ORIGINAL RESEARCH

Potential Cost-effectiveness of Early Identification of Hospital-acquired Infection in Critically Ill Patients

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Abstract

Rationale: Limitations in methods for the rapid diagnosis of hospital-acquired infections often delay initiation of effective antimicrobial therapy. New diagnostic approaches offer potential clinical and cost-related improvements in the management of these infections.

Objectives: We developed a decision modeling framework to assess the potential cost-effectiveness of a rapid biomarker assay to identify hospital-acquired infection in high-risk patients earlier than standard diagnostic testing.

Methods: The framework includes parameters representing rates of infection, rates of delayed appropriate therapy, and impact of delayed therapy on mortality, along with assumptions about diagnostic test characteristics and their impact on delayed therapy and length of stay. Parameter estimates were based on contemporary, published studies and supplemented with data from a four-site, observational, clinical study. Extensive sensitivity analyses were performed. The base-case analysis assumed 17.6% of ventilated patients and 11.2% of nonventilated patients develop hospital-acquired infection and that 28.7% of patients with hospital-acquired infection experience delays in appropriate antibiotic therapy with standard care. We assumed this percentage decreased by 50% (to 14.4%) among patients with true-positive results and increased by 50% (to 43.1%) among patients with false-negative results using a hypothetical biomarker assay. Cost of testing was set at $110/d.

Measurements and Main Results: In the base-case analysis, among ventilated patients, daily diagnostic testing starting on admission reduced inpatient mortality from 12.3 to 11.9% and increased mean costs by $1,640 per patient, resulting in an incremental cost-effectiveness ratio of $21,389 per life-year saved. Among nonventilated patients, inpatient mortality decreased from 7.3 to 7.1% and costs increased by $1,381 with diagnostic testing. The resulting incremental cost-effectiveness ratio was $42,325 per life-year saved. Threshold analyses revealed the probabilities of developing hospital-acquired infection in ventilated and nonventilated patients could be as low as 8.4 and 9.8%, respectively, to maintain incremental cost-effectiveness ratios less than $50,000 per life-year saved.

Conclusions: Development and use of serial diagnostic testing that reduces the proportion of patients with delays in appropriate antibiotic therapy for hospital-acquired infections could reduce inpatient mortality. The model presented here offers a cost-effectiveness framework for future test development.

Keywords: cost-benefit analysis; ventilator-associated pneumonia; cross infection; early diagnosis

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Infection poses a substantial risk to hospitalized patients, particularly those in intensive care units (ICUs). Recent estimates indicate that 1.7 million hospital-acquired infections (HAIs) occur annually in U.S. hospitals, costing $9.8 billion and causing approximately 100,000 deaths (1). Hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), accounts for approximately 20% of all HAIs; however, the high mortality rate of 10 to 50% results in the greatest relative number of HAI deaths (~36,000 annually) (1, 2). HAP-associated morbidity is expectedly high, with extended hospital stays ranging from 11 to 25 days and an increase in costs of $10,000 to $49,000 per episode of VAP (3–5). These costs do not include an estimate of the broader personal and societal costs.

The disproportionate HAI-associated morbidity and mortality will always make prevention the primary goal. A secondary goal is early identification and appropriate treatment, which has repeatedly been shown to decrease mortality in the setting of severe sepsis or shock (6–8). However, empiric antibiotic therapy in the absence of shock is not necessarily beneficial (9, 10). Outcomes including mortality improve when antibiotics are limited to those patients who actually have infection and for the shortest duration necessary (9, 10). These competing interests create a challenge for providers as they attempt to identify which patients will benefit and which might be harmed.

This balance is difficult to accomplish. Patients rarely declare their infectious complications with resounding clarity. Instead, a nonspecific change in clinical status often triggers a search for infection or other potential causes. Unfortunately, the tools necessary to make a precise diagnosis are inadequate. Currently available microbiological diagnostic techniques have limitations including low sensitivity, low specificity, or lengthy time to result (11). An improved approach to diagnostic testing is needed. In particular, a timely and accurate HAI diagnostic could guide empiric or tailored therapy while minimizing overuse or misuse of antimicrobials. This, in turn, is expected to improve health outcomes, shorten length of stay (LOS), and reduce medical costs.

We conducted a prospective observational cohort study of patients at risk for HAI to identify novel, host-derived biomarkers to differentiate patients with infection from those without. This study provided data regarding onset of infection, timing and appropriateness of antimicrobial therapy, and in-hospital outcomes. As an adjunct to that study, we sought to develop a decision-analytic framework that could be used to evaluate the potential cost-effectiveness of a diagnostic test that could shorten the time to identify patients with HAI and initiate appropriate antibiotic therapy compared with standard diagnostic procedures.

Methods

Prospective Cohort Study

Enrollment in this prospective, multicenter, observational cohort study targeted hospitalized patients 18 years of age or older at Duke University Medical Center, Duke Regional Hospital, Durham Veterans Affairs Medical Center, and the University of North Carolina-Chapel Hill Hospital. The purpose of this prospective cohort study was to understand the clinical and molecular risk factors for HAI and their temporal dynamics. Each hospital's institutional review board for human studies approved the protocols, and written consent was obtained from the subjects or their surrogates.

HAI included surgical site infection (12), central line–associated bloodstream infection (13), catheter-associated urinary tract infection (14), *Clostridium difficile*–associated diarrhea (15), HAP (16), and VAP (16). Participants were enrolled if they developed suspected HAI or were at risk for HAI by virtue of intubation (without active infection at the time of enrollment and expected duration of intubation $>$ 2 d). Biological, demographic, laboratory, and clinical data were collected for up to 14 days. Follow-up assessments, including survival and discharge disposition, occurred 14 and 30 days after onset of infection.

Model Structure

A deterministic decision-analytic model was designed to estimate costs representing the health system perspective and survival in hospitalized patients at high-risk for HAI. Model estimates were derived from our prospective cohort study or from published medical literature, as detailed below.

The decision tree shown in Figure 1 represents the choice between a standard diagnostic evaluation and one augmented by a novel HAI diagnostic test (referred to as "biomarker assay"). The nature of the assay is unspecified, to imply that any number of diagnostic modalities can be represented in this decision-analytic model.

Hospitalized patients requiring mechanical ventilation bear a higher risk of infection than nonventilated patients. Moreover, these ventilated patients are frequently sedated, limiting their ability to communicate symptoms suggestive of a new infection. We therefore analyzed the impact of a hypothetical diagnostic assay separately for ventilated and nonventilated patients. Patients who are ventilated are at risk of developing VAP or non-VAP HAI. The structure was the same for nonventilated patients except that they are not at risk of developing VAP.

