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Frequency of Antibiotic Overtreatment and Associated Harms in Patients Presenting With Suspected Sepsis to the Emergency Department: A Retrospective Cohort Study

Claire N. Shappell,[1] Tingting Yu,[2] Michael Klompas,[2,3] Anna A. Agan,[2] Laura DelloStritto,[2] Brett A. Faine,[4] Michael R. Filbin,[5] Nicholas M. Mohr,[4] Steven T. Park,[6] Kamryn Plechot,[6] Emily Porter,[5] David Roach,[3] Sarah E. Train,[7] Anne Zepeski,[4] and Chanu Rhee[2,3]

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [2]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA; [3]Division of Infectious Diseases, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [4]Department of Emergency Medicine, University of Iowa Health Care, Iowa City, Iowa, USA; [5]Department of Emergency Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA; [6]Division of Infectious Diseases, Department of Medicine, University of California, Irvine School of Medicine, Orange, California, USA; and [7]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

Background. Treatment guidelines recommend rapidly treating all patients with suspected sepsis with broad-spectrum antibiotics. This may contribute to antibiotic overuse. We quantified the incidence of antibiotic overtreatment and possible antibiotic-associated harms among patients with suspected sepsis.

Methods. We reviewed the medical records of 600 adults treated for suspected sepsis with anti–methicillin-resistant *Staphylococcus aureus* and/or antipseudomonal β-lactam antibiotics in the emergency departments of 7 hospitals, 2019–2022, to assess their post hoc likelihood of infection, whether narrower antibiotics would have sufficed in retrospect, and possible antibiotic-associated complications. We used generalized estimating equations to assess associations between likelihood of infection and hospital mortality.

Results. Of 600 patients, 411 (68.5%) had definite (48.0%) or probable (20.5%) bacterial infection and 189 (31.5%) had possible but less likely (18.3%) or definitely no (13.2%) bacterial infection. Among patients with definite/probable bacterial infection, 325 of 411 (79.1%) received antibiotics that were overly broad in retrospect. Potential antibiotic-associated complications developed in 104 of 600 (17.3%) patients within 90 days, most commonly new infection or colonization with organisms resistant to first-line agents (48/600 [8.0%]). Mortality was higher for patients with less likely/definitely no bacterial infection versus definite/probable bacterial infections (9.0% vs 4.9%; adjusted odds ratio [aOR], 2.25 [95% confidence interval{CI}, 1.70–2.98]), but antibiotic-associated complication rates were similar (14.8% vs 18.5%; aOR, 0.79 [95% CI, .60–1.05]).

Conclusions. Among 600 patients treated with broad-spectrum antibiotics for possible sepsis, 1 in 3 most likely did not have a bacterial infection, 4 in 5 of those with bacterial infections were treated with regimens that were broader than necessary in retrospect, and 1 in 6 developed antibiotic-associated complications.

Keywords. sepsis; antibiotics; antimicrobial stewardship.

Sepsis is a major cause of morbidity and mortality globally [1–3]. Rapid administration of antibiotics to patients with suspected sepsis is a cornerstone of treatment guidelines and quality initiatives, including the Surviving Sepsis Campaign (SSC) and the US Centers for Medicare and Medicaid Services' Severe Sepsis/Septic Shock Management Bundle (SEP-1) [4–10]. The SSC's and SEP-1's time-to-antibiotic requirements put frontline providers in the challenging position of needing to act quickly despite incomplete diagnostic information whenever sepsis is on the differential diagnosis [11, 12]. Experts and professional societies have raised concern that these initiatives may have the unintended consequence of driving broad-spectrum antibiotic overuse in patients with noninfectious conditions and infections susceptible to narrower-spectrum agents [13–18].

The prevalence and consequences of antibiotic overtreatment for suspected sepsis, however, remain incompletely characterized. Previous studies have reported that 20%–40% of patients treated with antibiotics for suspected sepsis likely had noninfectious conditions or viral infections, but these studies were limited to single healthcare systems or geographic regions and were conducted prior to the coronavirus disease 2019 pandemic [19–22]. Similarly, studies using large electronic

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Correspondence: C. Shappell, Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (cshappell@bwh.harvard.edu); C. Rhee, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Drive, Suite 401 East, Boston, MA 02115 (crhee@bwh.harvard.edu).

