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e-Appendix 1.

PROPHETIC Study: United States Principal Investigators and Clinical Trials Transformation Initiative Project Team

In addition to the authors, the following individuals contributed to the PROPHETIC Study:

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Supplementary Methods

Study Definitions

High-Risk

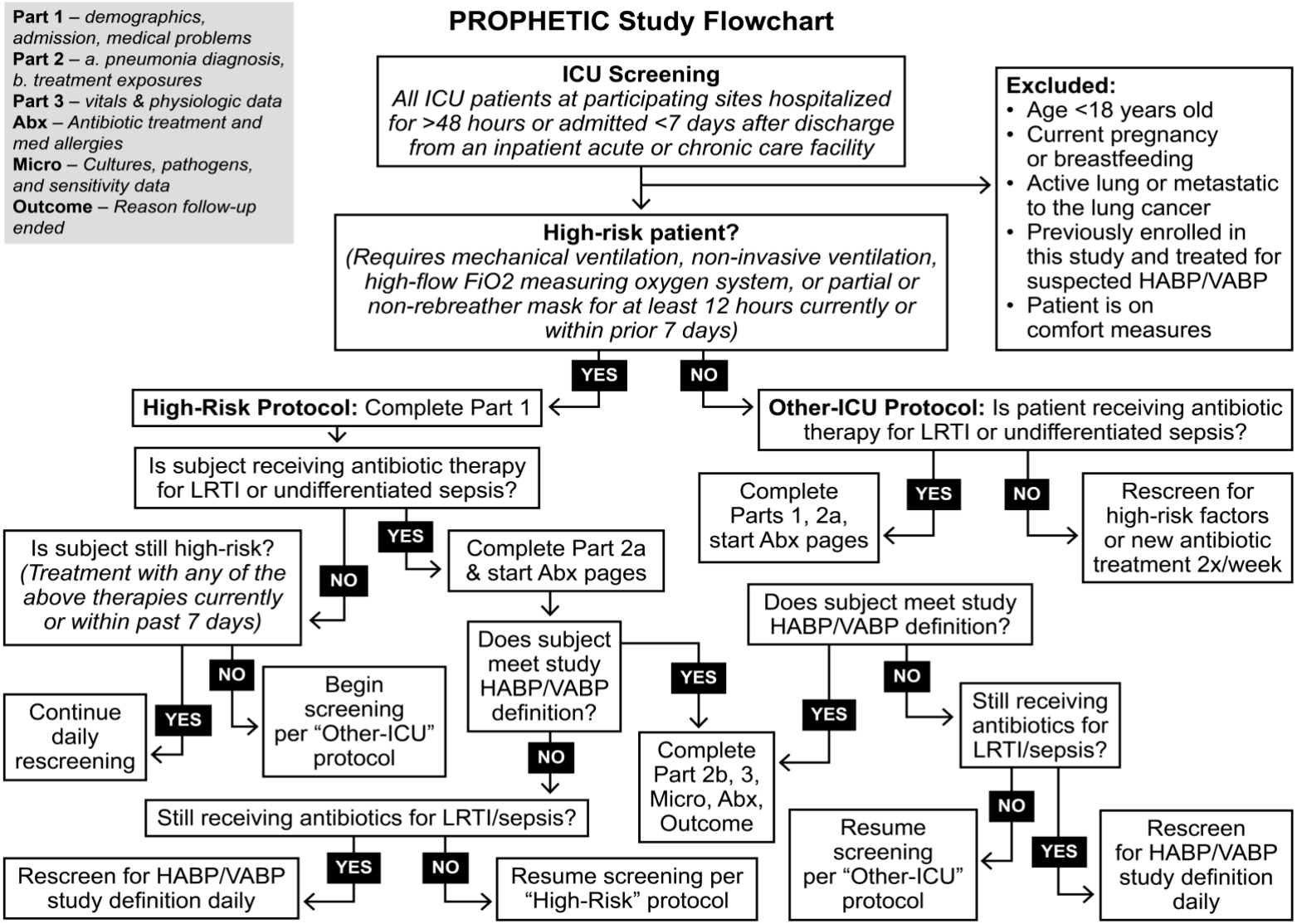
Treatment with one or more of the following respiratory modalities for at least 12 hours in any 24-hour period, either currently or within the prior 7 days
• Invasive mechanical ventilation • Noninvasive ventilation (bilevel positive airway pressure [BiPAP] or continuous positive airway pressure [CPAP]) for any indication other than obstructive sleep apnea • Noninvasive ventilation • High-flow, supplemental oxygen therapy via nasal cannula (systems with air/oxygen blender that deliver precise fraction of inspired oxygen (FiO_2) level) • High-flow supplemental oxygen therapy delivering at least 50% FiO_2 via aerosol facemask or tracheostomy collar • Supplemental oxygen therapy delivered via either partial or non-rebreather face mask

