost agent.[1,2]
  - Monitoring burden and nephrotoxicity risks with prolonged treatment.
  - MRSAB often requires extended durations of therapy.
- Two published studies have compared the costs of daptomycin and vancomycin for MRSAB.[3,4]
  - Daptomycin drug costs offset by medical cost reductions.
  - Neither reported incremental costs per outcome.
- Newer anti-MRSA antibiotics may be more effective and/or safer than vancomycin, but they are generally more expensive.

Objectives

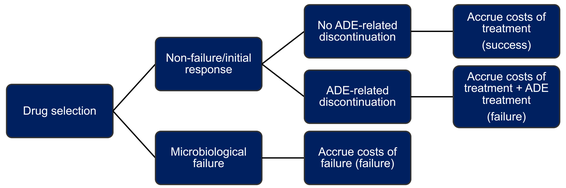
- Compare the cost-effectiveness of initial, directed antibiotic regimens for MRSAB.
- Identify factors influential in the cost-effectiveness of treatment.

Methods

- Exploratory decision-tree model from the perspective of the Veterans Health Administration (VA) (**Figure 1**).
  - Estimated cost-effectiveness of directed antibiotics for VA patients with MRSAB for 4 (primary) and 6 weeks.
  - Initial IV therapy: vancomycin, daptomycin, linezolid, ceftaroline + daptomycin, and dalbavancin.
- Inputs from literature, expert opinion, and VA databases (costs).
- Primary effectiveness outcome = composite of:
  - Microbiological failure at ~7-days, and
  - Adverse drug event (ADE)-related treatment discontinuation.
- Incremental cost-effectiveness ratios (ICERs) (cost in USD 2019 per composite treatment failure avoided) reported.
- One-way and probabilistic sensitivity analyses with willingness-to-pay (WTP) threshold = $40,000 (cost of failure on vancomycin).[5,6]

Methods

Figure 1. Decision-tree Cohort Model



ADE = adverse drug event. Patients remained hospitalized until microbiological failure or initial response. Microbiological failure: patients stopped the initial antibiotic and accrued costs of an extended hospital stay and salvage treatment. Non-failure: patients were discharged, and continued outpatient parenteral antibiotic therapy. ADE: occurred after 7 days of treatment, patient discontinued antibiotic.

Table 1. Model Inputs

Model Parameter	Base Case	Low	High
Days[7]			
inpatient treatment	7	4	12
extended inpatient stay from microbiological failure (multiplier)	2	1	4
outpatient treatment	21	14	30
Risk of Microbiological Failure at ~7-days[8]			
dalbavancin	20.0%	12.8%	29.8%
daptomycin	18.8%	14.0%	22.1%
daptomycin/ceftaroline	15.0%	9.2%	18.8%
linezolid	14.0%	13.0%	40.0%
vancomycin	27.2%	14.0%	42.4%
Risk of Adverse Drug Event-related Discontinuation[9]			
ceftaroline	12.8%	2.7%	21.0%
dalbavancin	2.1%	1.1%	3.4%
daptomycin	4.3%	3.1%	7.6%
linezolid	14.3%	6.1%	20.0%
vancomycin	11.2%	4.3%	16.7%
Antibiotic (cost per day in USD 2019)[10]			
ceftaroline 600 mg every 8 hours	346	276	415
dalbavancin 1.5 Gm weekly	492	393	590
daptomycin 6 mg/kg daily (80 kg patient)	84	68	101
linezolid 600 mg IV twice daily	33	27	40
linezolid 600 mg PO twice daily	3	3	6
vancomycin 1.5 Gm twice daily	10	8	11
Other Inpatient (cost per day in USD 2019)[11]			
hospitalization day (acute medicine)	3,374	2,699	4,049
Monitoring (cost per day in USD 2019)[11]			
daptomycin: 1 CPK test per week	0.37	0.30	0.44
vancomycin: 1 trough every 3 days	2.20	1.76	2.64
Outcome-Specific Costs (USD 2019)[6,12]			
outpatient nurse visits and weekly labs	686	549	823
outpatient ADE-related discontinuation treatment	4,101	3,281	4,921