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health record datasets have found that <10% of patients treated for suspected sepsis are infected with resistant organisms, but these studies only assessed antimicrobial appropriateness using culture results without accounting for patients' allergies or history of antibiotic-resistant infections, which may have appropriately influenced prescribing [23, 24]. Finally, studies comparing patients treated for suspected sepsis who were ultimately found to have infectious versus noninfectious etiologies have reported mixed outcomes and did not assess potential antibiotic-associated harms [19–21].

We therefore undertook an updated evaluation of patients treated with broad-spectrum antibiotics for suspected sepsis in 7 emergency departments (EDs) to determine their post hoc likelihood of infection and need for broad-spectrum agents, potential harms, and outcomes.

MATERIALS AND METHODS

Study Design, Setting, and Patients

We reviewed the medical records of 600 adults treated for suspected sepsis (defined as drawing blood cultures, measuring lactate [any result], and administering intravenous antibiotics) who received broad-spectrum therapy (≥1 intravenous anti–methicillin-resistant *Staphylococcus aureus* [MRSA] and/or antipseudomonal β-lactam antibiotic) [23] in the EDs of 7 hospitals, in California (University of California, Irvine Medical Center, N = 150), Iowa (University of Iowa Hospitals and Clinics, N = 150), and Massachusetts (Brigham and Women's Hospital, Massachusetts General Hospital, Brigham and Women's Faulkner Hospital, and Newton-Wellesley Hospital, Salem Hospital, N = 300) between 2019 and 2022.

Medical Record Reviews

Study staff abstracted data using standardized REDCap forms (Supplementary Appendix) [25] Reviewers were attending physicians, fellows, or clinical pharmacists in emergency medicine, infectious diseases, or pulmonary/critical care. Reviewers analyzed all available data from the index hospitalization and previous or subsequent encounters including clinical notes, vital signs, biochemical and microbiology results, diagnostic imaging, and pathology reports. Reviewers classified the post hoc likelihood of infection as definite, probable, possible but less likely, or definitely no bacterial infection (case definitions adapted from previous studies [22] with minor updates for clarification based on discussion among the study team; see Box in the Supplementary Materials). For definite/probable bacterial infections, reviewers assessed the primary source of infection, causative organism, whether antibiotics received in the ED were adequate to treat the causative pathogen or syndrome, and whether narrower antibiotics (eg, ceftriaxone or lower-generation cephalosporins) could have sufficed in retrospect. Determinations of antibiotic adequacy and necessity were based on antibiotic susceptibilities if a causative organism was cultured (ie, antibiotics were adequate if the isolate was sensitive to that agent, and necessary if the isolate was not sensitive to a narrower-spectrum antibiotic), or on presenting syndrome if no causative organism was identified, including history of resistant organisms recovered during the preceding 3 years. For example, antipseudomonal coverage was considered necessary for culture-negative febrile neutropenia, even without positive cultures (see Supplementary Appendix for full guidance to reviewers). For patients with possible but less likely or definitely no bacterial infection, reviewers assessed the most probable alternative etiology. For all patients, reviewers assessed for adverse events potentially related to the initial antibiotic course including *Clostridioides difficile* infection with 90 days; new colonization or infection with a resistant organism within 90 days; or acute kidney injury, skin reactions, non–*C. difficile* diarrhea, drug fever, cytopenias, elevated liver function tests, delirium, or other antibiotic-associated effects during the index hospitalization. Patients' demographics, initial vital signs, laboratory results, and *International Classification of Diseases, 10th Revision* (*ICD-10*) discharge diagnosis codes were electronically extracted. Comorbidities were derived from *ICD-10* codes using the Agency for Healthcare Research and Quality Elixhauser mortality index (version 2024.1) [26].

Prior to undertaking chart reviews, consensus definitions for likelihood of infection and case examples were reviewed. At each site, the first 15 cases were independently reviewed by at least 2 reviewers and discrepant cases discussed to encourage consensus in how definitions were applied. Thereafter, cases were reviewed individually, with challenging cases flagged by reviewers for group discussion during monthly investigator meetings, and final determinations were based on group consensus (see Table 1 for example cases).