Hospital-Acquired or Ventilator-Associated Bacterial Pneumonia

At least one criterion from each section must be present to meet definition of pneumonia

Radiographic Criteria
• Chest radiograph showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia within 48 hours of all other diagnostic criteria being present
 	
Respiratory Signs or Symptoms
• New onset or worsening: cough, dyspnea, tachypnea (respiratory rate ≥ 25 breaths per minute for patients ≥18 years), or expectorated sputum production
• New requirement for invasive mechanical ventilation
• Hypoxemia, defined as any of the following:
  ○ A partial pressure of oxygen (PaO_2) <60 millimeters of mercury measured by arterial blood gas (ABG)
  ○ A worsening (decrease >10%) of the PaO_2/FiO_2 ratio
  ○ Pulse oximetry reading of <90%
  ○ New supplemental oxygen requirement
  ○ Greater than 2 liter per minute increase in amount of supplemental oxygen required for patients on chronic supplemental oxygen therapy
  ○ Need for acute changes, after 2 days stability, in ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO_2/FiO_2) or needed changes in the amount of positive end-expiratory pressure
• New onset of suctioned respiratory secretions
 	
Systemic Inflammation
• Documented body temperature ≥38 degrees Celsius or ≤ 35 degrees Celsius (core body temperature)
• Leukocytosis, defined as total peripheral white blood cell count ≥10,000 cells/cubic millimeter
• Leukopenia, defined as total peripheral white blood cell count ≤4,500 cells/cubic millimeter
• Greater than 15% immature neutrophils (bands) noted on peripheral blood film
 	
Timing of Symptom Onset
• Signs/symptoms of pneumonia first noted >48 hours after hospital admission
• Signs/symptoms of pneumonia first noted >48 hours after initiation of mechanical ventilation
• Signs/symptoms of pneumonia first noted <7 days after discharge from an inpatient acute or chronic care facility

e-Figure 1. PROPHETIC Study Flowchart.

