SUPPLEMENTARY MATERIALS

Concordance Between Initial Presumptive Versus Final Adjudicated Diagnoses of Infection Among Patients Meeting Sepsis-3 Criteria in the Emergency Department

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Study setting
Patients presenting to the emergency department (ED) of two community hospitals, one regional referral hospital, and one tertiary teaching hospital in Utah from July 2013 to January 2017 were eligible for study inclusion. All study hospitals were part of a vertically integrated health system including 23 hospitals in Utah and Idaho. During the study period, the health system operated an integrated antibiotic stewardship program at all study hospitals. Key program components relevant to the present study included standardization of empiric antibiotic regimens used in the ED and inpatient units via electronic health record tools, development and dissemination of infection related guidelines, post-prescription review with feedback on all inpatient units conducted by the antibiotic stewardship team, and computerized decision support for ED patients with possible pneumonia [1].

Adjudication personnel
Initial medical record review for identification of ED-diagnosed source of infection and adjudication of the final presence and source of infection was completed by a team of experienced clinical research coordinators (including CJK) and medical students (SRM and ERM) formally trained using a structured protocol for medical record review and adjudication. A small number of data abstractions were completed by a critical care physician (IDP). Validation of final source of infection adjudication and adjudication of infection probability in the randomly selected 10% subset was performed subsequently by one medical student (GAH) trained using a structured review protocol developed by a team of critical care (IDP and SMB), infectious disease (EAS and BJW), and emergency medicine (JRB) physicians. The senior author (IDP, critical care physician) also performed a small number of reviews and performed validation of a random subset of 21% of the infection probability adjudications performed by the medical student reviewer.

Identification of ED clinician suspicion of infection
Study personnel verified that all patients included in the study were suspected by the ED clinician to have an infection. Patients who met inclusion criteria but were not suspected by the ED clinician to have an infection were not included in the study (N=5, see main manuscript Figure 1). This exclusion was based on explicit documentation by the ED clinician that antibiotics were given for a reason over than a suspected infection (e.g. in cirrhotic patient with GI hemorrhage or post-exposure prophylaxis for sexual assault).

Identification of ED-diagnosed source of infection
Study personnel initially recorded ED-diagnosed infection source as one of 11 categories: pneumonia/pulmonary, urinary tract infection (UTI), skin and soft tissue, abdominal/GI, osteoarticular, bloodstream/endocarditis, central nervous system/meningitis, unknown, multiple, other specific source, and not infected. This was simplified to 7 categories for data analysis: pneumonia/pulmonary, UTI, skin and soft tissue, abdominal/GI, unknown, other (including osteoarticular, central nervous system/meningitis, bloodstream/endocarditis, and multiple), and not infected. Patients were identified as having a suspected infection of unknown source diagnosed by the ED clinician when (1) there was explicit documentation from the ED provider (e.g. “no specific source of infection is apparent” or “I am uncertain about the source of infection”) or (2) a specific source of infection was not documented and no specific source diagnosis was implied by clinicians documentation and clinical care actions (e.g. absence of clinician documentation such as “I note patient has airspace opacities on CXR, will treat with ceftriaxone/azithromycin”). Infectious source was not assumed from external imaging or diagnostic studies without supporting clinical reasoning from the bedside clinician. For example, if a patient had clinical notation that the source of infection was from a biliary/GI source with an additional opacity on a chest x-ray which the ED clinician discounted or did not remark upon, then the source of infection would be GI. If, however, in that situation the ED physician noted that the opacity represented a possible pneumonia, then adjudicators would indicate “multiple” as the source of infection. However, where a primary source of infection was associated with systematic spread (e.g. UTI with bacteremia) or metastatic infection (e.g. endocarditis with septic pulmonary emboli), the source of infection was assigned as the “originating” source. Identification of a suspected source of infection in the medical record review process did not exclude residual uncertainty for the ED physician.