Statistical Analysis

Determinations of post hoc likelihood of bacterial infection were dichotomized into "definite/probable" and "less likely/definitely not." Determinations of antibiotic necessity were also combined into 2 groups: (1) "likely overtreated," which included patients with less likely/definitely no bacterial infection or who had definite/likely infection but received antibiotics that were broader than necessary in retrospect; and (2) "likely not overtreated." We focused on post hoc determinations of antibiotic necessity rather than whether antibiotics were "appropriate" or "reasonable" at the time of prescribing. Differences between groups were assessed using Wilcoxon rank-sum test for continuous variables and Pearson χ^2 statistic for categorical variables.

Generalized estimating equations (GEEs) were fitted to calculate adjusted odds ratios (aORs) for in-hospital death based on likelihood of bacterial infection. Vital sign and laboratory

Table 1. Representative Case Examples From Each Category of Post Hoc Likelihood of Bacterial Infection

Category, No. (%) and Definition	Description of Case
Definite bacterial infection, 288/600 (48.0%): Pathologic diagnosis of infection OR operative recovery of pus OR positive culture from a normally sterile site that is not likely to be a contaminant, OR positive cultures from a nonsterile site with supportive corollary evidence of infection at that site OR imaging findings or other microbiologic studies diagnostic for infection with a compatible clinical syndrome (probability ≥90% that bacterial infection was present and responsible for patients' presentation)	A male patient in his 60s with history of DM, GERD, and HTN presented to the ED with one day of acute abdominal pain and a fever to 39.0°C. His ED course was notable for tachycardia, normotension, leukocytosis (WBC count 22 000/L with 82% neutrophils), unremarkable basic metabolic panel, and lactic acid <2.0 mmol/L. CT abdomen and pelvis showed a perforation of the distal small bowel with an adjacent hyperattenuating fluid collection. He was treated with cefepime and metronidazole in the ED and taken urgently to the operating room for exploratory laparotomy, where he was found to have purulent ascites and an obvious large tumor of the ileum. Intraoperative cultures of ascitic fluid grew *Klebsiella pneumoniae* (pan-susceptible) and rare *Citrobacter* species (pan-susceptible). He was narrowed to ciprofloxacin and metronidazole to complete a 4-day postoperative course and discharged home on hospital day (HD) 8 without additional antibiotics. He did not suffer any potentially antibiotic-associated harms. The mass on his ileum was found to be a gastrointestinal stromal tumor. Adjudicated as definite bacterial infection based upon purulent fluid described in operative note and positive ascitic fluid cultures. Antibiotics were determined to be adequate for the causative pathogens but overly broad in retrospect given that both cultured organisms were susceptible to narrower-spectrum antibiotics (eg, ceftriaxone) and he improved clinically on the narrow regimen. This case is an example of a patient who received guideline- and clinically appropriate care in the ED that was also, in retrospect, overly broad due to use of an empiric antipseudomonal β-lactam. A male patient in his 60s with history of polysubstance use disorder, hepatitis C, and asthma presented from home with shortness of breath and cough productive of brown sputum. He was afebrile and hemodynamically stable in the ED but had worsening hypoxemia requiring intubation and mechanical ventilation. He developed hypotension and required vasopressors after intubation. He was treated with cefepime and doxycycline in the ED. Workup was notable for a sputum culture that grew moderate *Streptococcus pneumoniae* and few MSSA. An extended respiratory viral panel was negative. His antibiotics were narrowed to ceftriaxone. The patient clinically improved, was extubated, and eventually discharged. He did not suffer any antibiotic-associated harms. Adjudicated as definite bacterial infection based upon clinical syndrome and respiratory culture that grew *Streptococcus pneumoniae* and MSSA. Antibiotics were determined to be adequate but overly broad in retrospect given that both cultured organisms were sensitive to ceftriaxone and he improved on the narrower regimen. A male patient in his 50s with history of poorly controlled DM presented with back pain for 2–3 days and sudden-onset weakness in his lower followed by his upper extremities, which rapidly progressed to diffuse paralysis, respiratory failure, and shock after arrival. He was intubated and mechanically ventilated in the ED. He was afebrile initially but developed fever to 40.4°C later in the ED. His WBC count was 8300/L with 33% bands. He was treated with vancomycin, cefepime, and metronidazole in the ED. Blood cultures were positive within 8 hours for MSSA in 4 of 4 bottles and remained positive on serial blood cultures for 10 days. An infectious diseases consultation initially recommended vancomycin and oxacillin while awaiting culture sensitivities, then recommended oxacillin monotherapy, followed by oxacillin and daptomycin when cultures remained positive. Further workup demonstrated cardiac vegetations and widespread septic emboli affecting the lungs, cervical spine, and bones. He was not felt to be a candidate for surgical intervention given progressive multiorgan failure. The patient's family ultimately decided to focus on his comfort and to minimize further interventions. He died in the hospital. Adjudicated as definite bacterial infection based upon blood cultures growing MSSA with multiple sites of secondary infection. Antibiotics were determined to be adequate based upon organism sensitivities despite the need for a second anti-MSSA agent later in the hospital course. ED antibiotics were adjudicated as overly broad given that the causative pathogen (MSSA) would have been covered by a narrower-spectrum antibiotic such as oxacillin, and therefore empiric anti-MRSA and antipseudomonal β-lactam agents were broader than necessary in retrospect. The patient did develop kidney and liver dysfunctions, but these were deemed more likely related to shock than to the antibiotics he received in the ED, so he was adjudicated as having no antibiotic-associated harms. This case is another example of a patient whose antibiotic regimen in the ED was reasonable given his fulminant shock and multiorgan failure, but which was also, in retrospect, overly broad.