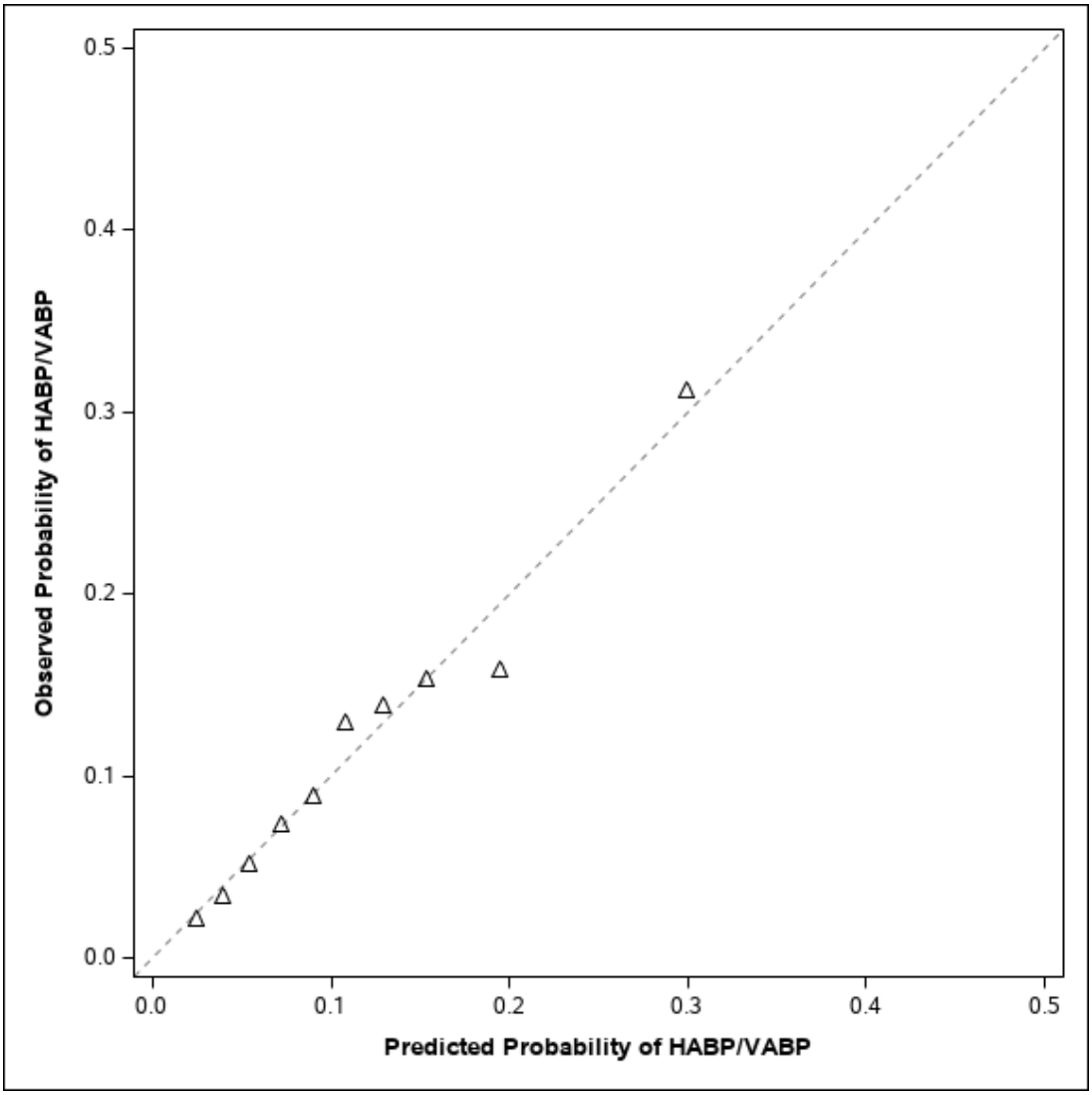


e-Table 1. Summary of diagnostic outcome for high-risk patients treated for possible HABP/VABP.

Diagnostic Outcome	Treated Patients (N=1464)
HABP/VABP Study Definition Fulfilled, N (%)	537 (36.7)
Did Not Meet HABP/VABP Study Definition, N (%)	927 (63.3)
Radiographic Criteria	590 (63.6)
Respiratory Signs/Symptoms	274 (29.6)
Systemic Inflammation	154 (16.6)
Timing of Symptom Onset	526 (56.7)

Patients not meeting HABP/VABP study definition lacked criteria from at least one diagnostic criteria domain.

e-Figure 2. Calibration plot for multivariable hospital-acquired and ventilator-associated pneumonia model.

