PREDICTED ECONOMIC BENEFITS OF A NOVEL BIOMARKER FOR EARLIER SEPSIS IDENTIFICATION AND TREATMENT: A COUNTERFACTUAL ANALYSIS

Carly J Paoli, PharmD, MPH[1]; Mark Reynolds, PhD[1]; Courtney Coles, PhD, MPH[2]; Matthew Gitlin, PharmD[2]; Elliott Crouser, MD[3]

[1]Beckman Coulter, Inc., Brea, CA USA; [2]Blue Path Solutions, Los Angeles, CA, United States; [3]Ohio State University Wexner Medical Center, Columbus, OH, United States

INTRODUCTION

As the leading cause of death in US hospitals, improved recognition and treatment of sepsis is an important worldwide healthcare priority.[1]

A critical benefit of early sepsis recognition is the prompt administration of empiric antibiotics.[2,3] Delays in prescribing antibiotics for septic patients can increase their probability of in-hospital mortality by as much as 7.6% per hour.[4,5]

Although international guidelines and real-world evidence support the early administration of antibiotics for sepsis patients, many still do not receive antibiotics within SEP-1 recommended intervals.[5]

Monocyte distribution width (MDW) is a novel biomarker recently shown to detect sepsis in ED settings with promising sensitivity and specificity.[7,8] The MDW parameter is specifically available on the UniCel DxH 900 analyzer (Beckman Coulter, Inc).

Although the clinical benefits of earlier time to antibiotics (TTA) have been reported in a number of published studies, it is still unclear what the health economic benefit might be. The objective of this study was 1) to simulate potential reductions in TTA using MDW+SOC; and 2) to simulate the potential economic benefit of earlier TTA for sepsis patients presenting in the ED using this new technology.

METHODS

Simulated Reduction in TTA with MDW

Pivotal Trial

A non-interventional pivotal trial was conducted at three large medical centers to assess the clinical value of MDW.[8] The pivotal trial included patients who presented to the ED, remained in the hospital for at least 12 hours and were confirmed to have sepsis (based on independent double adjudication and arbitration if discordant) using Sepsis-2 definition.

Methods to Estimate MDW+SOC TTA

Data from the pivotal trial were used to estimate the values of three key model inputs:

A. The actual TTA for SOC:
   - The TTA for each sepsis patient was calculated by subtracting the time of administration of antibiotics from the time the patient arrived in the ED. The mean TTA was then calculated.

B. The estimated proportion of patient who could have benefitted:
   - Due to the non-interventional nature of the trial, the proportion of sepsis patients that would benefit from MDW was estimated based on two key factors: 1) a positive MDW test result (>20) and 2) administration of antibiotics after their healthcare provider would have received the MDW test result as a component of the initial complete blood count (CBC).
   - It was assumed it would take 30 minutes for the healthcare provider to obtain the accompanying MDW test result.
   - Scenario analyses were conducted for longer turnaround time assumptions of 45 minutes or 60 minutes.

C. The simulated weighted mean TTA for MDW+SOC:
   - In the MDW arm, the mean TTA was calculated among two populations: those assumed to be identified via MDW and those assumed to not be identified via MDW.
   - To simulate the effect of MDW, if the two factors outlined above (B) were satisfied, the sepsis patient was counterfactually assigned a new TTA based on the availability of the MDW test result.
   - The mean TTA was then re-calculated among sepsis patients who could have benefitted from MDW to guide their therapy.
   - The weighted mean TTA of the two groups (see **Figure 1**) was calculated to represent the mean TTA for MDW in the model.

Cost Consequence Analysis

Model Design

A cost-consequence analysis from a hospital perspective was undertaken using a deterministic decision tree to estimate the potential health economic benefit of using MDW+SOC versus SOC alone over a time horizon representing the hospitalization period (**Figure 1**). **Table 1** provides an overview of the model.