Probable bacterial infection, 123/600 (20.5%): Does not meet criteria for definite infection but has a compatible clinical syndrome AND no clear alternate explanation (or if multiple potential explanations, bacterial infection is most likely) (probability 50%–89%)	A female patient in her 40s with a history of complicated pregnancies, preeclampsia-associated stroke with residual motor deficits >5 years prior to presentation, pulmonary embolism on rivaroxaban, morbid obesity, and obstructive sleep apnea presented to the ED with acute-onset right lower quadrant abdominal pain and vomiting that woke her from sleep, as well as subjective fever and chills, new cough, and shortness of breath. In the ED, her temperature was 38.3°C, she was tachycardic in 110s beats/min, BPs were 90s–100s/60s mm Hg, respiratory rate was 20 breaths/min, and oxygen saturation was 92% on room air. Her WBC count was 14 000/L with 90% neutrophils. Her lactic acid was 2.3 mmol/L and improved to 1.8 mmol/L on recheck. CXR showed a right middle lobe opacity compatible with pneumonia. CT abdomen/pelvis showed no intra-abdominal pathology other than a right ovarian cyst with rupture; of note, lung bases were well imaged through the bottom approximately one-third of lung fields and were unremarkable (no consolidations), including the right middle lobe. She was treated with piperacillin-tazobactam in the ED for possible sepsis due to pneumonia vs intra-abdominal infection and admitted to the medicine floor, where doxycycline was added for possible pelvic inflammatory disease. A gynecology consultation felt the ovarian cyst was likely functional and unrelated to the presentation; they recommended testing for gonorrhea and chlamydia, which were positive and negative, respectively. Microbiology was otherwise notable for 10 000–50 000 mixed organisms on urine culture; blood cultures were negative. Her fever and hypoxemia resolved over 2–3 days and she was discharged with amoxicillin-clavulanic acid to complete a 7-day course for pneumonia. Adjudicated as probable bacterial infection based upon fever, mildly elevated WBC count, possible finding of pneumonia based on CXR, which was not definitive, as well as a positive test for gonorrhea during admission; it was not determined to be definite given that the CXR finding was not corroborated on (nondedicated) CT images, and the positive bacterial test result for gonorrhea did not fit perfectly with her presenting clinical syndrome. Alternative noninfectious explanations were considered, including that the presentation was related to an acutely ruptured ovarian cyst complicated by aspiration pneumonitis, but bacterial infection was felt to be more likely (>50%). Her antibiotics were adjudicated as presumably adequate based upon clinical improvement and overly broad given that she did not have an organism identified that was resistant to first-line agents, nor a history of resistant organisms, nor was an antipseudomonal β-lactam required for her presenting syndrome. A male patient in his 40s with history of IV drug use presented with arm pain. He reported a recent injury at work where his arm was cut by a piece of metal. The area developed erythema and induration with some purulent drainage; he reported unroofing and expressing additional purulent drainage at home. In the ED, he was afebrile and hemodynamically stable. His WBC count was elevated. He was given vancomycin and cephalexin and admitted but left against medical advice with a prescription for a course of oral antibiotics. Blood cultures were negative; a wound culture was not obtained. The patient did not have any immediate or relevant future encounters in the healthcare system. Adjudicated as probable bacterial infection based upon description of purulent drainage from the wound; not definite given no culture or imaging obtained. Antibiotics were adjudicated as adequate based upon presumption of improvement, and were considered not to be overly broad based upon his presenting syndrome (severe skin/soft tissue infection with purulent drainage compatible with MRSA).
Possible but less likely bacterial infection, 110/600 (18.3%): Potentially compatible clinical syndrome and/or cultures, may have received course of antibiotics, but potential alternative diagnosis more likely (including viral infection without bacterial superinfection) (probability 11%–49%)	A male patient in his 80s with history of end-stage liver disease due to alcoholic cirrhosis complicated by known esophageal varices, ascites, previous spontaneous bacterial peritonitis, hepatorenal syndrome, atrial fibrillation not on anticoagulation, and recent admission for influenza complicated by secondary MRSA pneumonia and MRSA bacteremia treated with vancomycin followed by linezolid until 5 days before presentation. He developed acute confusion and increased abdominal girth at rehab without outward signs of bleeding. In the ED, he was afebrile with a WBC count 7300/L. He was initially normotensive (BP 130/60 mm Hg) but became acutely hypotensive (BP 70s/40s mm Hg) and developed rapid ventricular response to his baseline atrial fibrillation (130 beats per minute). He was started on vasopressors. His hemoglobin was 6.6 from baseline ~8, and his lactate was 2.8 mmol/L. A CXR showed low lung volumes with patchy opacities most consistent with atelectasis but possibly reflecting aspiration or recurrent pneumonia. He was treated with vancomycin and cefepime for possible sepsis, as well as with 4 units of pRBCs and 1 unit of platelets, octreotide, and pantoprazole in the ED. He had one episode of melena while in the ED; gastroenterology was consulted and urgent esophagogastroduodenoscopy did not identify active bleeding nor potential culprit lesions. He was admitted to the ICU. Infectious workup was negative including blood cultures, diagnostic paracentesis, urinalysis, influenza/RSV, and MRSA and VRE surveillance swabs. His antibiotics were switched to vancomycin, ceftriaxone, and azithromycin. His pressor requirement initially resolved on HD 2; however, his hypotension recurred on HD 3. This was treated with additional pRBC and platelet transfusions. His antibiotics