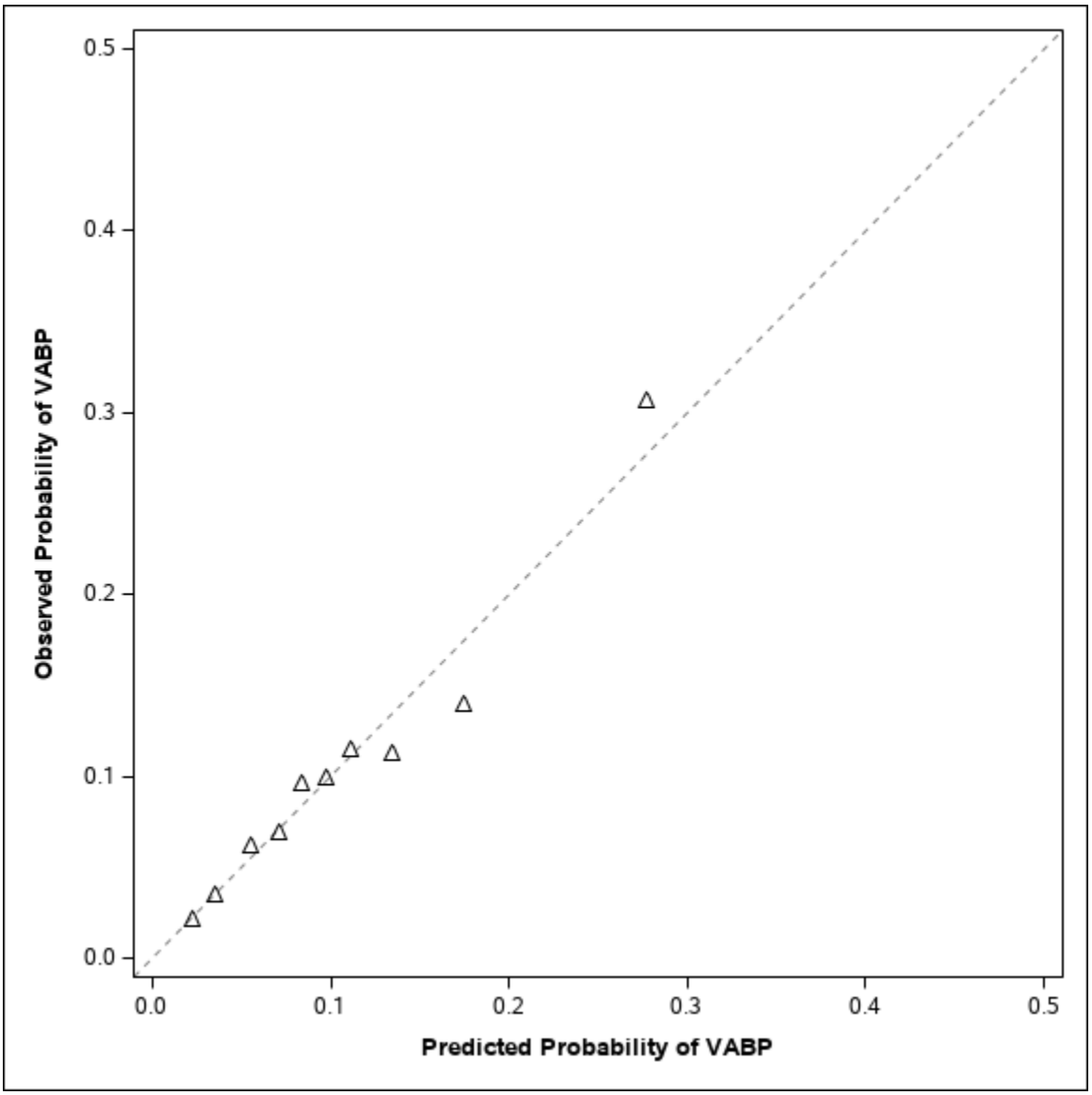


e-Table 2. High-Risk Patient Characteristic and Treatment Exposure Associations with Ventilator-Associated Pneumonia Development