Conditional on infection, patients were then grouped according to the probability that they received timely or delayed appropriate antimicrobial therapy. We incorporated hypothetical test characteristics (i.e., sensitivity and specificity) for the biomarker assay strategy by modeling true positives and false negatives among those with infection and true negatives and false positives among those without an infection. The modeled benefit from biomarker assay testing is a reduction in the probability that patients with infection receive delayed appropriate antimicrobial therapy. Patients in all groups are at risk of all-cause in-hospital mortality. However, patients receiving delayed antimicrobial therapy experience a higher risk of in-hospital mortality.

Model Inputs

Table 1 summarizes the model parameters and their corresponding values applied in the base-case analysis and the values tested in sensitivity analysis. Probabilities corresponding to the development of various types of infections were derived using the midpoint (10%) of the rates of VAP among ventilated patients recently reported by Klompas and colleagues (17) along with North American data reported from the large Extended Prevalence of Infection in Intensive Care (EPIC II) study (18). Estimates of the probability of receiving delayed antibiotic treatment with standard care (28.7%) and the increased risk of mortality with delayed versus timely

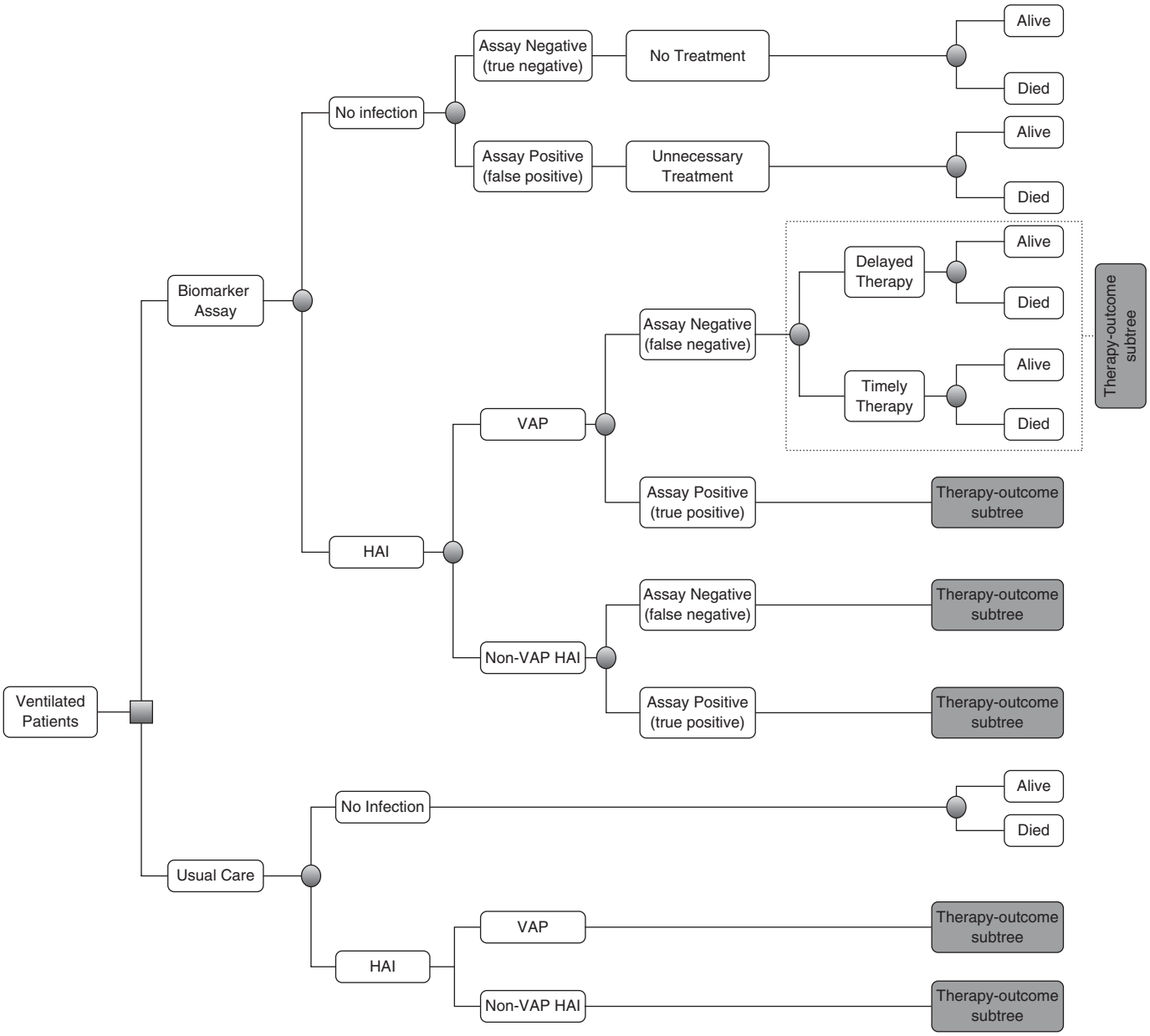

Figure 1. Decision tree for ventilated patients. HAI = hospital-acquired infection; VAP = ventilator-associated pneumonia.

therapy (odds ratio, 3.4) were based on a large U.S.-based cohort study by Vazquez-Guillamet and colleagues (19). In sensitivity analyses, probability of delayed therapy varied from 19.9 (20) to 69.0% (21), and the odds ratio for mortality resulting from delayed appropriate therapy varied from 2.23 (22) to 7.68 (6).

Risk estimates in the literature represent a mixture of patients with timely and delayed antibiotic therapy. We therefore computed probabilities of death with timely therapy by incorporating the increased odds of death with delayed therapy and the overall risk of death in all patients with a given type of infection. Then, we computed the probability of death with delayed therapy by multiplying the relative risk of mortality (converted from the odds ratio) with delayed therapy by the probability of death in patients receiving timely treatment. For instance, Rosenthal and colleagues reported that 25% of patients died with VAP (23). Combining estimates reported by Vazquez-Guillamet and colleagues (19) and Rosenthal and colleagues (23), we calculated the probability of death as 18% in ventilated patients with VAP receiving timely treatment and 43% in patients receiving delayed treatment. The relative risk of ventilation status on mortality derived from Vincent and colleagues (18) was used to compute a 9% mortality rate with timely treatment and a 26% mortality rate with delayed treatment for nonventilated patients with HAI.

