Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplemental Methods

Study Cohorts

We identified all hospitalizations admitted via the emergency department to nationwide Veterans Affairs (VA) and Kaiser Permanente Northern California (KPNC) hospitals (2013-2018) with 2+ systemic inflammatory response syndrome (SIRS) criteria during the 24 hours prior to 48 hours after emergency department arrival. We used SIRS criteria to identify hospitalization with potential infection because these criteria are consistent with host response to infection, are commonly used to support a diagnosis of infection in clinical practice, and identify a stable population over time, in contrast to other approaches (*e.g.*, culture order, diagnosis) which would be biased by changes in diagnosis and management over time.[1]. SIRS criteria were the following: 1) abnormal white blood cell count (>12 X 10^9/L or <4 X 10^9/L); 2) abnormal body temperature (>38°C or <36°C); 3) heart rate >90 beats/min;
4) respiratory rate >20 breaths/min.[2]

From these SIRS-positive hospitalizations, we then identified hospitalizations for sepsis and septic shock as in prior work[3,4] using a definition adapted from the US Centers for Disease Control and Prevention's Adult Sepsis Event surveillance definition for community-onset sepsis that requires evidence of suspected infection and acute organ dysfunction[5].

Suspected infection was identified by systemic antimicrobial therapy initiated within 12 hours of presentation to the emergency department and continued for at least 4 days (or death prior to 4 days while on antimicrobial therapy). When assessing whether patients received at least 4 days of therapy, we considered both inpatient antimicrobials and antimicrobials prescribed

within 1 calendar day of hospital discharge. We did not require blood cultures to confirm suspected infection because we deemed 4 days of antimicrobials to be sufficient evidence that clinicians believed infection was present, and because some guidelines (*e.g.* American Thoracic Society / Infectious Diseases Society of America guidelines) recommend "not routinely obtaining blood cultures in adults with community-acquired pneumonia managed in the hospital setting".[6]

We identified six acute organ dysfunctions within 48 hours of arrival to the emergency department: acute renal dysfunction, acute liver dysfunction, acute hematologic dysfunction, acute respiratory failure (*i.e.*, receipt of invasive mechanical ventilation), shock (*i.e.*, receipt of an intravenous vasopressor), and lactate elevation (lactate >2.0 mmol/L). Acute renal, liver, and hematologic dysfunction required both an abnormal laboratory value and a departure from the patient's baseline. Acute renal dysfunction was defined as creatinine >1.2 mg/dl and a 50% increase from baseline. Patients with preexisting end-stage renal disease, as identified by diagnostic codes, were not eligible to have acute renal dysfunction. Acute liver dysfunction was defined as total bilirubin >2.0 mg/dl and a 100% increase from baseline. Acute hematologic dysfunction was defined as a platelet count ,100 cells/ml and a 50% decrease from baseline. The CDC's Adult Sepsis Event definition defines baseline organ function pragmatically as the best value during hospitalization. However, because VA and KPNC are integrated healthcare systems, longitudinal laboratory data was available for many patients. Thus, based on our prior research, we defined baseline organ function using the best laboratory value during hospitalization and the 180 days preceding arrival to the emergency department.[3] To have

sufficient observations to measure temporal trends in time-to-antibiotics, we excluded hospitals with fewer than 15 sepsis hospitalizations during the study period.

Broadness of Antibacterial Spectrum

Broadness of antibacterial coverage was quantified using Spectrum Score[7,8], a numeric score (range 0-64) that quantifies the broadness of any individual antibacterial agent or combination of antibacterial agents (*e.g.*, no antibacterial coverage=0; vancomycin=13; piperacillin/tazobactam=42.25.; vancomycin plus piperacillin/tazobactam=44.5)[8]. Spectrum Score was developed by a modified Delphi panel of physician and antimicrobial stewardship experts[8], and subsequently shown to have excellent sensitivity and specificity for identifying antibacterial de-escalation[7]. We expanded the spectrum score to incorporate additional antibacterial agents which are included in the CDC's Adult Surveillance Definition's list of qualifying antimicrobials,[5] but—because they are rarely used in practice—were not reported in the Spectrum Score derivation or validation studies.[7,8]