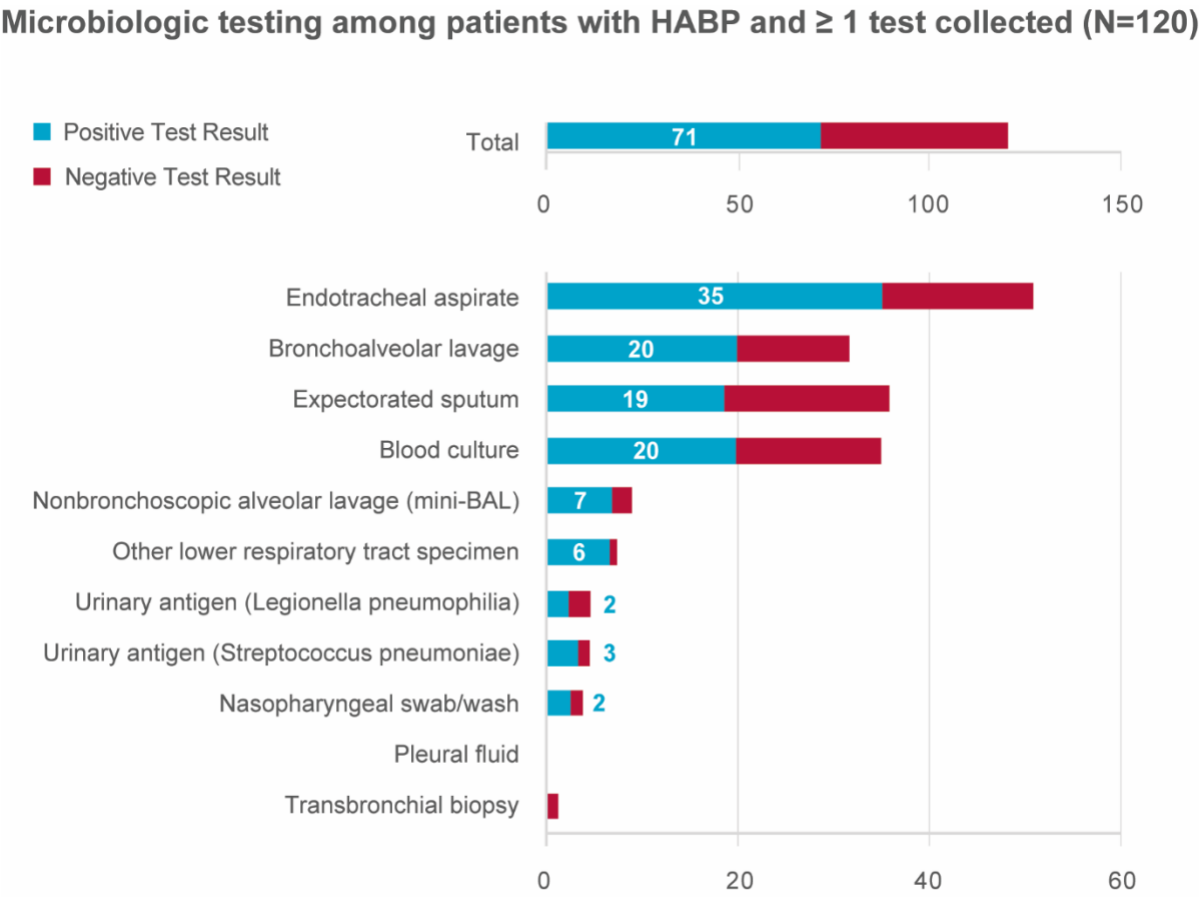
Factor	Type 3 Wald Chi-Square	Beta Coefficient	Adjusted Odds Ratio (95% CI)	P-Value
ICU admission diagnosis	57.27			
Acute hypercapnic respiratory failure		-0.12	0.89 (0.43, 1.84)	0.755
Acute hypoxemic respiratory failure		0.09	1.09 (0.66, 1.79)	0.733
Acute myocardial infarction		-0.12	0.89 (0.36, 2.19)	0.802
Altered mental status or seizures		-0.02	0.98 (0.56, 1.71)	0.939
Cerebrovascular accident		0.56	1.76 (0.93, 3.31)	0.080
Sepsis or septic shock		-0.19	0.82 (0.45, 1.52)	0.534
Trauma		1.36	3.89 (2.26, 6.69)	<.001
Shock (excluding septic shock)		0.19	1.21 (0.67, 2.18)	0.531
Other		0.14	1.15 (0.72, 1.83)	0.563
Planned post-operative ICU admission			reference	
Enteral nutrition	40.99	1.16	3.19 (2.24, 4.56)	<.001
Aspiration risk	34.84	0.80	2.22 (1.70, 2.89)	<.001
Admission source	12.43			
Skilled nursing, long term acute care		0.46	1.58 (0.92, 2.72)	0.094
Non-procedure; clinic or direct admission		0.39	1.47 (1.11, 1.96)	0.008
Scheduled procedure		-0.22	0.80 (0.49, 1.31)	0.381
Other		0.29	1.33 (0.92, 1.93)	0.125
Emergency department			reference	
Systemic antibacterials within 90 days	8.06	0.35	1.42 (1.12, 1.82)	0.005
Blood product transfusion in the last 7 days	4.75	0.27	1.31 (1.03, 1.67)	0.029
Proton pump inhibitor therapy/H2-blocker therapy	2.15	0.22	1.25 (0.93, 1.68)	0.143
Diabetes mellitus	1.46	-0.16	0.85 (0.66, 1.10)	0.227
ICU length of stay (days), per 1-day increase	1.20	0.01	1.01 (0.99, 1.03)	0.274
Noninvasive mechanical ventilation	0.26	0.09	1.10 (0.77, 1.56)	0.612
Female sex	0.17	-0.05	0.95 (0.76, 1.19)	0.682
Corticosteroids at current hospitalization	0.10	0.05	1.05 (0.76, 1.46)	0.753

Abbreviations: CI = confidence interval; ICU = intensive care unit; OR = odds ratio
Characteristics and treatment exposures recorded at time of high-risk population enrollment.
3712 patients at risk for VABP included in analysis; patients without invasive mechanical ventilation exposure or developing pneumonia <48 hours after starting invasive mechanical ventilation excluded.
Risk factors selected using backward selection with α=0.1 for model inclusion and clinical expertise.
C-statistic: 0.698 (0.671, 0.726)

e-Figure 3. Calibration plot for multivariable ventilator-associated pneumonia model