Adjudication of final presence/absence and source of infection
Study personnel utilized all available information including clinical diagnosis, clinical syndrome, and objective data to adjudicate the final presence/absence of infection and assign the source of infection into one of the previously-described 11 categories which were simplified to 7 categories for analysis as for ED-diagnosed source identification. Specific sources of information for retrospective review included patients’ hospital discharge summary, inpatient progress notes, specialist consultation notes (with particular attention to consultations by infectious disease

specialists), documentation from subsequent hospitalizations and clinic visits, microbiologic testing including both culture-based and molecular tests, and other radiologic, diagnostic, and laboratory testing. Patients were determined to be "not infected" if the bedside clinician made the clinical interpretation that infection was absent and/or an infection was deemed of sufficiently low probability that the patient was not administered a complete antimicrobial course. Infection was determined to be "present" if patients had a consistent clinical syndrome and diagnostic data associated with microbiologic confirmation, the absence of a more likely diagnosis, and/or clinical treatment response to appropriate therapy. Final adjudicated source of infection was identified based on preponderance of the available evidence. Where patients had evidence of multiple primary sources of infection, infection source was classified as "multiple." As for ED-diagnosed infection source identification, infection with systemic spread or metastatic infection from a primary source was classified based on the "originating" source. Patients for whom no specific source of infection was identified at final determination but who exhibited signs and symptoms of infection and received and appeared to respond to a full course of antimicrobial therapy were classified as "unknown" source [2].

Adjudication of final infection probability

General and source-specific criteria for retrospective adjudication of the final probability of infection was present during the ED encounter based on all available data were adapted by a team of experienced pulmonary/critical care medicine (IDP and SMB), infectious disease (EAS and BJW), and emergency medicine (JRB) physicians from the criteria described by Klein Klouwenberg et al. [3], other published criteria [2, 4-8], and criteria developed by the Centers for Disease Control and Prevention (CDC) [9] (see Supplementary Tables 1-8 for details). In general, "definite" infection was defined as a consistent infectious syndrome plus a positive culture or other diagnostic test for a pathogen consistent with the infectious syndrome. Results of microbiologic testing were evaluated in the context of the patient's infectious syndrome to avoid false positives, with source-specific criteria adapted from prior literature and CDC guidelines for excluding contaminant organisms (Supplementary Table 9) [2, 4, 7, 10, 11]. "Probable" infection was defined as a clinical syndrome that lacked confirmatory microbiologic testing but was highly consistent with the diagnosed infection (generally 2-3+ signs, symptoms, and/or laboratory/imaging findings) and was more likely than alternative diagnoses as the cause of the patient's syndrome and/or responded to appropriate treatment. "Possible" infection was defined as a clinical syndrome likely consistent with the diagnosed infection (generally 1-2+ symptoms, signs, and/or laboratory/imaging findings) and of sufficient clinical concern to merit a full course of antimicrobial therapy (if applicable) though alternative diagnoses were considered to be as or more likely than infection and/or there was a lack of response to appropriate therapy. Finally, patients were determined to be not infected if the bedside clinician made the clinical interpretation that infection was absent and/or an infection was deemed of sufficiently low probability that the patient was not administered a complete antimicrobial course. For specific infections not included in our general criteria, we applied detailed criteria from Klein Klouwenberg et al. [3] informed by our general criteria. As with prior studies adjudicating infection probability [3], differences in the frequency and yield of confirmatory diagnostic testing between infectious syndromes (e.g. pneumonia versus urinary tract infection) may influence the prevalence of "probable" versus "definite" infection likelihood. Consistent with the approach used by Valik et al. [2], patients who did not have a specific source of infection identified at final determination but exhibited signs and symptoms of infection and received and appeared to respond to a full course of antimicrobial therapy were classified as "unknown" source of infection and "possible" infection probability.

Adjudication of viral infections

Patients with viral pneumonia, viral gastroenteritis, or other viral syndromes with accompanying positive diagnostic test were considered "definite" infections and not a false-positive diagnosis if they also met other criteria (i.e. consistent clinical syndrome and lack of more likely alternative diagnosis) as required for the specific infection source. We did not adjudicate whether patients with viral pneumonia were "overtreated," i.e. received an antibiotic in the absence of a concurrent or secondary bacterial pneumonia.