Table 1. Continued

Category, No. (%) and Definition	Description of Case
	were continued but not broadened. He developed worsening confusion, which was felt to be multifactorial. The patient changed his goals of care to focus on comfort and died in the hospital on HD 6. An autopsy was not performed. Adjudicated as possible but less likely bacterial infection based upon clear alternative diagnosis (GI bleeding in the setting of end-stage liver disease), which could explain the presentation fully; however, the patient was covered empirically with antibiotics and had a recent definite serious bacterial infection such that the reviewers felt the probability of a concurrent bacterial infection was >10%.
	A female patient in her 80s with history of deep vein thrombosis on warfarin, advanced dementia (bed-bound at baseline), HTN, and squamous cell carcinoma of the face with recent surgical excision 3 days prior presented from her long-term nursing facility with nausea and witnessed brief syncope/transient loss of consciousness without trauma, with spontaneous recovery. In the ED, she was afebrile, heart rate was 80 beats/min, and BP was 84/49 mm Hg. Her lactate was 2.8 mmol/L. Her WBC count was 9700/L (63% neutrophils); labs were otherwise unremarkable except for sodium of 132 mEq/L, which was near her baseline. A head CT and CXR were both normal. Her surgical wound was examined by the surgery team and found to be clean and without signs of infection. A urinalysis showed 11 WBCs and 6 squamous cells. Blood pressure and lactate both improved (1.0 mmol/L) with IV fluids. She was treated with vancomycin and cefepime for possible urosepsis and admitted to general medicine. Blood cultures later grew CoNS in 1 of 4 bottles; repeat cultures were negative. Urine culture grew >100 000 *Escherichia coli*, which was sensitive to cefoxitin and piperacillin-tazobactam but resistant to meropenem, ciprofloxacin, and levofloxacin. Repeat urinalysis via straight catheterization on HD 2 showed 4 WBCs and 21 squamous cells; cultures were no growth. Vancomycin was discontinued after 1 dose; cefepime was continued for a total of 3 days, then discontinued. She remained normotensive despite resumption of her outpatient antihypertensive medications. She was discharged on HD 5 without additional antibiotics. Adjudicated as possible but less likely bacterial infection based upon a potentially compatible clinical syndrome without definitive evidence of infection (blood culture was likely a contaminant, she did not have urinary symptoms, urine culture was poor quality, urinalysis had relatively few WBCs). Dehydration or other noninfectious cause was felt more likely given her rapid improvement with fluid resuscitation and persistent normotension despite short antibiotic course.
	A male patient in his 60s with a history of alcohol use disorder, complicated alcohol withdrawals, COPD, and HTN presented to the ED with abdominal pain and vomiting for 3 months and desire for monitored alcohol detoxification. In the ED, he was afebrile and hemodynamically stable. Labs were notable for a WBC count 13 200/L (80% neutrophils), electrolyte derangements (hypokalemia, hypomagnesemia, hypophosphatemia), normal kidney function, lipase 19 U/L, total bilirubin 1.3 mg/dL, and lactate 3.7 mmol/L. He received IV fluids, with repeat lactate 2.6 mmol/L. CXR was unremarkable. CT head was normal. CT abdomen/pelvis showed mucosal hyperemia and wall thickening of the terminal ileum, cecum, ascending and proximal transverse colon suggestive of possible terminal ileitis/colitis, and a new left lower lobe opacity with cavitation that was not present on CT chest 5 months earlier. He was given vancomycin and cefepime in the ED for possible sepsis related to colitis vs cavitary pneumonia and admitted to medicine. His admission was complicated by an episode of acute altered mental status after receipt of phenobarbital load for alcohol withdrawal, which required ICU transfer. Other workup for infection was negative including negative T-spot, negative sputum cultures for bacteria or mycobacteria, and a lung biopsy that showed resolving infection with negative organism stains. He did not have diarrhea, and no stool studies were sent. He did not receive additional antibiotics during his hospitalization. He was discharged and did not have additional encounters to the same healthcare system. Adjudicated as possible but less likely bacterial infection based upon no definitive evidence of an acute bacterial infection, some inconclusive evidence of colitis on CT and resolved infection on lung biopsy, and a more likely noninfectious explanation for the presentation (abdominal pain, elevated lactate, and metabolic disarray related to chronic heavy alcohol use and reduced oral intake).