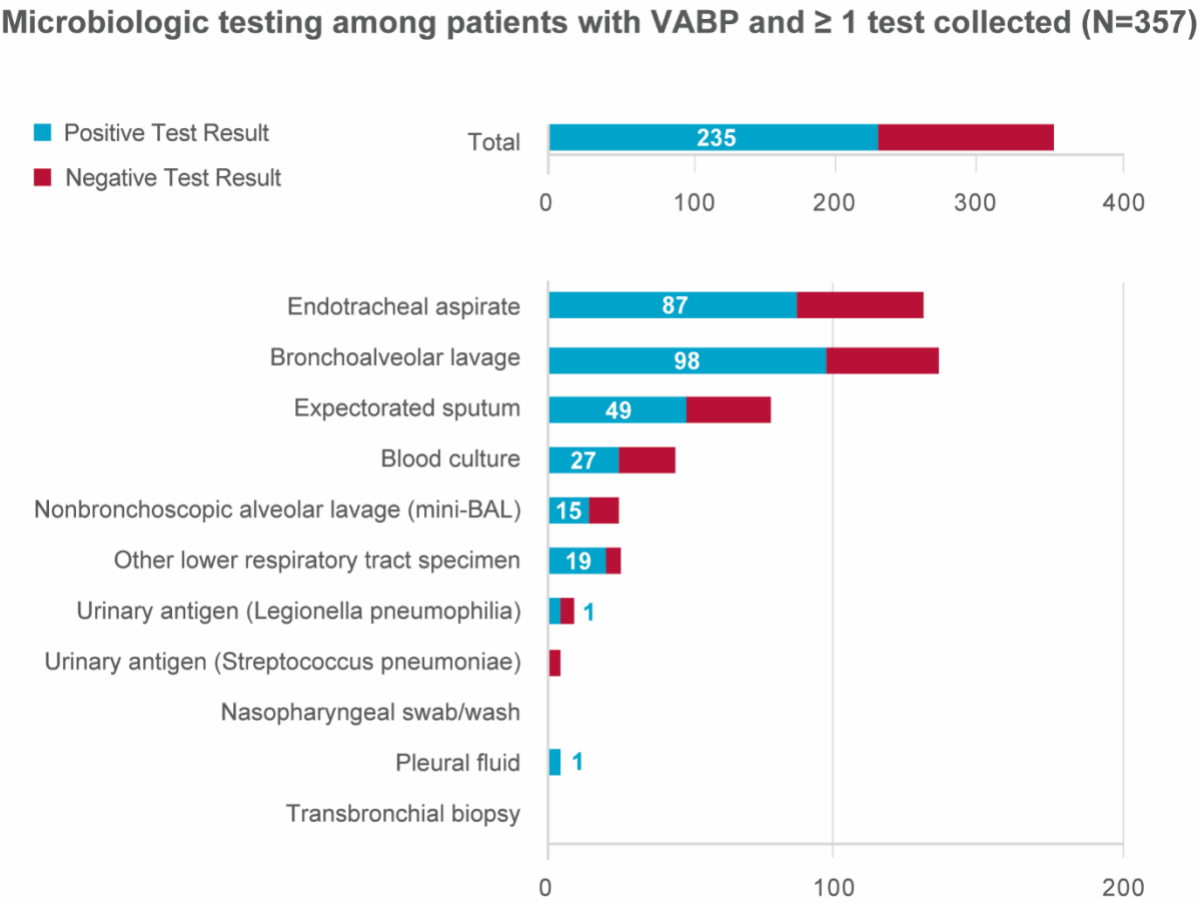


e-Figure 4. Microbiologic testing among patients with hospital-acquired bacterial pneumonia