To compute life-years saved, we applied estimated years of remaining life expectancy from the National Center for Health

Table 1. Model parameters in base-case analysis and sensitivity analysis

Model Parameters	Base-Case Value		Source
Probability of VAP in ventilated patients	10% (5–15%)		Midpoint of 5–15% reported by Klompas *et al.* (17)
Probability of non-VAP HAI in ventilated patients	7.6% (3.8–11.4%)		Ratio of non-VAP: VAP HAIs (0.431/0.568) reported by Vincent *et al.* (18) for U.S. sites multiplied by 10% probability of VAP
Probability of developing HAI in ventilated patients	17.6% (8.8–26.4%)		Sum of the probability of VAP (10%) and non-VAP HAI (7.6%)
Probability of developing HAI in nonventilated patients	11.2% (5.6–16.8%)		Probability of HAI in ventilated patients (17.6%) was divided by the relative risk of HAI in ventilated versus nonventilated patients (1.57, converted from adjusted OR = 1.69) reported by Vincent *et al.* (18)
Sensitivity of biomarker assay testing	90% (70–100%)		Assumption
Specificity of biomarker assay testing	90% (70–100%)		Assumption
Probability of delayed treatment with VAP or non-VAP HAI	Usual Care: 28.7% (19.9–69.0%)		Assumptions: Base-case: 28.7% reported by Vazquez-Guillamet *et al.* (19) Sensitivity analysis: estimates ranged from 19.9% (Kumar et al. [20]) to 69% (Tsukamoto *et al.* [21])
	With testing, true positive: 14.4% (5.7–23.0%)		Assumptions: Base-case: 50% relative reduction in delayed treatment versus usual care; sensitivity analysis: 20–80% relative reduction
	With testing, false negative: 43.1% (34.4–51.7%)		Assumptions: Base-case: 50% relative increase in delayed treatment versus usual care; sensitivity analysis: 20–80% relative increase
Probability of in-hospital mortality in ventilated patients without infection	10%		Mortality rates for noninfected ICU patients reported by Rosenthal *et al.* (10%) (23) and by Vincent *et al.* (11%) (18)
Probability of in-hospital mortality in nonventilated patients without infection	6%		Probability of death among ventilated patients without infection (10%) divided by the relative risk of death among ventilated versus nonventilated patients (1.55 derived from adjusted OR of 1.9 reported by Vincent *et al.* (18)
	With Timely Therapy	With Delayed Therapy	
Odds ratio for mortality with delayed versus timely antibiotic therapy	3.40 (2.23–7.68)		Base-case: Vazquez-Guillamet *et al.* (19) Sensitivity analysis: estimates ranged from 2.23 (Inchai *et al.* [22]) to 7.68 (Iregui *et al.* [6])
Probability of in-hospital mortality in ventilated patients with VAP	18%	43%	Derived from adjusted OR (3.40) for mortality with delayed versus timely antibiotic therapy and the probability of delayed treatment (20%, Kumar *et al.* [20]) when accounting for baseline risk of death among all patients with specific infection types: 25% with VAP; 21% with non-VAP HAI (Rosenthal *et al.* [23])
Probability of in-hospital mortality in ventilated patients with non-VAP HAI	15%	37%	
Probability of in-hospital mortality in nonventilated patients with HAI	9%	26%	17% probability of in-hospital mortality in ventilated patients with non-VAP HAI divided by the relative risk of ventilation status on risk of death of 1.55 derived from OR = 1.9 reported by Vincent *et al.* (18)

(Continued)

Table 1. (*Continued*)

Model Parameters	Base-Case Value		Source
Length of stay in ventilated patients without HAI, d	14.4 (14)		Base-case, mean LOS from prospective cohort study. Sensitivity analysis: median LOS from prospective cohort study; assumption: 2-d increase in LOS with delayed therapy
Length of stay in nonventilated patients without HAI, d	7.9 (7)		
	With Timely Therapy	With Delayed Therapy	
Length of stay in ventilated patients with VAP, d	25.5 (20)	27.5 (22)	
Length of stay in ventilated patients with non-VAP HAI, d	34.0 (19)	36.0 (21)	
Length of stay in nonventilated patients with HAI, d	18.3 (10.5)	20.3 (12.5)	
Cost per day in hospital	$3,308 ($996–$7,243)		Base-case: 2013 costs (25) attributable to VAP ($40,144) divided by LOS (13.1) and adjusted to 2015 dollars: $3,308 Sensitivity analysis: Kahn *et al.* (26) midpoint of marginal direct variable costs ($744) adjusted to 2015 dollars: $996 2013 costs (25) attributable to CLABSI ($45,814) divided by length of stay (10.4) and adjusted to 2015 dollars: $7,243
Cost per day of biomarker assay testing	$110 ($15–$200)		Base-case: Alexander *et al.* (28) cost of PNA-FISH diagnostic testing and adjusted to 2015 dollars: $110 Sensitivity analysis: Estimated cost of MALDI-TOF, institutional data (on file): $15
Negative effects of false-positive test	2-d LOS increase (0–4) 0.2%-point increase in mortality (0–1%)		Assumptions
Negative effects of false-negative test	3-d LOS increase (0–6) 1%-point increase in mortality (0–5%)		Assumptions: mortality increase applied in addition to increased mortality resulting from delayed treatment
Remaining life expectancy among patients discharged alive	16.9 yr (8 yr)		Base-case: United States Life Tables, 2009; Volume 62, January 6, 2014; Table A. Expectation of age (age 60 yr, all races, origins, both sexes) discounted by 3% per year (24) Sensitivity analysis: life expectancy of 8.7 for ICU patients aged 60 to 74 yr (30)

Definition of abbreviations: CLABSI = central line-associated bloodstream infection; HAI = hospital-acquired infection; ICU = intensive care unit; LOS = length of stay; MALDI-TOF = matrix-assisted laser desorption/ionization time-of-flight; OR = odds ratio; PNA-FISH = peptide nucleic acid fluorescence *in situ* hybridization; VAP = ventilator-associated pneumonia.
Estimates used for sensitivity analysis are presented in parentheses following the base-case value.

Statistics for patients of all races and both sexes, conditional on age at hospitalization (24).