Multi-drug resistant (MDR) culture positivity

Organisms and their antibiograms were analyzed from electronic health record data accessed through the Veterans Informatics and Computing Infrastructure (VINCI). All available data for organisms were standardized to SNOMED CT, antimicrobial susceptibility tests to LOINC, and results to "susceptible," "intermediate," or "resistant" categories. Organism names sometimes contained antimicrobial susceptibility test results that were not present among antimicrobial susceptibility test results. To avoid missing these resistant organisms, virtual antimicrobial susceptibility tests and results were generated for algorithmic processing (e.g., for

"vancomycin-resistant *Enterococcus"* without an explicit vancomycin test, we would add an antimicrobial susceptibility test of vancomycin and a result of "resistant" so that vancomycin resistance would be properly captured). The antimicrobial component of the LOINC codes were organized according to published patterns relating organisms and salient drug classes.[9] This process removed tests that are generally not recommended for an organism as well as those that represent constitutive antimicrobial resistance (e.g., ampicillin tests for *Klebsiella* which are always resistant). Tests indicating the presence of the mecA gene or PBP2A were used along with antimicrobial susceptibility test results to infer methicillin resistance. The presence of carbapenemases were used to infer resistance to all beta-lactam-containing antimicrobial formulations generally susceptible to carbapenemases. MRSA, VRE, CRE, and ESBL were identified by antibiogram profiles consistent with their eponymous antimicrobial resistances. Multidrug-resistant *Acinetobacter* and *Pseudomonas* were identified by resistance to at least 1 antimicrobial from at least 3 antimicrobial classes according to the organism-specific drug classes noted above.

eTable 1. Study Flow			
	VA	KPNC	Total
Total Hospitalizations (2013-2018)	3,312,960	1,183,317	4,496,277
via Emergency Department	2,280,366	622,051	2,902,417
With 2+ SIRS criteria	1,100,996	459,130	1,560,126
Limited to 152 hospitals with 15+ sepsis hospitalizations	1,100,393	459,130	1,559,523

eTable 2. VA Patients Hospitalized With Potential Infection and Sepsis		
	SIRS-positive Hospitalizations	Sepsis Hospitalizations
Total Hospitalizations, N	1,100,393	165,146
Patient characteristics		
Age in years, median (IQR)	67 (60, 75)	69 (62, 77)
Male sex, N (%)	1,046,520 (95.1)	159,404 (96.5)
Race, N (%)		
White/Caucasian	783,199 (71.2)	118,681 (71.9)
Black/African-American	238,064 (21.6)	33,534 (20.3)
Other or missing	79,130 (7.2)	12,931 (7.8)
Comorbidities*, N (%)		
Congestive heart failure	357,049 (32.5)	54,889 (33.2)
Neurologic disease	166,835 (15.2)	31,540 (19.1)
Chronic pulmonary disease	510,044 (46.4)	77,844 (47.1)
Liver disease	182,097 (16.6)	30,358 (18.4)
Any diabetes	484,066 (44.0)	83,297 (50.4)
Diabetes with complication	297,905 (27.1)	55,601 (33.7)
Any cancer	232,945 (21.2)	41,274 (25.0)
Metastatic cancer	73,382 (6.7)	13,722 (8.3)
Renal disease	305,118 (27.7)	58,519 (35.4)
Acute organ dysfunction, N (%)		
Elevated lactate	158,003 (14.4)	78,849 (47.8)
Renal	260,429 (23.7)	101,223 (61.3)
Shock	28,423 (2.6)	16,824 (10.2)
Hepatic	53,333 (4.9)	20,524 (12.4)
Hematologic	55,808 (5.1)	21,407 (13.0)
Respiratory	17,566 (1.6)	10,577 (6.4)
Number of acute organ dysfunctions, N (%)		
None	686,868 (62.4)	0
One	297,425 (27.0)	108,394 (64.6)
Two	84,820 (7.7)	38,106 (23.1)
Three or more	31,280 (2.9)	18,646 (12.3)
Hospital outcomes		
Length of hospitalization in days, median (IQR)	4 (3, 7)	7 (4, 11)
In-hospital mortality, N (%)	29,957 (2.7)	12,176 (7.4)
30-d mortality, N (%)	75,590 (6.9)	20,844 (12.6)

*Comorbidities were defined using the Elixhauser Comorbidity Index, and identified from diagnostic codes during hospitalization plus all healthcare encounters (inpatient plus outpatient) in the 540 days prior to emergency department presentation.