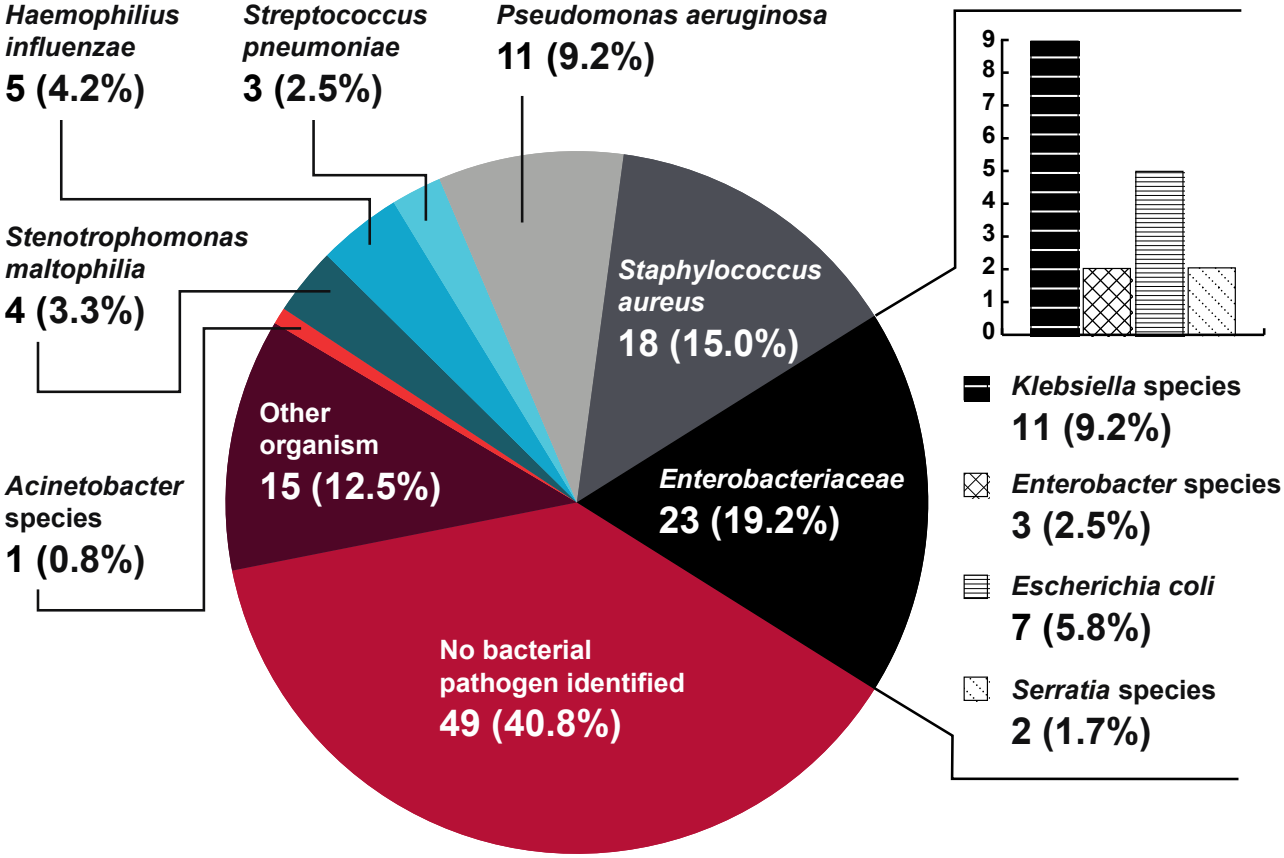
* Microbiology testing data reported for 120 of 143 (84%) HABP patients
† ≥1 positive microbiologic test was reported in 71 of 120 (59%) HABP patients with microbiology data reported

e-Figure 5. Microbiologic testing among patients with ventilator-associated bacterial pneumonia