Unit costs were limited to the daily cost per day in the hospital and the daily cost of the biomarker assay. The daily cost of inpatient care was estimated at $3,308 based on a recent metaanalysis of costs associated with health care–acquired infections (25). Daily inpatient costs were varied from $996 (26) to $7,243 (25) per day in sensitivity analyses. These daily cost estimates were applied to LOS estimates measured in the observational cohort study described above. In the base-case analysis, we set the cost of the biomarker assay at $110 per day. This was based on costs for existing sepsis-related diagnostics. For example, the cost of matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) was estimated to be $15/test at our institution, after accounting for capital equipment, installation, annual contracting, technician time, and consumables. We also considered procalcitonin, for which the Centers for Medicare and Medicaid Services reimbursed $36.45 in 2015 (27). Finally, peptide nucleic acid fluorescence *in situ* hybridization (PNA-FISH) costs were derived from Alexander and colleagues (28). After adjusting to 2015 dollars, this yielded an assay cost of $110. Sensitivity analysis used a range of $15 to $200.

All medical costs included in the model are incurred over a relatively short time period. Therefore, we did not apply a discount rate to costs. For estimated survival, we applied the recommended discount rate of 3% per year (29). Hypothetical patients represented in our base-case analyses were assumed to be 60 years old.

Base-Case Analysis

We performed two sets of base-case analyses: one for ventilated patients and one for nonventilated patients. In both sets of analyses, we assumed that testing with the biomarker assay was initiated on the day of admission and continued until patients developed an infection, died, or were discharged. For the biomarker assay testing strategy, we assumed that test sensitivity and specificity were both 0.9 with daily monitoring, a performance threshold considered high enough to impact medical decision making. We assumed that a positive assay would reduce the probability of receiving delayed treatment by 50%.

In the case of true positives, the mortality benefit resulting from fewer patients receiving delayed therapy was applied. However, for false positives, the baseline risk of mortality in individuals without infection was applied; but, we assumed that patients would receive unnecessary therapy and testing that would extend the hospital stay by 2 days and would also increase mortality by 0.2 percentage points. In cases where daily assays were negative for an individual with an infection (i.e., false negatives), we assumed a 50% increase in the probability of receiving delayed therapy versus usual care and imposed a 3-day extension to hospital stay and 1 percentage point increased risk of in-hospital death (as a result of delayed therapy).

Sensitivity and Threshold Analyses

Sensitivity analyses were conducted to reflect uncertainty across model inputs that were believed to be influential on the results. Specifically, we varied sensitivity and specificity of the diagnostic testing strategy, probability of developing HAI, probability of receiving delayed treatment, percentage reduction in delayed treatment versus usual care with true-positive results and percentage increase in delayed therapy with false-negative results with testing, negative consequences of false-positive and false-negative tests on mortality and LOS, probability of in-hospital mortality in patients with infection, relative risk of in-hospital mortality with delayed antibiotic therapy, additional days of hospitalization for those receiving delayed treatment, cost per inpatient day, the daily cost of diagnostic testing, LOS, and patient age. We also performed threshold analyses to determine the minimum or maximum values for model inputs that would result in an incremental cost-effectiveness ratio equal to $50,000 per life-year saved.

Results

Clinical Population

A total of 219 patients hospitalized at Duke University Hospital, Duke Regional Hospital, Durham Veterans Affairs Medical Center, or the University of North Carolina Health Care system were enrolled in this prospective study between 2011 and 2012. Because this was an observational study, no treatment or intervention was used.

Mean age was 58.5 years (range, 19–87 yr), 69% of patients were men, 162 were white (74%), and 52 were black (24%). Thirty-day mortality from the time of enrollment was 16.0% (35/219), with a median of 5 (interquartile range, 2.5–12) days to death. Of the 219 enrolled patients, 90 (41%) had infection at the time of enrollment, 29 (13%) developed infection after enrollment, 53 (24%) had no infection during the observation period, and 47 (21%) subjects had illness that was inconclusive for infection. Eighty-eight patients were intubated but without infection at the time of enrollment. Of this group, 33 (38%) remained uninfected, 24 (27%) developed infection within 1 week, 1 developed infection after more than 1 week, and 30 (34%) had complications that were indeterminate for infection. Among ventilated patients, in-hospital mortality was 19.2% among those who developed VAP, 7.7% among those who developed other non-VAP HAI, and 18.2% among ventilated patients who did not develop an infection.

In light of the highly selected nature of this cohort, it was only used to define days to discharge, intubation, infection diagnosis, and appropriate antimicrobial therapy as measured in ventilated/uninfected patients, ventilated patients with subsequent HAI, and nonventilated patients with subsequent HAI.

Ventilated Patients

The proportion of ventilated patients (with or without infection) who received delayed antibiotic therapy decreased from to 5.1 to 3.0% as a result of earlier diagnosis due to testing. When accounting for the $110 daily test cost beginning on the day of admission, total inpatient costs per patient were $58,235 in the biomarker assay group and $56,595 in the standard care group, representing a $1,640 increase (Table 2). In terms of health outcomes, the biomarker assay strategy among ventilated patients was estimated to reduce inpatient mortality from 11.88 to 12.33%, leading to a gain in life-years saved of 0.08 per patient. When combining the estimated increase in costs with gains in life expectancy, the resulting cost-effectiveness ratio was $21,389 per life-year saved. Results were similar when we assumed that diagnostic testing would begin on the date of intubation, with an estimated net cost increase of $1,537 and an

Table 2. Base-case results

	With Serial Diagnostic Testing	Standard Care	Difference
Ventilated patients			
Length of stay	17.19	17.11	0.08
Total costs, $	58,235	56,595	1,640
Inpatient mortality, %	11.88	12.33	−0.45
Life-years (discounted)	14.92	14.85	0.08
ICER		$21,389 per life-year saved	
Nonventilated patients			
Length of stay	9.28	9.11	0.18
Total costs, $	31,512	30,131	1,381
Inpatient mortality, %	7.13	7.32	−0.19
Life-years (discounted)	15.73	15.70	0.03
ICER		$42,325 per life-year saved	

Definition of abbreviation: ICER = incremental cost-effectiveness ratio.

incremental cost-effectiveness ratio of $20,050 per life-year saved.

Nonventilated Patients

Nonventilated patients were analyzed separately owing to their lower risk of HAI, specifically VAP, and lower overall mortality than ventilated patients. Among patients who were not ventilated, the biomarker assay strategy decreased the percentage of patients receiving delayed antibiotic therapy from 3.2 to 1.9%. At $110 per day for testing (base-case estimate), total inpatient costs were $1,381 higher in the diagnostic testing group at $31,512 compared with $30,131 in the standard care group. Inpatient mortality was lower with the diagnostic testing strategy at 7.13% compared with 7.32% with standard care. With an estimated gain of 0.03 life-years per patient, the resulting incremental cost-effectiveness ratio was $42,325 per life-year saved.