eTable 3. KPNC Patients Hospitalized With Potential Infection and Sepsis		
	SIRS-positive Hospitalizations	Sepsis Hospitalizations
Total Hospitalizations, N	459,130	108,109
Patient characteristics		
Age in years, median (IQR)	69 (56, 81)	71 (59, 81)
Male sex, N (%)	223,478 (48.7)	56,180 (52.0)
Race, N (%)		
White/Caucasian	303,627 (66.2)	72,677 (67.2)
Black/African-American	54,837 (11.9)	11,274 (10.4)
Other or missing	100,666 (21.9)	24,158 (22.4)
Comorbidities*, N (%)		
Congestive heart failure	148,012 (32.2)	35,938 (33.2)
Neurologic disease	96,553 (21.0)	26,143 (24.2)
Chronic pulmonary disease	190,546 (41.5)	47,293 (43.8)
Liver disease	93,533 (20.4)	27,042 (25.0)
Any diabetes	176,419 (38.4)	48,032 (44.4)
Diabetes with complication	149,772 (32.6)	41,178 (38.1)
Any cancer	67,627 (14.7)	19,604 (18.1)
Metastatic cancer	35,418 (7.7)	10,744 (9.9)
Renal disease	170,112 (37.1)	45,624 (42.2)
Acute organ dysfunction, N (%)		
Elevated lactate	110,894 (24.2)	77,009 (71.2)
Renal	75,375 (16.4)	38,906 (36.0)
Shock	24,548 (5.4)	17,391 (16.1)
Hepatic	15,446 (3.4)	8,480 (7.8)
Hematologic	24,600 (5.4)	14,147 (13.1)
Respiratory	24,254 (5.3)	14,443 (13.4)
Number of acute organ dysfunctions, N (%)		
None	273,513 (59.6)	0
One	126,028 (27.5)	68,645 (63.5)
Two	39,029 (8.5)	24,157 (22.4)
Three or more	20,560 (4.4)	15,307 (14.1)
Hospital outcomes		
Length of hospitalization in days, median (IQR)	4 (3, 6)	5 (3, 8)
In-hospital mortality, N (%)	24,605 (5.4)	11,938 (11.0)
30-d mortality, N (%)	46,100 (10.0)	17,708 (16.4)

*Comorbidities were defined using the Elixhauser Comorbidity Index, and identified from diagnostic codes during hospitalization plus all healthcare encounters (inpatient plus outpatient) in the 540 days prior to emergency department presentation.

eTable 4. Antimicrobial Prescribing and Outcomes Among Patients With Sepsis by Year, Adjusted for Patient Characteristics								
	2013-2018 (N=273,255)	2013 (N=42,507)	2014 (N=42,568)	2015 (N=43,564)	2016 (N=45,142)	2017 (N=48,978)	2018 (N=50,496)	*p* for trend
Receipt of antimicrobial therapy								
Time to first antimicrobial, hours, median (IQR)	4.0	4.4	4.3	4.1	4.0	3.8	3.7	<0.001
Time to first antimicrobial, hours, mean	3.9	4.2	4.1	4.0	3.9	3.8	3.7	<0.001
Antimicrobial within 12 hours, %	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	1.0
Antimicrobial within 24 hours, %	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	1.0
Antimicrobial within 48 hours, %	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	1.0
Days of therapy to day 30, mean	11.0	11.4	11.3	11.1	10.9	10.7	10.5	<0.001
Days of therapy to day 30, median	10.8	10.8	10.7	10.5	10.4	10.2	10.0	<0.001
Broadness of antibacterial coverage								
Receipt of broad-spectrum* coverage within 48 hours								
Spectrum Score 40+, %	74.1%	76.0%	75.3%	74.6%	73.8%	73.1%	72.3%	<0.001
Spectrum Score 45+, %	61.3%	63.3%	62.6%	61.8%	61.0%	60.2%	59.4%	<0.001
Receipt of broad-spectrum coverage within 30 days								
Spectrum Score 40+, %	83.0%	85.0%	84.3%	83.5%	82.7%	81.9%	81.1%	<0.001
Spectrum Score 45+, %	74.0%	76.2%	75.4%	74.5%	73.7%	72.8%	71.9%	<0.001
Cumulative Spectrum Score (48 hours), mean	44.5	45.3	44.9	44.6	44.3	44.0	43.7	<0.001
Cumulative Spectrum Score (30 days), mean	48.4	49.3	49.0	48.6	48.3	48.0	47.6	<0.001
Outcomes								
Mortality								
In-hospital, %	8.8%	10.4%	9.8%	9.2%	8.6%	8.0%	7.5%	<0.001
30-day, %	14.1%	16.3%	15.4%	14.6%	13.8%	13.0%	12.3%	<0.001
Length of stay in days								
Among all hospitalizations, median	7.1	7.4	7.4	7.2	7.1	6.8	6.6	<0.001
Hosps with live discharge, median	6.4	6.7	6.7	6.5	6.4	6.2	5.9	<0.001
New antimicrobial resistance **								
New MDR culture, %	5.2%	6.6%	6.0%	5.5%	5.0%	4.5%	4.1%	<0.001
New MDR blood culture, %	0.8%	1.1%	1.0%	0.9%	0.8%	0.7%	0.7%	<0.001