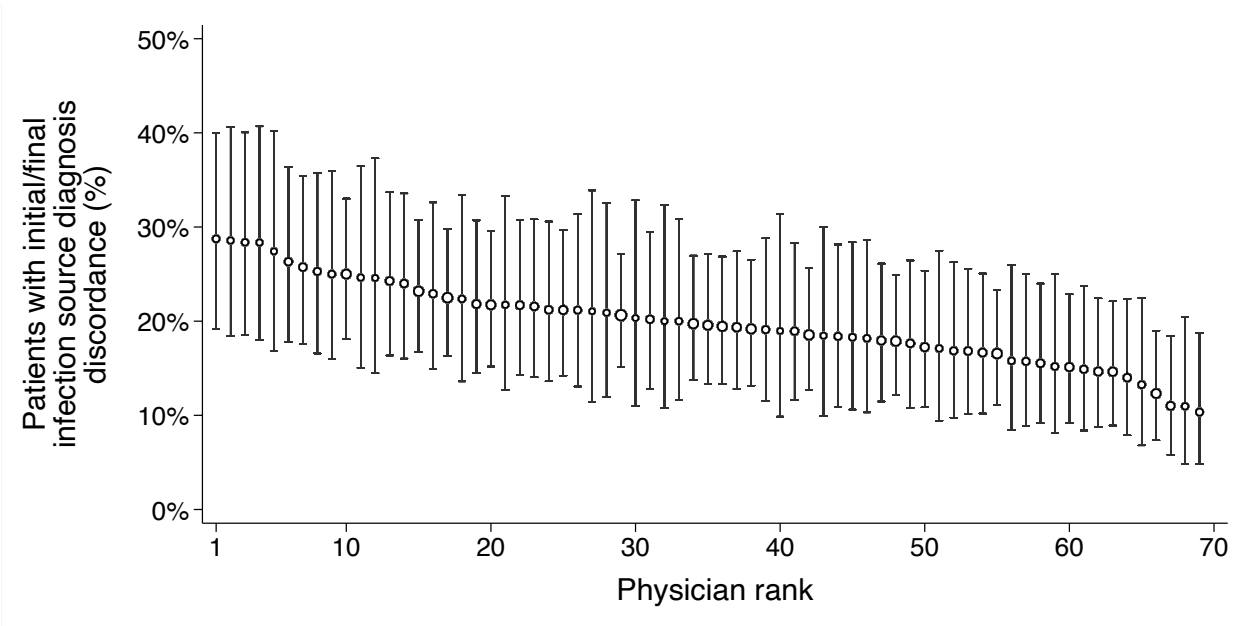
Definition and selection of risk factors and covariates

Potential risk factors for false-positive diagnosis and source diagnosis discordance were selected a priori: source of infection diagnosed in the ED; age; sex; race/ethnicity (Hispanic, non-Hispanic other, non-Hispanic white); arrival to ED from a long-term care facility; Charlson Comorbidity Index [12, 13]; Sequential Organ Failure Assessment (SOFA) score [14, 15]; white blood cell (WBC) count; first-available temperature (classified as <36 °C, 36-38 °C, or >38 °C), Glasgow coma scale (GCS) (categorized as ≤14 vs 15), heart rate; hypotension in the ED (any systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg or administration of vasopressors); and the ED

occupancy rate (ratio of patient to licensed ED beds) at the time patient arrived to ED [16, 17]. Nighttime ED arrival was defined as midnight to 6:59 AM. Acuity scores were assigned at ED triage by trained nurses [18], and the lowest two acuity scores were combined for analyses.

Potential confounders identified a priori and included as fixed effect covariates in the multivariable model evaluating physician-level variation for initial/final source diagnosis discordance were age, sex, Charlson Comorbidity Index, SOFA score, first-available temperature, heart rate, GCS, presence of hypotension, nighttime ED arrival, and ED triage acuity score.

Potential confounders identified a priori and included as covariates in the multivariable model evaluating the association of false-positive infection diagnosis and source diagnosis-discordance with mortality were age, sex, arrival from a long-term care facility, Charlson Comorbidity Index, SOFA score, first-available temperature and GCS, hypotension in the ED, and study site.



Supplementary Figure 1. Physician-level variation for initial/final infection source diagnosis discordance.

Variation for initial/final infection source diagnosis discordance among 69 ED physicians who saw at least 50 patients who had infection confirmed. After risk-adjustment, variation in discordance rate was non-significant (p=0.48).

Supplementary Table 1. General probability adjudication criteria

Not infected	Infection clinically determined to be absent (i.e. alternative diagnosis made) and/or infection deemed of sufficiently low probability that patient not administered a complete antimicrobial course.
Possible	Clinical suspicion for infection (usually indicated by a course of antimicrobial therapy if applicable) and clinical syndrome likely consistent with the infectious diagnosis (generally 1-2+ symptoms, signs, and/or laboratory/imaging findings) but alternative diagnosis considered to be as or more likely than infection and/or lack of response to appropriate therapy.
Probable	Clinical syndrome consistent with the infectious diagnosis (generally 2-3+ signs, symptoms, and/or laboratory/imaging findings) and infection considered more likely than other diagnoses as the cause of the patient's syndrome or clinical response to appropriate treatment but no positive culture or positive microbiologic diagnostic test for a pathogen consistent with the infectious syndrome.
Definite	Infectious syndrome consistent with the infectious diagnosis and a positive culture or positive microbiologic diagnostic test for a pathogen consistent with the infectious syndrome.

