Daptomycin versus Vancomycin for Empiric Treatment of Methicillin-Resistant *S. aureus* among Hospitalized Patients: An Institutional Cost-Breakpoint Analysis

by

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A project submitted in partial fulfillment of the requirement for the degree of

MASTER OF SCIENCE

IN

PHARMACY

(PHARMACY ADMINISTRATION)

Non-Thesis Project Option

University of Houston

College of Pharmacy

May 2013

Abstract

Background: Bacteremia caused by methicillin-resistant *Staphylococcus aureus* is associated with increased hospitalization days, costs, and mortality. Daptomycin was shown to be noninferior to vancomycin in a phase III clinical trial; however the study was limited by low rates of MRSA infection and before the emergence of strains with reduced susceptibility to vancomycin.

Purpose: The purpose of this study was to perform a cost-breakpoint analysis comparing daptomycin versus vancomycin as empiric therapy for methicillin-resistant *Staphylococcus aureus* bacteremia.

Methods: Data from a phase III, randomized clinical trial comparing daptomycin to vancomycin was used to build a cost breakpoint model. Costs and clinical outcomes associated with drug purchase, toxicity management, vancomycin-resistance, and likelihood of empiric therapy correctly given to patients with confirmed S. aureus bacteremia were added to the model. The model was then used to assess when daptomycin may be beneficial for empiric treatment.

Results: The decision model was able to mimic the results of the phase III clinical trial. Holding other parameters constant, the results showed that empiric treatment correctly directed to *S. aureus* bacteremia of at least 40% (assumed MIC: 0.5 mcg/ml), a MIC of 1.0 – 1.5 mcg/ml (correct empiric therapy: 30%), or a MIC of 2.0 (correct empiric therapy: 20%), daptomycin was more cost-effective than vancomycin as empiric MRSA bacteremia treatment.

Conclusion: With increasing vancomycin MRSA MIC against *S. aureus*, daptomycin may be an appropriate choice of empiric therapy for suspected bacteremia is certain

cases.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is responsible for the majority of hospital infections in the United States. MRSA infections are associated with 59.5% of all cases of *S. aureus* bacteremia in intensive care units (ICUs) of health care facilities throughout the country. [1] MRSA infections are associated with an excess of up to 8 hospitalization days and $17, 422 in costs in comparison with methicillin-susceptible *Staphylococcus aureus* (MSSA). Furthermore, MRSA increases in-hospital mortality rates.[2 - 3]

Appropriate empiric antibiotic treatment, defined as correctly providing antimicrobial therapy to a patient prior to identification of the organism, has a tremendous impact on patients' outcomes. [4 - 5] The Infectious Disease Society of America (IDSA) recommends that empiric antibiotic therapy begin at the first sign of sepsis. In general, culture and sensitivity results take 2-4 days to be revealed.[6] Specifically for suspected MRSA bacteremia, IDSA guidelines recommend vancomycin as the treatment of choice depending on the susceptibility of MRSA to vancomycin. Based on current breakpoints, in cases where the MRSA MIC to vancomycin is > 2 mcg/ml, an alternative therapy should always be chosen. [6] Studies have also shown that despite being within the range of vancomycin susceptibility (e.g. 0.5 < MIC $\leq$ 2 mcg/ml), MRSA isolates with a MIC $\geq$ 1 mcg/ml have been found to be associated with poorer outcomes. For example, Sakoulas, et al. found that 55.6% of patients with *S. aureus* infections with a MIC < 1 mcg/ml experienced treatment success, while those with isolates with a MIC of 1 – 2

mcg/ml had a success rate of only 9.5%. [7] Similarly, other studies have shown increased hospital lengths of stay, poorer end of therapy responses, and decreased eradication rates with vancomycin MICs of 1-2 mcg/ml. [8-10] This phenomenon has come to be known as the "MIC Creep." [11]

Daptomycin is an alternative agent for the treatment of MRSA infections. Importantly, daptomycin resistance is not affected by resistance to vancomycin. Although very effective for *S. aureus* bacteremia, daptomycin is also more costly. A phase III clinical trial of daptomycin showed it to be noninferior to vancomycin for *S. aureus* bacteremia and less toxic. [12] In this study, 44.2% of patients receiving daptomycin experienced clinical success compared to 41.7% of patients receiving vancomycin (absolute difference, 2.4%; 95% confidence interval, -10.2% to 15.1%). Furthermore, more patients receiving vancomycin suffered from renal dysfunction (26.3%), compared to patients receiving daptomycin (11%; $p = 0.004$).[12] However, this study did not enroll patients with MRSA isolates within the MIC creep zone (vancomycin MRSA MIC 1-2 mcg/ml). The prevalence of MRSA bacteremia in the study was 38.3% of *S. aureus* isolates, substantially less than that currently reported throughout the United States, about 60%. [1, 13- 14] For these reasons, the ability to use the results of this well executed phase III study to current practice is limited.