Sensitivity Analyses

The findings from the model were consistent when varying the sources used for several model inputs. Increasing the age of the hypothetical cohort from 60 years to 80 years to demonstrate the impact of shorter expected survival postdischarge increased the magnitude of the incremental cost-effectiveness ratios by 65% (Figures 2 and 3). Assuming that ICU survivors have a higher mortality than age- and sex-matched control subjects in the general population (30–33), we modeled the effect of an 8-year life expectancy instead of the base-case 16.9 years. This increased the incremental cost-effectiveness ratio from $21,389 to $45,284 for the ventilated group and from $42,325 to $89,608 for the nonventilated group. Halving the baseline probabilities of in-hospital death across infection types nearly doubled the magnitude of the incremental cost-effectiveness ratios among the ventilated and nonventilated analyses.

The base-case scenario assumed an odds ratio of 3.4 for mortality due to delayed appropriate antimicrobial therapy (19). Replacing this with an odds ratio of 2.23 based on Inchai and colleagues (22) increased the incremental cost-effectiveness ratio by about 40% to $34,100 per life-year saved for ventilated patients and $72,192 per life-year saved for nonventilated patients (Figures 2 and 3). The odds ratio of in-hospital mortality with delayed antibiotic therapy could be as low as 1.8 in ventilated and 2.9 in nonventilated patients to maintain incremental cost-effectiveness ratios less than $50,000 per life-year saved. Varying the probability of HAI among ventilated and nonventilated patients had greater impact on the incremental cost-effectiveness ratios when the probabilities of HAI were lower (Figure 4). Threshold analyses revealed that among ventilated patients, the probability of developing HAI could be as low as 8.4% and still maintain an incremental cost-effectiveness ratio less than $50,000 per life-year saved. The risk of developing an HAI among nonventilated hospitalized patients is generally lower than in ventilated patients, as is the risk of mortality.

Threshold analyses revealed that the risk of HAI in nonventilated patients could be as low as 9.8% to maintain an incremental cost-effectiveness ratio of less than $50,000 per life-year saved. Threshold analyses also revealed that the probability of receiving delayed treatment (28.7% in base-case) could be as low as 13% for ventilated patients and 24% for nonventilated patients, while incremental cost-effectiveness ratios remained lower than $50,000 per life-year saved. Varying assumptions that impacted LOS or cost per day had relatively little impact on the magnitude of the incremental cost-effectiveness ratios. The incremental cost-effectiveness ratios changed very little when varying the LOS extension for patients with delayed therapy to 0 days or 4 days (2 d in the base-case) (Figures 2 and 3). Varying the cost per inpatient day also had relatively minor effects on the incremental cost-effectiveness ratios. Applying a lower cost published by Kahn and colleagues (26) representing the marginal cost per day in the ICU ($996 in 2015), rather than the average daily cost, was found to reduce the magnitude of the incremental cost-effectiveness ratios due to the assumption that false-positive findings would lead to longer hospital stays with biomarker assay testing.

In the base-case analysis, for patients who develop HAI and have a positive biomarker assay (i.e., true positives), we assumed that daily biomarker testing would reduce the risk of delayed therapy by 50% (from 28.7 to 14.4%). Limiting the impact to a 20% reduction had major impact, increasing the incremental cost-effectiveness ratio to $78,048 per life-year saved for ventilated patients and $179,333 per life-year saved for nonventilated patients. For patients who have HAI but diagnostic testing fails to detect the infection (false negative), we assumed diagnostic testing would result in a 50% increase in the probability of delayed antibiotic therapy (i.e., from 28.7 to 43.1%) in the base-case analysis. When increasing the effect to an 80% increase, the incremental cost-effectiveness ratio increased slightly to $23,308 per life-year saved for ventilated patients and $45,917 per life-year saved for nonventilated patients.

The base-case analysis also modeled negative effects of false-positive tests resulting from unnecessary use of antibiotic therapy in patients without infection. This included a 2-day increase in LOS and additional deaths in 2 out of 1,000 patients. If false-positive test results increased LOS by 4 days and increased mortality to 10 in 1,000 patients, the incremental cost-effectiveness ratios increase by about 50% for ventilated patients ($32,522) and more