Definitely no bacterial infection/highly unlikely, 79/600 (13.2%): Clear alternative diagnosis found and no evidence of bacterial infection (probability ≤10%)	A female patient in her 50s with history notable for systemic lupus erythematosus on chronic prednisone and methotrexate, adrenal insufficiency, and back pain presented for an outpatient procedure and was found to be somnolent and hypotensive, requiring ED transfer. In the ED, she was afebrile, arousable to voice, and had a BP in the 80s/50s mm Hg. Her WBC count was 14 500/L. CXR showed minimal patchy opacities in the bases. Blood cultures were negative. She received vancomycin and cefepime in the ED. Endocrinology was consulted and felt the presentation was consistent with adrenal crisis; she was started on hydrocortisone with rapid resolution of her mental status changes and hypotension. She received 1 additional dose of piperacillin-tazobactam in the hospital and then was discharged without antibiotics. Adjudicated as definitely no bacterial infection, as the presenting altered mental status and hypotension were felt by her care team to be most likely related to adrenal crisis, she had no objective signs of infection beyond mild leukocytosis, and she improved fully without a full course of antibiotics.
	A female patient in her 60s with recent allogeneic stem cell transplant for chronic myelomonocytic leukemia presented from clinic with subjective fevers. Review of systems was negative except for chronic nasal congestion and dry cough, which the patient reported were present at baseline due to seasonal allergies. She had received a dose of granulocyte stimulating factor several hours before onset of subjective fevers. In the ED, her maximum temperature was 37.4°C; all other vital signs were normal. Her WBC count was 5900/L. She received cefepime in the ED and was admitted to oncology where she also received vancomycin and azithromycin. CXR, urinalysis, and respiratory viral culture were all unremarkable. Blood cultures were drawn and were finalized with no growth. She developed diarrhea while in the hospital; *C. difficile* testing was negative, and the diarrhea was felt to be related to GVHD. She was discharged to complete a 5-day course of azithromycin. As an outpatient, she developed liver function test elevations and rash within 90 days, both of which were felt to be related to GVHD and not related to antibiotics. Adjudicated as definitely no bacterial infection, as the presenting subjective fevers were felt by her care team to be most likely related to engraftment of her allogeneic stem cell transplant or receipt of granulocyte stimulating factor and there were no objective signs of infection. All potential antibiotic-associated effects were more likely related to other causes, so she was adjudicated as not suffering antibiotic-associated harm.
	A male patient in his 60s with HIV (x30 years, compliant with antiretroviral therapy, most recent CD4 count >700 cells/mm^3) and remote non-Hodgkin lymphoma with autologous stem cell transplant presented to the ED with fever, cough, sore throat, myalgias, and diarrhea that began a few days prior. In the ED, he was febrile to 38.8°C, normotensive with normal heart rate, and had an oxygen saturation of 96% on room air. CXR was unremarkable, and CT chest was negative. Labs were notable for a WBC count 7800/L, lactate 1.1 mmol/L, procalcitonin 0.09 ng/mL. He received vancomycin, cefepime, and levofloxacin in the ED and was admitted to medicine for fever workup. Infectious disease was consulted; additional infectious workup was negative including blood cultures, urine *Streptococcus* and *Legionella* antigens, and T-spot. An extended respiratory viral panel was obtained and was positive for parainfluenza 3. He was discharged without antibiotics on HD 3. Adjudicated as definitely no bacterial infection given positive test for parainfluenza, which sufficiently explained the patient's presentation, absence of objective evidence of bacterial infection, and clinical improvement without antibiotics.