Supplementary Table 2. Pneumonia probability adjudication criteria

Possible	Clinical suspicion for pneumonia and clinical syndrome likely consistent with pneumonia but alternative diagnosis (e.g., aspiration pneumonitis) as or more likely. The clinical syndrome should include ≥1 of the following: 1. New cough or change in character of chronic cough 2. New onset of purulent sputum or change in character of sputum 3. Fever (>38.0 °C) or hypothermia (<36.0 ˚C) 4. Leukocytosis (≥12,000 WBC/mm^3) or leukopenia (≤4000 WBC/mm^3) 5. New or worsening hypoxemia (SpO2 <90% on room air or requirement for new or increased supplemental oxygen to maintain SpO2 ≥90%) 6. New or progressive airspace opacities on chest imaging 7. New or worsening dyspnea 8. Rales, bronchial breath sounds, or egophony on physical exam
Probable	Clinical syndrome consistent with pneumonia (usually ≥2 of signs/symptoms listed for "possible" pneumonia or a positive pulmonary test for infection not meeting criteria for definite*) and pneumonia considered more likely than other diagnoses and/or recovery after appropriate treatment without a pertinent positive diagnostic test or culture.
Definite	Meets clinical criteria for probable pneumonia plus has a diagnostic test or culture for a pulmonary pathogen including: 1. Pathogen cultured from blood (excluding normal respiratory & oral flora) 2. Pathogen in high concentration from a quantitative (≥10^3 – 10^4 CFU/mL) or semi-quantitative lower respiratory tract sample 3. Molecular (antigen or PCR) detection of viral pathogen, *Bordetella pertussis, Mycoplasma pneumonia,* or *Chlamydia pneumoniae* from respiratory source 4. Positive rapid diagnostic tests such as Legionella or pneumococcal 5. Culture of viral pathogen from a respiratory source 6. Diagnostic single antibody titer (IgM) or fourfold increase in paired sera (IgG) for pathogen 7. Histopathologic evidence of pneumonia 8. Isolation of etiologic agent from lung abscess or pleural empyema.

* Culture of bacterial pathogen from endotracheal aspirates and expectorated sputum will generally *not* be considered evidence of definite infection. Determination will be decided on a case-by-case basis taking into account the overall clinical picture and culture parameters including:

- Length of time of intubation (if applicable) before sample was taken
- Density of bacterial growth on culture (generally 3-4+ may be considered definite)
- Identity of cultured bacteria
- Culture purity (monomicrobial more convincing than polymicrobial)

Supplementary Table 3. UTI probability adjudication criteria

Possible	Clinical suspicion for UTI and clinical syndrome likely consistent with UTI but alternative diagnosis as or more likely. The clinical syndrome should include ≥1 of the following: 1. Fever (>38.0 °C) or hypothermia (<36.0 ˚C) 2. Urinary urgency 3. Urinary frequency 4. Dysuria 5. Clinical pyuria 6. Localized pain at involved site (e.g. flank pain) 7. Urinalysis with positive leukocyte esterase 8. Urine microscopy with >10 WBC/hpf but <30 WBC/hpf without evidence of contamination (i.e. minimal or no epithelial cells, in general less than 5 epithelial cells/HPF)
Probable	Clinical syndrome consistent with urinary tract infection (usually ≥2 of signs/symptoms listed for "possible" UTI and at least one of below criteria) and UTI considered more likely than other diagnoses and/or recovery after appropriate treatment without a pertinent positive diagnostic tests or cultures. Can have one of these findings: 1. Urinalysis with positive nitrites 2. Urine microscopy with >30 WBC/hpf without evidence of contamination (i.e. minimal or no epithelial cells, in general less than 5 epithelial cells/HPF) 3. Bacteria seen in Gram stain of unspun urine 4. Frank pus expressed around the urinary catheter 5. Urine culture with ≤ 10^5 colonies/mL of a single uropathogen in a patient being treated with appropriate antimicrobial therapy 6. Radiographic evidence of infection (e.g., ultrasound, computed tomography, magnetic resonance imaging, radiolabeled scan)
Definite	Meets criteria for probable UTI plus has one of following 1. Urine culture with >10^5 colonies/mL with no more than two species of microorganisms 2. Urinary pathogen cultured from blood without more likely source 3. Evidence of infection on histopathologic specimen.