Taking all of this information into account, it would be logical to utilize empiric vancomycin if the MRSA MIC is less than 1 mcg/ml or use an alternative agent if the MIC is greater than 2 mcg/ml. However, the question remains as to what agent should be

employed for MRSA with predicted MICs between 1 and 2 mcg/ml. This is further complicated by the influence that economic factors play on healthcare decisions as well. Although a variety of studies have examined the effectiveness of daptomycin to vancomycin, few have analyzed these therapies from an economic standpoint. [15-17] Furthermore, there have been no studies to date assessing the costs associated with empirically treating suspected *S. aureus* bacteremia with these two agents. Thus, the objectives of this study was to create a decision analysis tree to replicate the phase III daptomycin vs. vancomycin clinical trial results, apply the model to current MRSA epidemiology in regards to current resistance levels and ability to correctly choose correct empiric therapy, and to provide guidance where daptomycin may be beneficial for empiric treatment for patients with suspected MRSA bacteremia.

Methods

Modeled population

In the phase II study, patients with *S. aureus* bacteremia with or without endocarditis who received a minimum of one dose of study medication were included in the analysis. Inclusion criteria included patients who were at least 18 years of age, with one or more blood cultures that were positive for *S. aureus* within 48 hours of initiating therapy. Patients were excluded if they had confirmed osteomyelitis, polymicrobial bacteremia, pneumonia, or a creatinine clearance less than 30 ml/min. [12]

Decision model

A decision model was created in two phases. The model creation phase (phase I) gathered data predominately from the phase III clinical study along with clinical and economic sub-studies that used the same dataset. [12, 18 - 19] The model was then run and clinical results were compared to the phase III study. In phase II, parameters were added to the model including ability to correctly choose correct empiric therapy and average vancomycin MRSA MIC. Model assumptions are shown in the decision model in Figure 1 and Table 1.

Data and assumptions

The majority of the variables added to the model, including the probability of MRSA, MSSA, and treatment failures and successes were taken directly from Fowler, et al. [12] Current epidemiologic data on vancomycin susceptibility were obtained from the published literature. [1, 14-13]

Costs

Many of the costs utilized in the model were gathered from a cost-effectiveness study that utilized data from the daptomycin clinical trial, in conjunction with costs estimated for a typical community hospital. [18] These costs included the acquisition costs of vancomycin and daptomycin, treatment failure follow up, and renal impairment management. Treatment failure follow up included costs associated with follow up drug acquisition and length of stay associated with the follow up therapy. The costs associated with having MRSA and MSSA bacteremia were taken from a retrospective cohort study that assessed

the morbidity, mortality, and hospital costs associated with MRSA and MSSA bacteremia. [3]

Antibiotic toxicities: Rhabdomyolysis and renal dysfunction

Data on renal dysfunction and vancomycin was taken from the previously mentioned cost-effectiveness study, as there was no other applicable data related specifically to the MRSA patients in the phase III clinical trial.[18] Due to limited availability of data on rhabdomyolysis associated with daptomycin therapy, it was assumed that the likelihood of the event was 0.01%. Because mortality data varied from study to study, a rate of 50% for patients with rhabdomyolysis was chosen, as it fell within the range of published literature. This figure was chosen assuming a worst case scenario, in which the patient experienced acute kidney injury within the ICU. [20 - 21] Due to lack of data regarding management of this event, its cost was assumed to be equal to that of managing renal impairment with vancomycin.

Mortality

Baseline mortality data was drawn from a subset analysis of patients that were infected with MRSA from the clinical trial. [19] It was also assumed that renal failure associated with vancomycin increased mortality by 1% (expert opinion). Meanwhile, treatment failure with vancomycin was associated with a 10% increase in mortality. This assumption was taken from studies that demonstrated an increased mortality rate associated with inappropriate empiric antibiotic treatment. [4- 5, 22] The cost associated with mortality was assumed to be $2000.