Abbreviations: BP, blood pressure; CoNS, coagulase-negative staphylococci; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CXR, chest X-ray; DM, diabetes mellitus; ED, emergency department; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GVHD, graft-versus-host disease; HD, hospital day; HIV, human immunodeficiency virus; HTN, hypertension; ICU, intensive care unit; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; pRBCs, packed red blood cells; RSV, respiratory syncytial virus; VRE, vancomycin-resistant enterococci; WBC, white blood cell.

values were transformed into binary variables using clinically relevant cutoffs. Rates of missingness were low; all missing laboratory values were presumed normal except for missing lactate (n = 1), and this record was excluded from analysis. Variable selection was performed based on the corrected quasi-likelihood information criterion using a forward stepwise search algorithm, allowing for inclusion of up to 5 covariates. Robust variance estimates incorporating small-sample adjustment were obtained [27]. These variance estimates were then used to compute 95% confidence intervals (CIs) and *P* values. A sensitivity analysis was performed to examine the association between likelihood of bacterial infection and a composite outcome of death or discharge to hospice. Associations between likelihood of bacterial infection and antibiotic overtreatment on a composite outcome of any antibiotic-associated complications were also evaluated using GEE models. Data preparation and analysis were performed using SAS version 9.4 (2016, Cary, North Carolina) and Stata version 17 (2022, College Station, Texas) software. Reporting of the study adheres to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational research. The study was approved by the institutional review boards of each study site.

RESULTS

Study Cohort, Clinical Characteristics, and Outcomes

Among 46 245 patents treated for suspected sepsis in the ED during the study period, 26 550 (57.4%) received anti-MRSA and/or antipseudomonal β-lactam antibiotics, of whom 600 were randomly selected for review (Figure 1). Median age was 64 (interquartile range [IQR], 51.5–75) years, 329 (54.8%) were male, 418 (69.7%) were non-Hispanic White, and comorbidities were common (median Elixhauser score, 9 [IQR, 1–18]). Median hospital length of stay was 6 (IQR, 4–10) days, 37 of 600 died in hospital (6.2%), and 39 of 600 were discharged to hospice (6.5%) (Table 2). Sepsis was explicitly documented on the differential diagnosis of ED providers for 379 of 600 (63.2%) patients, and sepsis or a bacterial infection was identified as the most likely final diagnosis per ED providers in 521 of 600 (86.6%).