Supplementary Table 4. Skin and soft tissue probability adjudication criteria

Possible	Clinical suspicion for skin/soft tissue infection (SSTI) and clinical syndrome likely consistent with SSTI but alternative diagnosis as or more likely. The clinical syndrome should include ≥1 of the following: 1. Pain or tenderness 2. Localized swelling 3. Redness 4. Heat
Probable	Clinical syndrome consistent with skin/soft tissue infection (usually ≥2 of signs/symptoms listed for "possible" SSTI that are not bilateral or ≥1 of above criteria plus ≥1 of below criteria) and SSTI considered more likely than other diagnoses. High clinical suspicion that includes pertinent signs and symptoms (see possible criteria) and/or recovery after appropriate treatment without a pertinent positive diagnostic test or culture. 1. Signs suggestive of inflammation on imaging 2. Bullae or vesicles in affected area 3. Fever (>38.0 °C) 4. Leukocytosis (≥12,000 WBC/mm^3) or leukopenia (≤4000 WBC/mm^3)
Definite	Meets criteria for probable SSTI with a positive diagnostic test or culture including: 1. Pathogen cultured from blood without more likely cause of infection. 2. Subcutaneous air or abscess on imaging 3. Purulent drainage, pustules, or abscess on exam 4. Pathogen cultured from site via tissue biopsy, deep tissue culture, aspirate, or other method at low risk of contamination. Normal skin flora are excluded unless obtained from a pure culture

Supplementary Table 5. Osteoarticular probability adjudication criteria

Possible	Clinical suspicion for osteoarticular infection and clinical syndrome likely consistent with osteoarticular infection but alternative diagnosis as or more likely. The clinical syndrome should include ≥1 of the following: 1. Fever (>38°C) 2. Localized swelling 3. Tenderness 4. Heat 5. Drainage at suspected site of infection 6. Pain with joint movement (if suspected joint or vertebral involvement) 7. Limitation of joint motion (if suspected joint or vertebral involvement)
Probable	Clinical syndrome consistent with osteoarticular infection (usually ≥2 of signs/symptoms listed for "possible" osteoarticular infection or ≥1 of above criteria plus ≥1 of below criteria) and osteoarticular infection considered more likely than other diagnoses and/or recovery after appropriate treatment without a pertinent positive diagnostic test or culture. 1. Radiographic evidence of infection (CT, MRI, rarely plain radiograph) 2. Synovial fluid or bursa aspirate with cell counts/differential and chemistries consistent with infection and not explained by non-infectious cause
Definite	High clinical suspicion that includes pertinent signs and symptoms with a positive diagnostic test or culture including: 1. Pathogen cultured from blood (without more likely source of infection), bone, or joint 2. Synovial fluid or bursa aspirate with positive gram stain consistent with potential pathogen 3. Evidence of infection on direct examination of the bone or joint during a surgical operation or histopathologic examination

Supplementary Table 6. Gastrointestinal and intrabdominal probability adjudication criteria

Possible	Clinical suspicion for intrabdominal or gastrointestinal infection and clinical syndrome likely consistent with intrabdominal or gastrointestinal infection but alternative diagnosis as or more likely. The clinical syndrome should include ≥1 of the following: 1. Fever (>38˚ C) 2. Diarrhea 3. Vomiting 4. Pertinent localized, radiating, or generalized pain (as per suspected intraabdominal infection) 5. Jaundice (for ascending cholangitis only) 6. Ileus 7. Abdominal distention
Probable	Clinical syndrome consistent with intrabdominal or gastrointestinal infection (usually ≥2 of signs/symptoms listed for "possible" intrabdominal or gastrointestinal infection or ≥1 of above criteria plus ≥1 of below criteria) and intrabdominal or gastrointestinal infection considered more likely than other diagnoses and/or recovery after appropriate treatment without a pertinent positive diagnostic test or culture. 1. Radiographic evidence of bowel pneumatosis, biliary tract obstruction, cholecystitis, enteritis, or colitis 2. Free air in the abdomen 3. Aspirate of peritoneal dialysate with ≥100 WBCs/mm^3
Definite	High clinical suspicion that includes pertinent signs and symptoms with a positive diagnostic test or culture including: 1. Peritoneal fluid with ≥250 PMNs/mm^3 2. Bowel perforation or intrabdominal abscess on surgical assessment 3. Radiographic evidence of intraabdominal perforation 4. Purulent drainage and/or positive Gram stain of aspirate or percutaneous drain 5. Pathogen cultured from intrabdominal aspirate or peritoneal fluid 6. Enteric pathogen cultured from blood without more likely source 7. Molecular diagnostic test or culture positive for enteric pathogen from stool 8. Positive serologic or microscopic assay for parasitic enteric pathogen 9. Positive hepatitis viral testing (positive antibody (IgM) test for HAV, HBV, HCV, HDV, HEV, cytomegalovirus (CMV) detected by PCR in blood, positive antigen for HBV (HbsAg), or positive PCR for EBV, CMV, HBV, HCV) in context of clinical hepatitis* 10. Positive *C. dificile* toxin test or anatomic or histopathologic evidence of pseudomembranous colitis.