Influence of MIC Increases

The influence of MIC increases was demonstrated by manipulating the success rates of vancomycin MRSA treatment. It was assumed that with every 0.5 mcg/ml increase in vancomycin MIC that the success rate would decrease by 25% (Table 2). [7, 10] Furthermore, this decrease of success by 25% was accompanied by a 10% increase in mortality. [23]

Duration of antibiotic therapy

For confirmed *S. aureus* bacteremia, treatment duration of 14 days was chosen per IDSA guidelines. [6] For confirmed non-*S. aureus* bacteremia, it was assumed that treatment duration would be 5 days of either vancomycin or daptomycin.

Analysis Plan

The cost-beakpoint study was done in two phases. The first phase involved replicating the results from the phase III clinical trial and subsequent studies. During the second phase, ability to correctly choose correct empiric therapy and changing clinical and economic outcomes based on vancomycin MRSA MIC were added to the model. Finally, a cost breakpoint model was used to determine when empiric daptomycin may be beneficial for empiric therapy in hospitalized patients with suspected MRSA bacteremia. In this model, the costs associated with the two empiric options were compared in order to find the point at which the preferred therapy changed based on cost perspective. All analyses were done from an institutional perspective. As such, drug acquisition costs,

costs associated with MRSA and MSSA bacteremia, and costs of treatment failure were included in the model. Other costs were not considered because they were thought to be the same or negligible regardless of treatment received. One-way sensitivity analyses of percent confirmed *S. aureus* bacteremia, MIC influences, and the cost of mortality were performed based on ranges identified in the literature or from expert opinion. TreeAge (version 3.5.7, TreeAge Software, Inc., Williamstown, MA) was used for all analyses.

Results

Phase I Analysis

The Phase I analysis resulted in a success rate of 41.9% and 44.4% and mortality rate 21.8% and 20.7% of for vancomycin and daptomycin, respectively. Table 3 shows a comparison of these results to the phase III clinical trial.

Phase II Analysis

Using the base analyses of 20% correctly directed empiric therapy and a MIC of 0.5 mcg/ml, the clinical success rate for vancomycin and daptomycin were 7.6% and 44.2%, respectively. The cost of empiric vancomycin was $5, 626, compared to a cost of $5, 920 for daptomycin. In sensitivity analysis, empiric therapy correctly given in patients with S. aureus bacteremia was fluctuated from 0-100%. In the worst case scenario (0% correct empiric therapy), cost associated with vancomycin treatment was $70 and $767 for daptomycin therapy. For a MIC of 2.0 mcg/ml, daptomycin was the preferred treatment option once the confirmed *S. aureus* level was 20%. Vancomycin was the preferred treatment option at all MICs until the level of confirmed *S. aureus* bacteremia reached 30% for MICs of 1.0 and 1.5. For a MIC of 0.5 mcg/ml, daptomycin became the

treatment option of choice at a confirmed *S. aureus* level of 40%. The cost differences between the therapies are represented in Tables 4 and 5. A sensitivity analysis was also conducted by fluctuating the average vancomycin MRSA MIC values. Using a model with 30% of empiric therapy correctly directed towards S. aureus bacteremia (60% MRSA), the cost differences between daptomycin and vancomycin therapies were $92, ($139), ($316), and ($695) for MICs of 0.5, 1.0, 1.5, and 2.0 mcg/ml respectively. At a level of 100% confirmed *S. aureus* bacteremia, the cost differences (60% MRSA) between the two options were greater, at ($1, 316), ($2, 087), ($2, 677), and ($3, 940). Because the cost of mortality is highly dependent on the complications associated with treatment, a one-way sensitivity analysis was also performed by altering the mortality costs to $5, 000, $10, 000, and $20, 000. All other parameters were held at their baseline values (e.g. 20% percent confirmed *S. aureus* bacteremia, 60% MRSA prevalence, and MIC of 0.5 mcg/ml). Despite the increase in mortality costs, vancomycin was the cheapest option, as seen in Table 6.