Figure 1 Cost Consequence Analysis Structure

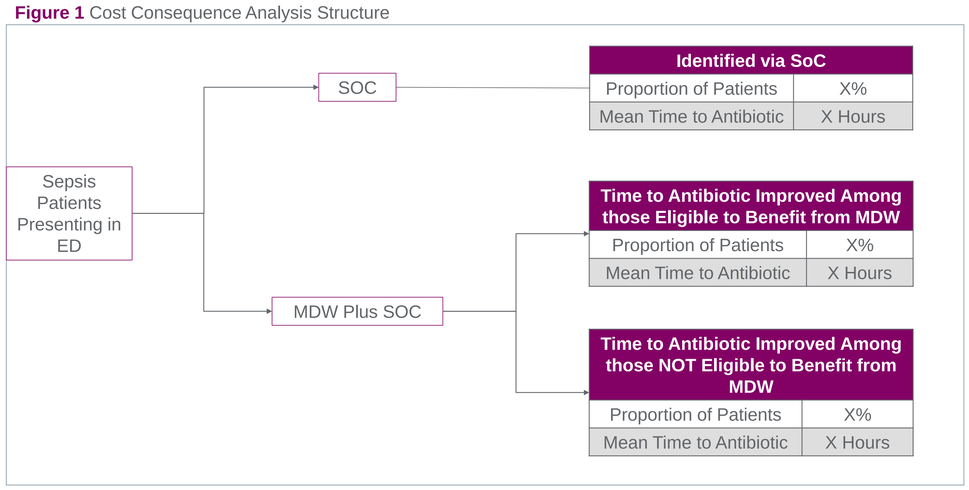


Table 1 Cost Consequence Model Overview

Overview	Description
Design	Cost consequence analysis using a deterministic decision tree
Intervention	Novel monocyte distribution width (MDW) biomarker
Comparator	Standard of care (SOC)
Population	Sepsis patients presenting in the emergency department (ED)
Perspective	Costs over the hospitalization period
Sources	• Pivotal clinical trial • Published observational research • Public cost databases
Inputs	• Mean time to antibiotics for SOC • Simulated mean weighted time to antibiotics for MDW • Relationship of time to antibiotics and mortality • Relationship of time to antibiotics and length of stay • Cost per hospital day for a sepsis hospitalization
Outcomes	• Absolute estimates and differences for MDW+SOC versus SOC • Outcomes include costs, mortality rate, and length of stay

Model Inputs

The model utilizes data from the literature and post-hoc analysis of the clinical evidence. The model inputs are outlined in **Table 2.**

The model is based on a mathematical relationship between TTA and the outcomes of interest **(Figure 2).** To estimate the clinical and economic benefits of reducing TTA, evidence on the relationship of TTA and the outcomes was identified from observational literature. Ferrer and colleagues (2014) stratified the unadjusted in-hospital mortality rate and LOS by TTA.[9] From the scatter plot, a best fit linear regression was plotted to determine the slope of the line. This equation was then used to estimate outcomes for each arm. Scenario analyses were conducted to test the robustness.

Analysis and Outcomes

Base Case Analysis

The key outcomes of interest were the in-hospital mortality rate, mean hospital LOS and the mean sepsis-related hospitalization costs. The analysis was conducted by applying the actual and simulated TTA for SOC and MDW+SOC, respectively, to the mathematical equations described in **Figure 2**.

- The in-hospital mortality rate, as well as mean LOS and costs per sepsis hospitalization, were calculated using the mean TTA observed for SOC and the simulated MDW+SOC.
- To calculate the mean costs associated with a sepsis hospitalization, the mean cost per day was multiplied by the estimated mean LOS.
- The hospital-level analysis was executed by extrapolating the patient-level results to represent the results at an average-sized hospital over the course of a calendar year.

Scenario Analyses

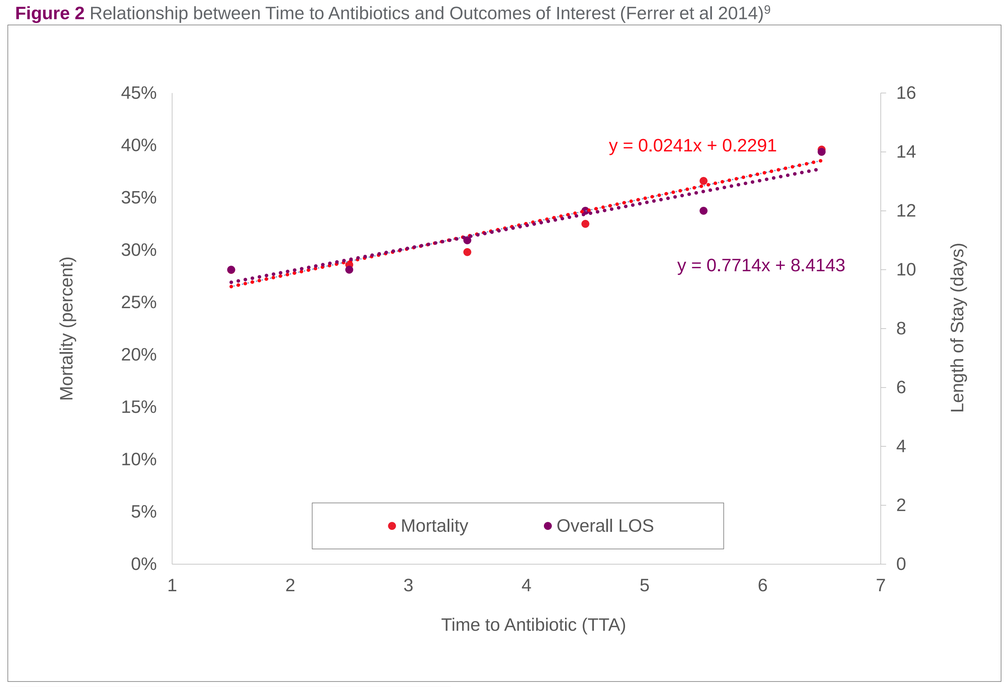
Three independent scenario analyses – while varying one single input for each – was conducted. The three scenarios tested were:

1. Time from phlebotomy to antibiotics administration: The scenario analysis tested the robustness of the results when it was assumed to take 45 or 60 minutes.
2. Size of the hospital: The potential economic benefit of adding MDW to SOC for a small (<100 beds, 108 sepsis hospitalizations annually) and a large hospital (≥500 beds, 1,024 sepsis hospitalizations annually) was estimated.
3. Effect of the relationship between the TTA and LOS and mortality:
   - The data from the Ferrer article used to estimate the relationship between mortality and LOS were unadjusted for severity; therefore, we conducted a scenario analysis using the adjusted in-hospital mortality rate.[9]
   - Because the patients in the Ferrer study had very advanced disease (>60% in septic shock) we also conducted a scenario analysis using data from the Seymour study[10] which all sepsis patients were admitted through the ED.

Table 2 Model Inputs

Model Input	Base Case Value	Source
Time to CBD-diff test result (simulating inclusion of MDW)	30 minutes	Median response from survey of US ED physicians
Mean time to empiric antibiotics for SOC	3.98	Trial data
Simulated mean weighted time to antibiotics with MDW	1.34	Simulated based on trial data
Relationship of time to antibiotics and mortality	y=0.0241x + 0.2291	[9]
Relationship of time to antibiotics and length of stay	y=0.7714x + 8.4143	[9]
Cost per hospital day for a sepsis admission	$2,541	[11,12]
Number of sepsis admissions/hospital/year	206	[12,13]

Figure 2 Relationship between Time to Antibiotics and Outcomes of Interest (Ferrer et al 2014)[9]



RESULTS

Pivotal Trial Analysis of SOC and MDW TTA

The population included in the pivotal trial was 51% female with a mean age of 61 years.[8] Based on the required variables needed to estimate the potential MDW benefits, 349 of the 385 patients were used to populate the model. There were 36 patients excluded due to no antibiotics being given. The other results are listed in **Table 3.**

Cost Consequence Analysis

Patient-level results are outlined in **Table 4**. Earlier identification and administration of antibiotics using MDW+SOC may result in an absolute reduction of in-hospital mortality of 4.6% among sepsis patients relative to SOC, a 16.5% reduction.

Adding MDW may result in $3,460 savings/sepsis patient. The adoption of MDW may reduce hospital LOS by nearly 1.48 day versus the standard of care. A summary of the scenario analyses is presented in **Table 5**.

Table 4. Results of MDW+SOC versus SOC: Per Patient Per Sepsis Hospitalization

Outcome	MDW+SOC	SOC	Absolute Reduction
Inpatient Mortality Rate	27.9%	32.5%	4.6% points
Mean Length of Stay	10.0 days	11.5 days	1.48 days
Mean Cost Per Sepsis Hospitalization	$23,466	$26,926	$3,460

Table 3 Time to Antibiotics for SOC and Simulated MDW Benefits

Variable	All Sites
SOC mean (median) TTA (hours) for sepsis patients	3.98 (3.30)
Proportion of sepsis patients who received antibiotics after CBC time stamp + 30 minutes (when provider would have received MDW results)	90.0% (n=314)
Proportion of sepsis patients who had a positive MDW (>20)	74.2% (n=259)
Proportion of sepsis patients who satisfy both requirements and may benefit from MDW	66.8% (n=233)
MDW mean (median) TTA (hours) for sepsis patients	1.34 (1.15)

Table 5 Scenario Analyses

Variable	Value	Source	Absolute Reduction
Time to MDW Test			
Base Case	**30 minutes**	**Assumption**	**$3,460 per patient**
Scenario #1	45 minutes	Assumption	$3,166 per patient
Scenario #2	60 minutes	Assumption	$2,889 per patient
Hospital Size			
Base Case	**206 sepsis hospitalizations annually**	**[12,13]**	**$712,783 per hospital**
Small Hospital (<100 beds)	108 sepsis hospitalizations annually	[12,13]	$373,692 per hospital
Large Hospital (≥500 beds)	1,024 sepsis hospitalizations annually	[12,13]	$3,543,153 per hospital
Mortality Rate			
Base Case	**y=0.0241x+0.2291**	**[9]**	**$3,460 per patient**
Severity-adjusted mortality rate from Ferrer	y=0.0143x+0.2279	[9]	$2,016 per patient
Severity-adjusted mortality rate from Seymour	y=0.0043x+0.2269	[10]	$234 per patient

CONCLUSION

The results of this counterfactual clinical and economic analysis suggest that the novel, innovative biomarker, MDW, has the potential to provide added clinical and health economic value among sepsis patients presenting to the ED, a population with a well-established significant clinical and economic burden to patients and hospitals in the US each year. Further research is required to confirm the actual reduction in TTA when MDW is used in real-world settings.

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