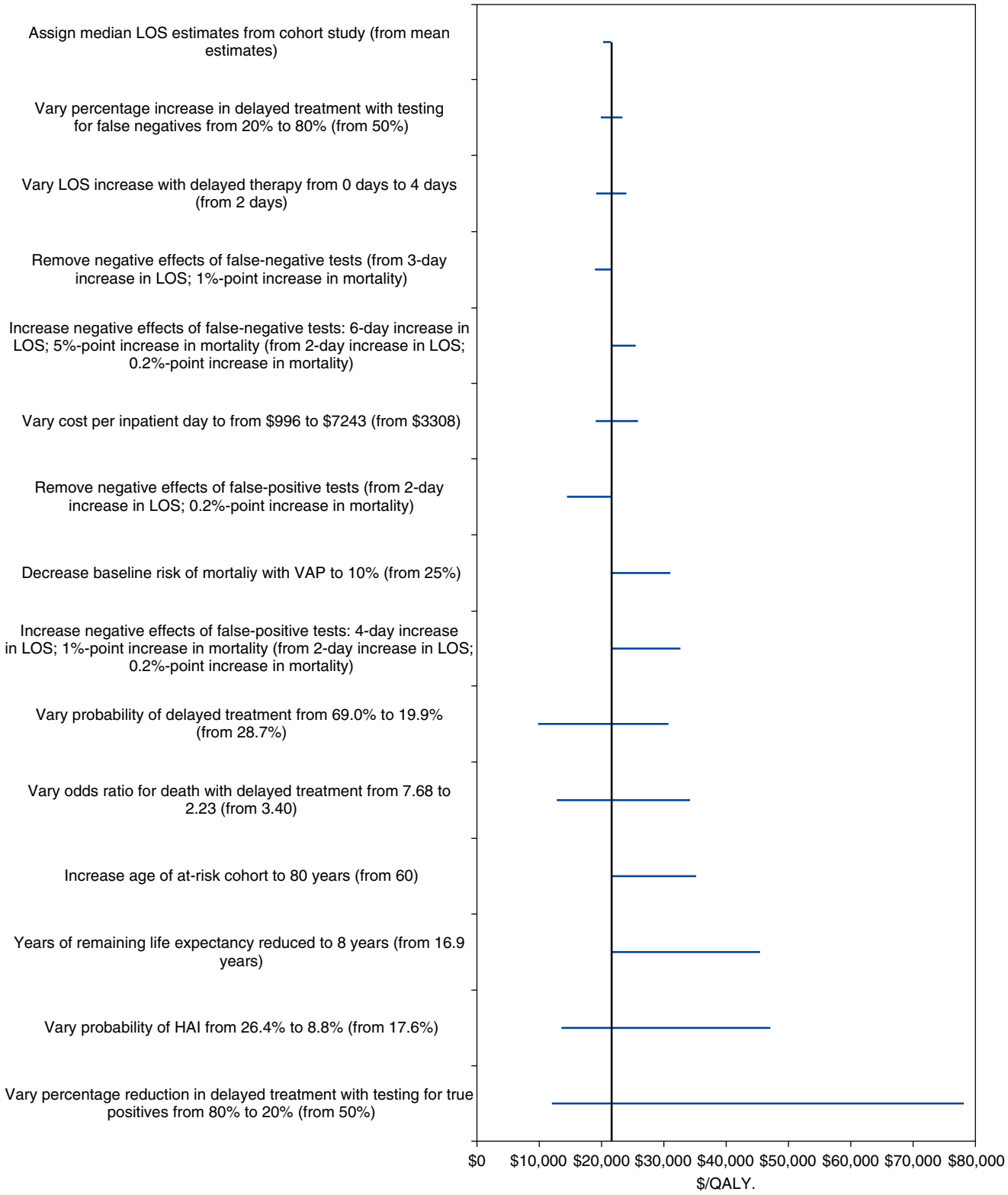

Figure 2. Tornado diagram representing results from sensitivity analysis: ventilated patients. The *vertical line* represents the incremental cost-effectiveness ratio (ICER) calculated in the base-case analysis, and the *horizontal lines* represent difference in ICERs between the base-case analysis and the sensitivity analysis. The lines on the right side of the vertical lines represent increases in ICERs when compared with the base-case ICER, and the lines on the left side represent decreases in ICERs when compared with the base-case ICER. HAI = hospital-acquired infection; LOS = length of stay; QALY = quality-adjusted life year; VAP = ventilator-associated pneumonia.

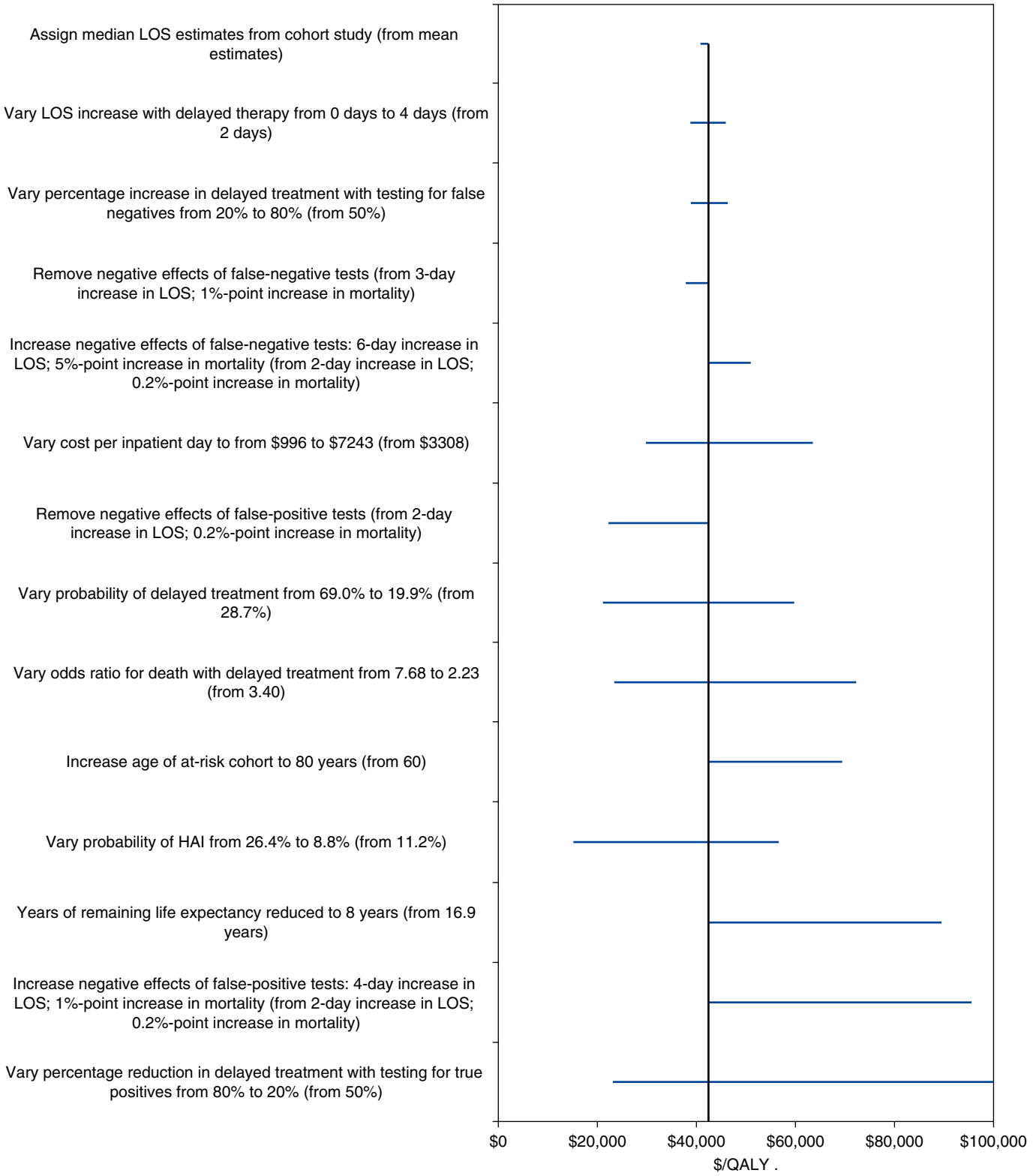

Figure 3. Tornado diagram representing results from sensitivity analysis: nonventilated patients. The *vertical line* represents the incremental cost-effectiveness ratio (ICER) calculated in the base-case analysis and the *horizontal lines* represent difference in ICER between the base-case analysis and the sensitivity analysis. The lines on the right side of the vertical lines represent increases in ICERs when compared with the base-case ICER and the lines on the left side represent decreases in ICERs when compared with the base-case ICER. HAI = hospital-acquired infection; LOS = length of stay; QALY = quality-adjusted life year.