Discussion

According to IDSA guidelines, empiric therapy should be administered as soon as possible in patients with suspected MRSA bacteremia. For patients with susceptible organisms, defined as a vancomycin MRSA MIC $\leq$ 2 mcg/ml the treatment of choice is vancomycin.[6] However, studies have shown that MRSA isolates with a MIC $\geq$ 1 mcg/ml have been associated with poorer outcomes.[7 - 10] Daptomycin, an alternative agent for MRSA infections is not affected by vancomycin resistance. Although a potent antimicrobial for MRSA infections, it is more costly than vancomycin. In the phase III

indication study, daptomycin was shown to have similar efficacy compared to vancomycin. However, in the indication trial, a low rate of patients with MRSA infection were enrolled of which none of these isolates had an elevated MIC to vancomycin. Furthermore, no studies have researched the costs associated with empiric treatment of suspected *S. aureus* bacteremia with these two agents.

In this current study, the results from the phase III clinical trial and related studies were replicated via a decision analysis model. In the second phase of the analysis plan, current epidemiological and MIC data were added to the model to assess when daptomycin may be beneficial as an empiric therapy. Based on data provided by the clinical trial and its subsequent studies, the results were successfully replicated. The overall trend in success rates, mortality rates, and costs associated with each therapy was similar between the previously published literature and the phase I analysis. The success rates for vancomycin (41.9%) and daptomycin (44.4%) were similar to that of the previously published literature. The costs of the two therapies were found to be $25, 038 and $24, 210.

The results of the phase II analysis used current estimates of MRSA bacteremia (60%), along with decreasing success rates associated with varying MICs. In addition to these considerations, proportion of empiric therapy correctly given for confirmed *S. aureus* bacteremia was also considered to evaluate appropriate empiric therapy. Beginning at a confirmed *S. aureus* bacteremia level of 40% and a MIC of 0.5 mcg/ml, daptomycin was considered to be a more beneficial option, yielding a cost of $11, 074, compared to $11,

183 for vancomycin. As the MIC increased, the level of confirmed *S. aureus* bacteremia required in order to consider daptomycin as the more optimal choice decreased. At MICs of 1.0–1.5 mcg/ml, a confirmed *S. aureus* bacteremia level of at least 30% resulted in daptomycin as the least costly option. The cost of empiric daptomycin therapy at these levels was $8, 497, while costs of vancomycin therapy were $8, 636 and $8, 813. At a MIC of 2.0 mcg/ml, correctly directed therapy at a level of 20% resulted in daptomycin as the least expensive option, at a cost of $6, 151. Such results can be expected, given that studies have found that increased vancomycin MICs are associated with poorer outcomes, as well as higher costs. [7-10]

Similar to other cost-effectiveness studies, there are limitations to this study. Given the nature of a decision analytic model, the findings were highly simulated. Therefore, it did not take into account all possible events and influences on outcomes. Additionally, costs variables taken from Bhavnani, et al. reflected estimates of a community hospital. As such, the costs may not be applicable to every institution. Taking all of this into consideration, these findings should be utilized for the sole purpose of guidance for empiric treatment. The results of this study are also highly contingent on the healthcare professional's predictive abilities. In order to maximize the model as a guide, it calls for more research to be done to elucidate the percentage of accurately predicted *S. aureus* bacteremia within each institution.

In conclusion, no study to date has assessed the levels at which daptomycin may be more beneficial than vancomycin as empiric MRSA bacteremia treatment. After successfully

building a decision model that mimicked the results of the daptomycin clinical trial and its successive studies, the model was expanded by fluctuating the proportion of empiric therapy correctly given for MRSA infection and differing MIC of vancomycin. The results suggested that with a MIC of 0.5 mcg/ml and confirmed *S. aureus* bacteremia of atleast 40%, with a MIC from 1.0 – 1.5 mcg/ml and confirmed *S. aureus* bacteremia of 30%, or with a MIC of 2.0 mcg/ml and confirmed *S. aureus* bacteremia of 20%, daptomycin is more cost-effective than vancomycin as empiric MRSA bacteremia treatment.

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Tables

Table 1. Baseline values for the decision model

Variable	Value	Range	Source
Confirmed S. aureus bacteremia	1.0	0 – 1.0	
Vancomycin Treatment Group			
Proportion of MRSA	0.383		[12]
Treatment success	0.31	0.04 – 0.31	[12], [7]
Treatment Failure	0.69	0.69 – 0.96	[12], [7], [10]
Renal Impairment	0.444		[18]
No Renal Impairment	0.556		[18]
Mortality	0.19	0.19 – 0.4	[19], [4], [22], [23]
Proportion of MSSA	0.383		[12]
Treatment Success	0.486		[12]
Treatment Failure	0.514		[12]
Renal Impairment	0.444		[18]
No Renal Impairment	0.556		[18]
Mortality	0.13	0.13 – 0.24	[19], [4], [22], [23]
Daptomycin Treatment group			