*Second review by experienced critical care or infectious disease investigator.

Supplementary Table 7. Bloodstream probability adjudication criteria

Possible	N/A
Probable	Clinical syndrome consistent with endocarditis plus either echocardiographic evidence of endocarditis (vegetation, abscess, or new regurgitation/prosthetic valve dysfunction) and ≥1 minor Duke criteria or ≥3 minor Duke criteria or vegetation on pacemaker leads.[†]
Definite	Bloodstream infection (with or without endocarditis or infection of intravascular line or hardware) with ≥1 positive recognized pathogen identified in blood cultures and no other apparent primary source of infection. For agents identified as potential contaminants (see Supplemental Table 8), clinical suspicion and identification of the same organism from ≥2 independent positive blood cultures drawn from separate sites (including at least 1 peripheral blood sample) or at separate (but proximate) times is required.

[†] Minor Duke criteria:

- Predisposition (injection drug use or prosthetic valve)
- Fever (≥38˚C)
- Evidence of septic emboli: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
- Serological evidence of active infection with organism consistent with IE (e.g. elevated *Coxciella burnetiid* phase I igG titer >800)

Adapted with permission from the Infectious Disease Society of America and Oxford University Press from Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30(4):633-8.

Supplementary Table 8. Central nervous system probability adjudication criteria

Possible	Clinical suspicion for central nervous system (CNS) infection – including meningitis, encephalitis, epidural abscess, intracranial abscess, ventriculitis, and infectious encephalitis - and clinical syndrome likely consistent with meningitis infection but no cerebrospinal fluid (CSF) sample available and alternative diagnosis as or more likely. The clinical syndrome should include ≥1 of the following: 1. Fever (>38°C) 2. Headache 3. Stiff neck 4. Meningeal signs 5. Cranial nerve signs 6. Changing level of consciousness 7. Petechia/thrombocytopenia 8. For epidural abscess only: Back pain
Probable	Clinical syndrome consistent with meningitis (usually ≥2 of signs/symptoms listed for "possible" meningitis or ≥1 of above criteria plus ≥1 of below criteria) and meningitis considered more likely than other diagnoses and/or recovery after appropriate treatment without a pertinent positive diagnostic tests or cultures. 1. Elevated CSF protein 2. Low CSF glucose 3. Radiographic evidence of intracranial or epidural abscess or meningeal enhancement demonstrated by MRI
Definite	High clinical suspicion for CNS infection that includes pertinent signs and symptoms with a positive diagnostic test or culture including: 1. CSF pleocytosis (>15 WBC/mm^3 after subtracting 1 WBC for every 1,000 RBCs) 2. Pathogen cultured or detected on microscopy of CSF, CNS abscess, or spinal abscess 3. PCR of CSF positive for viral pathogen 4. Positive antigen or antibody test of CSF *(*diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for organism) 5. Positive urine antigen test for *Streptococcus pneumoniae* without more likely source 6. Pathogen cultured from blood without more likely source

Supplementary Table 9. Common contaminant or commensal organisms† ineligible for consideration as pathogen when identified in body fluid cultures [2, 7, 10, 11, 19].