Outcomes in this table were predicted from linear or logistic regression models adjusted for age, sex, 30 Elixhauser comorbidities, individual SIRS criteria, and individual acute organ dysfunctions.
*A Spectrum Score of 40+ would include coverage with piperacillin/tazobactam (Spectrum Score 42.25), vancomycin plus piperacillin/tazobactam (Spectrum Score 44.5), or similar, while a Spectrum Score of 45+ would include coverage with vancomycin plus a carbapenem (Spectrum Score 45.25), or similar.
**MDR=multi-drug resistant pathogen, defined as a culture or swab positive for MRSA (methicillin-resistant staph aureus), VRE (vancomycin-resistant enterococcus), CRE (carbapenem-resistant Enterobacteriaceae), ESBL (extended-spectrum beta-lactamase-producing Enterobacteriaceae), MDR pseudomonas (a pseudomonas that is resistant to at least 1 antibacterial from at least 3 different antibacterial classes), or Acinetobacter, which was collected during calendar days 2-90 following emergency department arrival and no positive culture/swab for that organism in the 180 calendar days prior to emergency department arrival.

eTable 5. Relationship Between Hospital-Level Trends in Antimicrobial Timing for Patients With Sepsis and Hospital-Level Trends in Antimicrobial Prescribing for Patients With SIRS but Without Sepsis

	Spearman's Correlation	p-value	Slope (Robust Regression) (change per 1 hour decline in TTA)	p-value
Antimicrobial receipt				
within 12 hours	0.095	0.254	+0.003 (-0.001, 0.007)	0.125
within 24 hours	0.058	0.485	+0.002 (-0.001, 0.006)	0.203
within 48 hours	0.067	0.423	+0.002 (-0.001, 0.006)	0.221
Days of antimicrobial therapy	-0.105	0.205	-0.034 (-0.079, 0.010)	0.124
Receipt of broad-spectrum* antibacterial coverage within 48 hours				
48hr Specturm Score 40+	0.102	0.218	+0.002 (-0.002, 0.005)	0.380
48hr Spectrum Score 45+	0.140	0.092	+0.001 (-0.001, 0.004)	0.239
Receipt of broad-spectrum antibacterial coverage within 30 days				
30d Spectrum Score 40+	0.029	0.728	+0.001 (-0.002, 0.004)	0.593
30d Spectrum Score 45+	0.062	0.454	+0.001 (-0.001, 0.004)	0.338
Broadness of Antimicrobial Coverage				
within 48 hours	0.029	0.738	+0.037 (-0.139, 0.214)	0.676
within 30 days	0.005	0.951	+0.040 (-0.152, 0.232)	0.680

This table presents the relationship (correlation and association) of hospital's temporal trend in antimicrobial timing in sepsis hospitalizations (i.e., hospital trends shown in **Figure 1**) and antimicrobial prescribing trends among all SIRS-positive hospitalizations *without* sepsis. Conceptually, this analysis answers the question: as a hospital speeds up antimicrobial delivery in sepsis hospitalizations, what is the impact on SIRS-positive hospitalizations without sepsis?

*A Spectrum Score of 40+ would include coverage with piperacillin/tazobactam (Spectrum Score 42.25), vancomycin plus piperacillin/tazobactam (Spectrum Score 44.5), or similar, while a Spectrum Score of 45+ would include coverage with vancomycin plus a carbapenem (Spectrum Score 45.25), or similar

Interpretation: For all antimicrobial prescribing trends assessed, there was no correlation and no association with trend in antimicrobial timing for sepsis.

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