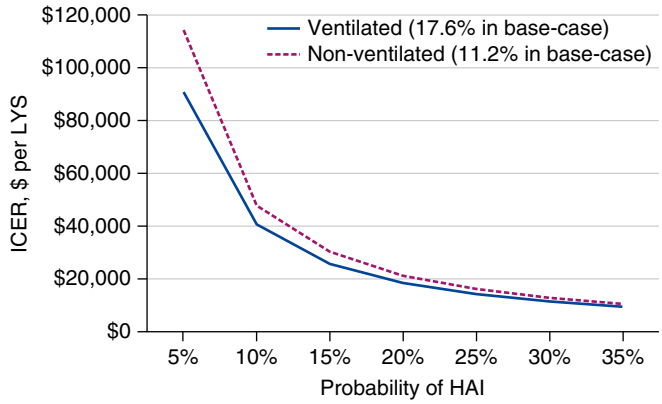

Figure 4. Impact of varying baseline probability of hospital-acquired infection (HAI) on incremental cost-effectiveness ratios (ICERs). LYS = life-year saved.

than doubled for nonventilated patients ($95,569). However, assuming that false-negative results increased LOS by 6 days and increased mortality to 50 out of 1,000 patients had a relatively small effect on the incremental cost-effectiveness ratios ($25,365 for ventilated patients and $50,965 for nonventilated patients). If the negative consequences of both false-positives and false-negatives are removed, the incremental cost-effectiveness ratios decrease to $11,844 for ventilated patients and $18,612 for nonventilated patients.

Sensitivity analysis related to the cost of diagnostic testing revealed that the incremental cost-effectiveness ratios were a linear function of daily testing cost (Figure 5). For each $10 increase in the daily cost, the incremental cost-effectiveness ratio increased by $1,616 in ventilated patients and $2,227 in nonventilated patients (Figure 3). The daily cost of monitoring could be as high as $287 for ventilated patients and $144 for nonventilated patients to maintain the incremental cost-effectiveness ratios at less than $50,000 per life-year saved.

Varying the sensitivity of the biomarker assay strategy had a greater impact on the magnitude of the incremental cost-effectiveness ratios than varying the specificity (Figure 6). When the test sensitivity and specificity were decreased to 80% (90% in base-case), the incremental cost-effectiveness ratio increased to $37,760 per life-year saved for ventilated patients and $103,698 for nonventilated patients. If specificity was 90%, test sensitivity could be as low as 73% for ventilated patients and 86% for nonventilated patients before the incremental cost-effectiveness ratio surpassed $50,000 per life-year saved.

Discussion

For the general population, HAIs present a small and often intangible risk to health. However, once hospitalized, the risk of acquiring an infection becomes very tangible, with a considerable impact on mortality, morbidity, and costs to the patient, the hospital, and the public. Infection-control measures will reduce but not eliminate the risk of acquiring an HAI. Moreover, the treatment of such infections has its own associated challenges. Delaying appropriate antimicrobial treatment clearly increases mortality. Yet the use of broad-spectrum antimicrobials when there may not actually be an infection also exposes the patient to risk.

The diagnostic tools guiding clinicians in this delicate balance are inadequate. As a result, there has been renewed interest in novel diagnostic techniques. Specifically, a diagnostic test offering a timely and accurate identification of incipient infection could speed the provision of appropriate therapy and avoid unnecessary antibiotic treatment, which will reduce subsequent costs in terms of antimicrobial resistance and medical expenditures. Another diagnostic strategy is one that quickly identifies resistant organisms so that appropriate antibiotic treatment can be started sooner. Indeed, there are many possible strategies to improve on the state of sepsis diagnosis. Through the use of economic modeling based on published and acquired data, we identify the parameters that are most influential to determining the cost-effectiveness of a putative diagnostic assay. Even though such diagnostics have yet to be developed and their clinical utility is hypothetical, the development and publication of a transparent economic modeling framework, agnostic about the diagnostic strategy, can prospectively address stakeholders' concerns about potential bias and can be applied to institution-specific infection rates, costs, and other inputs to aid in adoption decisions.

Results from our model reveal that a diagnostic with high sensitivity and specificity that leads to an absolute reduction from 5.1 to 3.0% (40% relative reduction) in the proportion of patients receiving delayed antibiotic therapy, testing at $110 per day, represents an efficient care-management strategy with cost-effectiveness ratios of about $21,000 per life-year saved in ventilated patients and $42,000 in nonventilated patients.

Sensitivity analyses revealed that large changes to most of the model's parameters would be necessary to generate incremental cost-effectiveness ratios that surpass $50,000 per life-year saved. The risk of HAI can vary significantly across patients' clinical characteristics and institutions. However, we found that a diagnostic test could be cost effective at the $50,000 per life-year saved threshold in ventilated patients with a risk of acquiring an HAI as low as 8.4% if the daily cost of testing is $110 or as low as 14.2% even if the daily cost of testing doubled to $220. We recognize, however, that an ideal diagnostic would lead not only to improved survival but also to reduced costs.

In our model, cost savings were entirely attributable to reductions in the LOS among patients who received earlier appropriate antimicrobial therapy because of testing. We did not assign longer (or shorter) stays for patients who died as a result of infection, but we applied a 2-day penalty for inappropriate treatment after a false-positive test result and a 3-day penalty for prolonged treatment after a false-negative test result.