Microbial organism	Presumed primary source of infection†				
	Blood	**Pulmonary**	**Urinary**	**Gastrointestinal or intrabdominal**	**Skin/soft tissue**
Coagulase negative staphlococci	Yes*	Yes	Yes	Yes	Yes*
Bacillus spp. (other than *B. anthrasis*)	Yes	Yes	Yes	Variable	Variable
Corynebacterium spp.	Yes	Yes	Yes	Yes	Yes
Proprionobacterium spp.	Yes*	Yes	Yes	Yes	Yes*
Cutibacterium	Yes*	Yes	Yes	Yes	Yes
Micrococcus spp.	Yes	Yes	Yes	Yes	Yes*
Diptheroids	Yes	Yes	Yes	Yes	Yes
Viridans group streptococci	No	Variable	Variable	No	No
Enterococci	No	Yes	No	No	Variable
Clostridium spp.	Yes*	Yes	No	No	No
Aerococcus	Yes*	Yes	Yes	Yes	Yes*
Rothia spp.	Yes*	Yes	Yes	Yes	Yes*
Gardnerella vaginallis	Yes	Yes	Yes	Yes	Yes
"Mixed flora"	Yes	Yes	Yes	Yes	Yes*
"Oral flora"	Yes	Yes	Yes	Yes	Yes
"Normal flora"	Yes	Yes	Yes	Yes	Yes
Candida	No	Yes*	Yes*	No if from biliary or peritoneal source	No if from deep tissue sample
Molds	No	No	Yes	Yes	Variable
GI parasites	Yes	Yes	Yes	No	Yes

* Indicates pathogen which may indicate true positive in context of the same organism identified from ≥2 independent positive cultures from a single source (e.g. two blood cultures collected at different blood sampling sites or times) or different but concurrent sources (e.g. both urine and blood), and/or clinical risk factors (e.g. immunosuppression, indwelling lines/hardware/devices).

† Table describes common contaminants. For cultures yielding organisms that are not canonical pathogens for a given infection site, adjudication was completed on a case-by-case basis in context of above criteria, other clinical data, and assistance from investigators with expertise in infectious disease.

Supplementary Table 10. Demographic and clinical characteristics of patients by infection probability.

Variable	Not infected (n = 77)	Possible (n = 79)	Probable and definite (n = 656)	P value
Age (years)	64.0 (±20.9)	65.4 (±17.6)	60.9 (±18.6)	0.073
Female sex	39 (50.6)	36 (45.6)	348 (53.0)	0.44
Race				0.36
Hispanic/Latino	3 (3.9)	10 (12.7)	60 (9.2)	
Non-Hispanic/Latino White	67 (87.0)	64 (81.0)	554 (84.5)	
Non-Hispanic/Latino other race	7 (9.1)	5 (6.3)	42 (6.4)	
Arrival to ED from long-term care facility	4 (5.2)	3 (3.8)	37 (5.6)	0.79
Arrival to ED by EMS	35 (45.5)	24 (30.4)	219 (33.4)	0.081
Charlson comorbidity index	3 (1-7)	4 (2-7)	3.5 (1-7)	0.63
SOFA score	4.5 (±2.4)	4.8 (±2.4)	4.7 (±2.7)	0.84
Initial vital signs and laboratory values				
Heart rate (beats/min)	100.8 (±20.0)	105.4	103.9	0.40
White blood cell count (1000/μL)	11.9 (±7.1)	12.1 (±7.0)	13.6 (±8.3)	0.083
Temperature				0.009
< 36 ˚C	11 (14.3)	7 (8.9)	56 (8.5)	
36-38 ˚C	48 (62.3)	46 (58.2)	319 (48.6)	
> 38 ˚C	18 (23.4)	26 (32.9)	281 (42.8)	
Glasgow Coma Scale ≤14	10 (13.0)	4 (5.1)	56 (8.5)	0.21
Hypotension in the ED	16 (20.8)	24 (30.4)	196 (29.9)	0.24
Lactate >2	30 (39.0)	27 (34.2)	248 (37.8)	0.79
ED occupancy rate	0.69 (±0.26)	0.63 (±0.26)	0.64 (±0.29)	0.31
ED-diagnosed source of infection				<0.001
Pulmonary	30 (39.0)	39 (49.4)	281 (42.8)	
Urinary	10 (13.0)	11 (13.9)	114 (17.4)	
Intraabdominal/gastrointestinal	4 (5.2)	6 (7.6)	53 (8.1)	
Skin and soft tissue	4 (5.2)	1 (1.3)	80 (12.2)	
Other	8 (10.4)	11 (13.9)	94 (14.3)	
Unknown	21 (27.3)	11 (13.9)	34 (5.2)	
Days of IV antibiotics to hospital day 7	1 (1-3)	3 (2-4)	3 (2-5)	<0.001
Unique antibiotics administered in ED	1.7 (0.7)	1.7 (0.6)	1.8 (0.6)	0.53
Initial antibiotic regimen total spectrum score	5.9 (2.9)	5.2 (2.5)	5.6 (2.7)	0.24

Results presented as mean (SD), median (IQR), or number of patients (%).
Abbreviations: ED, Emergency department; EMS, emergency medical services; SOFA, Sequential Organ Failure Assessment.