Results

Table 2. ICERs for 4-week Treatment Base-case Model

Strategy	Total Cost per Patient	Incremental Cost	Outcome	Incremental Effectiveness	ICER
IV linezolid	$29,323	-	-26%	-	-
daptomycin	$31,140	$1,817	-22%	4%	$44,980
vancomycin	$32,412	$1,272	-35%	-13%	Dominated
ceftaroline with daptomycin	$36,767	$5,627	-30%	-7%	Dominated
dalbavancin	$38,231	$7,091	-22%	0.4%	$1,691,945

Outcome: risk of composite failure. Incremental effectiveness: composite failure avoided. ICER=incremental cost-effectiveness ratio

Table 3. ICERs for 6-week Treatment Base-case Model

Strategy	Total Cost per Patient	Incremental Cost	Outcome	Incremental Effectiveness	ICER
IV linezolid	$30,200	-	-26%	-	-
daptomycin	$32,679	$2,479	-22%	4%	$61,381
vancomycin	$33,265	$586	-35%	-13%	Dominated
ceftaroline with daptomycin	$42,381	$9,702	-30%	-7%	Dominated
dalbavancin	$44,344	$11,665	-22%	0.42%	$2,783,325

- Linezolid and daptomycin were less expensive with fewer treatment failures than vancomycin for 4 and 6-week regimens (**Table 2-3**).
- Compared to linezolid, daptomycin cost ~$45-60K more per composite failure avoided.

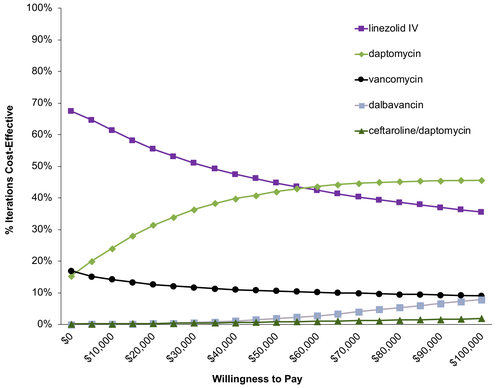
Table 4. 1-way sensitivity analysis at $40,000 WTP

Variable	Base Case Value	Threshold Value	Favored Strategy Below Threshold	Favored Strategy Above Threshold
Number of inpatient days	7	5.8	daptomycin	linezolid IV
Number of outpatient days	21	16.7		
Extended inpatient stay from microbiological failure (mult.)	2	1.83		
Daptomycin- microbiologic failure risk	18.8%	18.5%		
Daptomycin- ADE-based discontinuation risk	4.3%	3.7%		
Daily cost of daptomycin	$84	$73		
Daily cost of hospital day	$3,314	$2,775		
Linezolid- microbiologic failure risk	14.0%	14.3%	linezolid IV	daptomycin
Linezolid- ADE-based discontinuation risk	14.3%	14.8%		
Vancomycin- microbiologic failure risk	27.0%	16.4%	vancomycin	linezolid IV

- Daptomycin favored over linezolid if: (**Table 4**)
  - Hospitalization duration and treatment costs were reduced.
  - Daptomycin's risks of microbiologic failure and ADE-related discontinuation were lower than base-case values.
  - Linezolid's risks of microbiologic failure and ADE-related discontinuation were higher than base-case values.
- Vancomycin favored when its microbiological failure risk < 16.4%.

Results (cont.)

Figure 2. Probabilistic Sensitivity Analysis – Acceptability Curves for 10,000 Monte-Carlo Iterations



- Vancomycin was not favored in >80% of simulations over a broad range of WTP thresholds (**Figure 2**).
- Linezolid or daptomycin is favored when WTP is ~$40K-$75K.

Conclusions

- Daptomycin or linezolid are likely less expensive and more effective than vancomycin for initial treatment of MRSAB.
- Effectiveness and safety of linezolid are influential factors. More evidence is needed to support linezolid's safety with long-term use in MRSAB.

Limitations

- Results/conclusions reflect exploratory modeling and did not include events after end of treatment (e.g., recurrence).
- Drug and resource utilization costs reflect VA pricing, which is lower than in other US healthcare systems.

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