With these conservative assumptions, inpatient costs were lower by just $277 per ventilated patient and $582 per nonventilated patient with the diagnostic testing strategy versus usual care. Although these savings may seem relatively small from a budgetary perspective in comparison to

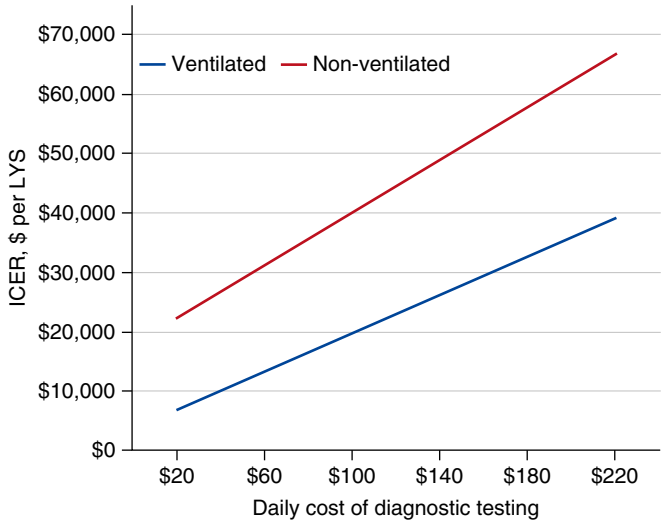

Figure 5. Impact of varying daily cost of diagnostic testing on incremental cost-effectiveness ratios (ICERs). LYS = life-year saved.

testing costs of $1,363 per ventilated patient and $799 per nonventilated patient, the relative value of testing is largely driven by the expected (absolute) reductions in inpatient mortality of 0.45 and 0.19% for ventilated and nonventilated patients, respectively. When accounting for these improvements in mortality, we found that costs of testing could increase to nearly $300 per day and maintain incremental cost-effectiveness ratios at $50,000 per life-year saved for ventilated patients. This cost is well above estimates for many currently available tests.

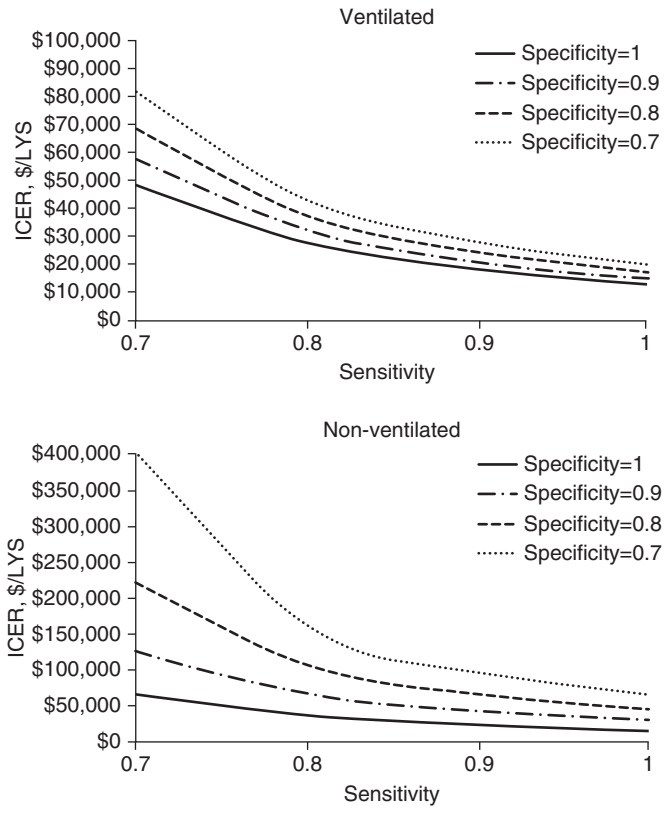

Figure 6. Impact of varying baseline sensitivity and specificity of diagnostic testing on incremental cost-effectiveness ratios (ICERs). LYS = life-year saved.

Most economic studies of HAI or sepsis focus on prevention or treatment interventions. Fewer describe the cost-effectiveness of diagnostic strategies, and those that do focus on a specific strategy to identify the causative organism in patients who have already demonstrated signs or symptoms of infection, such as polymerase chain reaction in patients with positive blood cultures (34) or a combination of IL-8 and C-reactive protein in neonates on first suspicion of a nosocomial bacterial infection (35). Despite these disparate diagnostic approaches, they show that more accurate and timely diagnostics are cost effective (with incremental cost-effectiveness ratio of €3,107/quality-adjusted life years) and at times are cost saving. The analysis presented here is consistent with those findings but differs in that it examines a screening diagnostic used in all patients at high risk for HAI before infection is confirmed by other means.

One particular strategy for the development of novel diagnostic tools is to target the host response in a more agnostic manner. Until now, most sepsis diagnostic studies focus on pathogen detection or on candidate host markers defined *a priori*. Though important, these strategies have limitations. Recent advances in systems biology and computational biology have created new opportunities. For example, gene-expression analysis has been used to differentiate active pulmonary tuberculosis from both latent tuberculosis and nontuberculous disease (36–38). Test characteristics were superior to currently available pathogen-detection techniques. More recently, host gene-expression signatures were identified that discriminated community-acquired pneumonia versus noninfectious disease on admission to the ICU (39). However, these strategies were applied to patients in whom clinical disease was well established. Instead, a more effective diagnostic would detect early disease, when clinical symptoms might be mild and when treatment would be most effective. Examples include viral respiratory infection (40), VAP (41, 42), post-trauma infection (43), and sepsis (44, 45). Although none of these particular gene-expression signatures has advanced to clinical use, they exemplify

new diagnostic strategies that can change how infection is diagnosed and subsequently managed (46).

Limitations

There are several limitations associated with the current study. First, the use of a model is a simplification of reality, requiring assumptions and an assembly of inputs from many sources. However, each of the model's assumptions and inputs are explicitly documented, and we conducted numerous sensitivity analyses to examine the impact of using alternative values for parameter estimates.

Despite reliance on numerous sources, the specific estimates required for the model were sometimes not available in the published medical literature. We also did not conduct probabilistic sensitivity analyses using Monte Carlo simulations that would allow values for each of the model parameters to vary simultaneously according to distributions assigned to represent their uncertainty. Given the need to rely on nonsampled estimates and assumptions (e.g., daily cost and impact of diagnostic testing, sensitivity and specificity of testing, impact of test results on receipt of delayed vs. timely therapy), we believed that artificially assigning distributions to these variables could obfuscate the exploratory nature of the modeling framework. Moreover, VAP is exceedingly difficult to accurately diagnose and is known to have high interobserver variability (47, 48). Consequently, the National Healthcare Safety Network has replaced VAP with VAE (ventilator-associated events) for surveillance purposes. However, this change does not eliminate the existence of VAP and underscores why a diagnostic, such as the type relevant to our modeling framework, would be of potential value.

Conclusions

A diagnostic biomarker that shortens the time to identify HAI in an at-risk population is cost effective under various conditions and cost parameters. The model presented here offers a decision-analytics framework with which the potential cost-effectiveness of new biomarkers can be evaluated. ■

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