Supplementary Table 11. Per-patient days of therapy through hospital day 7* for the 10 most-prescribed intravenous antibiotics by final infection presence.

Antibiotic	Days of therapy (mean [SD])*		P value
	Infected (n = 7568)	Not Infected (n = 699)	
Ceftriaxone	1.8 (1.9)	1.0 (1.2)	<0.001
Vancomycin	1.0 (1.6)	0.6 (1.0)	<0.001
Azithromycin	0.7 (1.0)	0.4 (0.7)	<0.001
Piperacillin/tazobactam	0.7 (1.5)	0.4 (1.1)	<0.001
Cefazolin	0.2 (0.8)	0.1 (0.4)	<0.001
Levofloxacin	0.3 (0.9)	0.2 (0.6)	<0.001
Ertapenem	0.1 (0.7)	0.1 (0.3)	<0.001
Meropenem	0.3 (1.0)	0.2 (0.7)	<0.001
Metronidazole	0.13 (0.66)	0.05 (0.27)	<0.001
Clindamycin	0.15 (0.69)	0.03 (0.29)	<0.001

* Average per-patient days of therapy through hospital day 7, death, or hospital discharge.

Supplementary Table 12. Demographic and clinical characteristics of patients with and without source diagnosis discordance.

Variable	Congruent Source Diagnosis (n = 6080)	Source Diagnosis Discordance (n=1488)	P value
Age (years)	61.4 (±18.4)	62.0 (±18.7)	0.26
Female sex	3070 (50.5)	790 (53.1)	0.072
Race[b]			0.63
Hispanic/Latino	535 (8.8)	141 (9.5)	
Non-Hispanic/Latino White	5119 (84.2)	1238 (83.2)	
Non-Hispanic/Latino other race	426 (7.0)	109 (7.3)	
Arrival to ED from long-term care	377 (6.2)	138 (9.3)	<0.001
Arrival to ED by EMS	1786 (29.4)	534 (35.9)	<0.001
Charlson comorbidity index	3 (1-6)	4 (2-7)	<0.001
SOFA score	4.6 (±2.6)	5.5 (±3.3)	<0.001
Initial vital signs and laboratory			
Heart rate (beats/min)	104.3 (±22.1)	106.2 (±23.4)	0.005
White blood cell count (1000/μL)	13.6 (±16.0)	13.4 (±7.7)	0.43
Temperature			<0.001
< 36 ˚C	470 (7.7)	150 (10.1)	
36-38 ˚C	3168 (52.1)	657 (44.2)	
> 38 ˚C	2442 (40.2)	681 (45.8)	
Glasgow Coma Scale ≤14	414 (6.8)	157 (10.6)	<0.001
Hypotension in the ED	1794 (29.5)	556 (37.4)	<0.001
Lactate >2	2323 (38.2)	682 (45.8)	<0.001
ED occupancy rate	0.65 (±0.29)	0.67 (±0.28)	0.059
ED-diagnosed source of infection			<0.001
Pulmonary	2817 (46.3)	271 (18.2)	
Urinary	1217 (20.0)	220 (14.8)	
Intraabdominal/gastrointestinal	526 (8.7)	62 (4.2)	
Skin and soft tissue	809 (13.3)	98 (6.6)	
Other	623 (10.3)	362 (24.3)	
Unknown	88 (1.5)	475 (31.9)	

Patients with source diagnosis discordance had a different initial source of infection determined by the ED clinician compared to the source of infection determined on final adjudication. Results presented as mean (SD), median (IQR), or number of patients (%). Abbreviations: ED, Emergency department; EMS, emergency medical services; SOFA, Sequential Organ Failure Assessment.

Supplementary Table 13. Characteristics of physicians included in physician-variation analysis.

Characteristics	Physicians (n = 69)
Age (years)	42.6 (±8.5)
Female sex	11 (15.9%)
Years of experience since medical school	14.8 (±8.8)
Board certified emergency medicine physicians	63 (91%)
Patients with sepsis analyzed per physician	96 (76-117)

Numbers presented as mean (SD) or number (percentage).

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