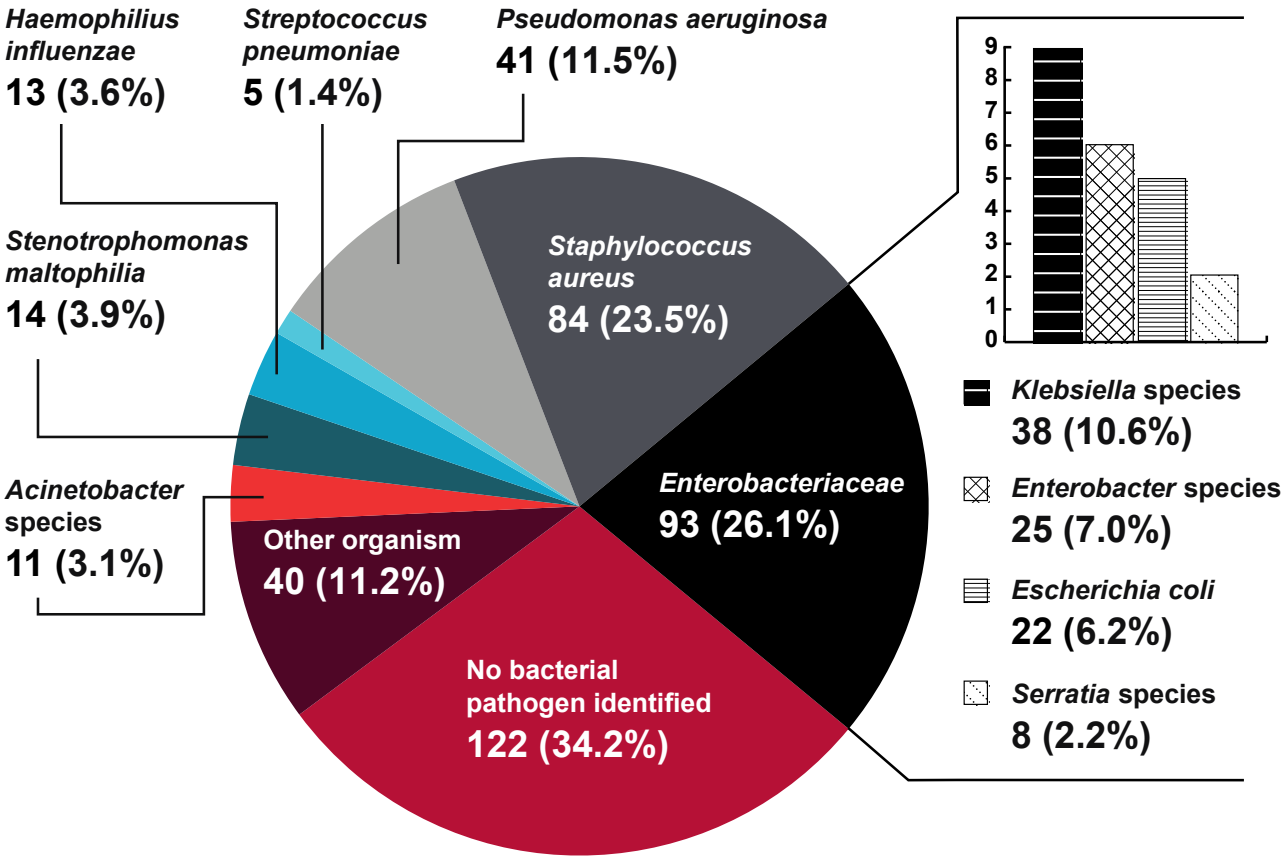
* Microbiology testing data reported for 357 of 394 (91%) VABP patients
† ≥1 positive microbiologic test was reported in 235 of 357 (66%) VABP patients with microbiology data reported

e-Figure 6. Microbiologic testing results among patients with hospital-acquired bacterial pneumonia



Microbiologic testing for bacteria available for 120 of 143 (84%) HABP patients.

e-Figure 7. Microbiologic testing results among patients with ventilator-associated bacterial pneumonia



Microbiologic testing for bacteria available for 357 of 394 (91%) VABP patients.

e-Table 3. HABP/VABP prevention measures typically utilized at study sites.

HABP/VABP Prevention Strategy	Study Sites (N=25)
Regular Oral Care with Chlorhexidine	25 (100%)
Elevate Head of Patient's Bed 30-45 degrees	25 (100%)
Daily Sedative Interruption	24 (96%)
Daily Spontaneous Breathing Trial	24 (96%)
Pharmacologic Stress Ulcer Prophylaxis	23 (92%)
Early Mobility Protocol	21 (84%)
Routine Monitoring of Gastric Residual Volume	13 (52%)
Endotracheal Tube with Subglottic Suctioning	10 (40%)
Early Tracheostomy (Before Ventilator Day 10)	8 (32%)
Automated Endotracheal Tube Cuff Pressure Control	5 (20%)
Prophylactic Antibiotic Treatment of MRSA Colonization	3 (12%)
Prophylactic Antibiotic Treatment of Colonization (other organisms)	0
Prophylactic Probiotic Administration	2 (8%)
Selective Oral Decontamination	2 (8%)
Selective Digestive Decontamination	0
Silver-Coated Endotracheal Tube	1 (4%)

25/28 (89%) sites reporting prevention strategies, representing 5647/5725 (99%) of patients enrolled.