Proportion of MRSA	0.375		[12]
Treatment Success	0.44		[19]
Treatment Failure	0.56		[19]
Rhabdomyolysis	0.0001		
No Rhabdomyolysis	0.9999		
Mortality	0.27	0.27 – 0.87	[19 ,20 , 21]
Proportion of MSSA	0.625		[12]
Treatment Success	0.446		[12]
Treatment Failure	0.554		[12]
Rhabdomyolysis	0.0001		
No Rhabdomyolysis	0.9999		
Mortality	0.08	0.08 – 0.68	[19 ,20 , 21]
Costs			
Vancomycin, non-S. aureus	$ 70		[18]
Daptomycin, non-S. aureus	$766.50		[18]
Vancomycin, S. aureus	$196		[18]
Daptomycin, S. aureus	$2, 146.20		[18]
MRSA bacteremia	$21, 577		[3]

MSSA bacteremia	$11, 688	[3]
Vancomycin treatment failure	$15, 479	[18]
Daptomycin treatment failure	$11, 242	[18]
Renal Impairment	$439	[18]
Rhabdomyolysis	$439	[18]
Mortality	$2, 000	

Table 2. Assumptions of MIC Influence on Clinical Success and Mortality

MIC	Success Rate	Mortality with Renal Impairment	Mortality without renal impairment
0.5	0.31	0.3	0.29
1.0	0.23	0.33	0.32
1.5	0.17	0.36	0.35
2.0	0.04	0.4	0.39

It was assumed that for every 0.5 mcg/ml increase in MIC, the success rate would decrease by 25% along with a 10% increase in mortality. [7, 10, 23]

Table 3. Comparison of Phase I Analysis to Published Literature

	Success (%)		Mortality (%)		Cost ($)	
	vancomycin	daptomycin	vancomycin	daptomycin	vancomycin	daptomycin
Fowler, et al[12]	41.7	44.2	16	15	---	---
Phase I Analysis	41.9	44.4	21.8	20.7	25, 038	24, 210

Table 4. Results of Phase II Analysis

	Costs ($)							
% S. aureus bacteremia	**MIC 0.5**		**MIC 1.0**		**MIC 1.5**		**MIC 2.0**	
	vancomycin	**daptomycin**	**vancomycin**	**daptomycin**	**vancomycin**	**daptomycin**	**vancomycin**	**daptomycin**
0	70	767	70	767	70	767	70	767
10	2, 848	3, 343	2, 925	3, 343	2, 984	3, 343	3, 111	3, 343
20	5, 626	5, 920	5, 781	5, 920	5, 899	5, 920	6, 151	5, 920
30	8, 405	8, 497	8, 636	8, 497	8, 813	8, 497	9, 192	8, 497
40	11, 183	11, 074	11, 491	11, 074	11, 727	11, 074	12, 232	11, 074
50	13, 961	13, 651	14, 347	13, 651	14, 641	13, 651	15, 273	13, 651
60	16, 739	16, 228	17, 202	16, 228	17, 556	16, 228	18, 313	16, 228

70	19, 518	18, 805	20, 057	18, 805	20, 470	18, 805	21, 354	18, 805
80	22, 296	21, 382	22, 913	21, 382	23, 384	21, 382	24, 395	21, 382
90	25, 074	23, 959	25, 768	23, 959	26, 298	23, 959	27, 435	23, 959
100	27, 852	26, 536	28, 623	26, 536	29, 213	26, 536	30, 476	26, 536

Table 5. Summary of Phase II Analysis Breakpoints

MIC	**0.5**	**1.0**	**1.5**	**2.0**
% S. aureus bacteremia	40	30	30	20
Cost Difference ($)	(109)	(139)	(316)	(231)

Table 6. Comparison of costs of therapies at various mortality costs

Costs ($)							
Baseline		**$5, 000**		**$10, 000**		**$20, 000**	
vancomycin	**daptomycin**	**vancomycin**	**daptomycin**	**vancomycin**	**daptomycin**	**vancomycin**	**daptomycin**
5, 626	5, 920	5, 766	6, 070	6, 091	6, 420	6, 556	6, 920

Figures

Figure 1. Decision Model of Empiric Therapy for S. aureus Bacteremia