The most common antibiotics administered in the ED were vancomycin (386/600 [64.3%]), cefepime (284/600 [47.3%]), piperacillin-tazobactam (233/600 [38.8%]), and metronidazole (69/600 [11.5%]) (Figure 2). Of 600 patients, 403 (67.2%) received at least 1 anti-MRSA antibiotic and 530 (88.3%) received at least 1 antipseudomonal β-lactam. Median duration of antibiotics (including discharge courses) was 9 (IQR, 5–16) days.

Likelihood of Bacterial Infection in Retrospect

Among the 600 cases, 288 (48.0%) cases were adjudicated as definite bacterial infection, 123 (20.5%) probable bacterial infection, 110 (18.3%) possible but less likely bacterial infection, and 79 (13.2%) definitely no bacterial infection. Twenty-seven of 600 (4.5%) cases were flagged for group discussion as challenging cases. The definite/probable bacterial infection group included more men and had lower Elixhauser mortality scores compared to the less likely/definitely not infected group but were otherwise demographically similar. Compared to the less likely/definitely not infected group, definite/probable infection cases had longer lengths of stay (median, 7 [IQR, 4–10] vs 6 [IQR, 4–9] days) and antibiotic courses (median, 12 [IQR, 8–18] vs 4 [IQR, 2–7] days) (Table 2).

Among patients with definite/probable bacterial infection, the most common sources of infection were urinary (91/411 [22.1%]), skin/soft tissue (83/411 [20.2%]), and pulmonary (76/411 [18.5%]). Causative bacterial organisms were identified in 257 of 411 patients (62.5%), most commonly *Escherichia coli* (56/411 [13.6%]), *S. aureus* (41/411 [10.0%]), *Streptococcus* species (31/411 [7.5%]), and *Klebsiella* species (31/411 [7.5%]) (Supplementary Figure 1). Sixty-one of 256 (23.8%) patients with a causative organism identified required coverage broader than ceftriaxone in retrospect, most commonly for Enterobacterales resistant to ceftriaxone (24/256 [9.4%]) or *Pseudomonas aeruginosa* (17/256 [6.6%]) (Supplementary Table 1 for infection details).

Antibiotic Adequacy in Retrospect

Among patients with definite/probable infection, 377 of 411 (91.7%) received antibiotics that were definitely (237/411 [57.7%]) or presumably (140/411 [34.1%]) adequate against the causative pathogen or syndrome. Of 34 patients who definitely (31/411 [7.5%]) or presumably (3/411 [0.7%]) did not receive adequate antimicrobials, 21 (61.8%) had a causative pathogen resistant to first-line agents, most commonly Enterobacterales resistant to ceftriaxone (10/34 [29.4%]), vancomycin-resistant enterococci (5/34 [14.7%]), or *C. difficile* infection (5/34 [14.7%]) (Supplementary Table 2). The proportions of patients receiving each of the 8 most commonly prescribed intravenous antibiotics in the ED did not differ between those who received adequate versus inadequate antibiotics in retrospect (Supplementary Table 3).

Need for Extended-Spectrum Antibiotics in Retrospect

Empiric anti-MRSA antibiotics were necessary in retrospect in 84 of 403 patients (20.8%) based on presenting syndrome (eg, severe skin/soft tissue infection without positive cultures; 57/84 [67.9%]), resistant gram-positive organisms (22/84 [26.2%]), or documented antibiotic allergies (5/84 [6.0%]). Empiric antipseudomonal β-lactam antibiotics were necessary in 99 of 530 patients (18.7%) based on presenting syndrome (eg, neutropenic fever, 55/99 [55.6%]) or *P. aeruginosa* or other ceftriaxone-resistant organism identified (44/99 [44.4%]). Twenty-two of 411 patients (5.3%) received antipseudomonal

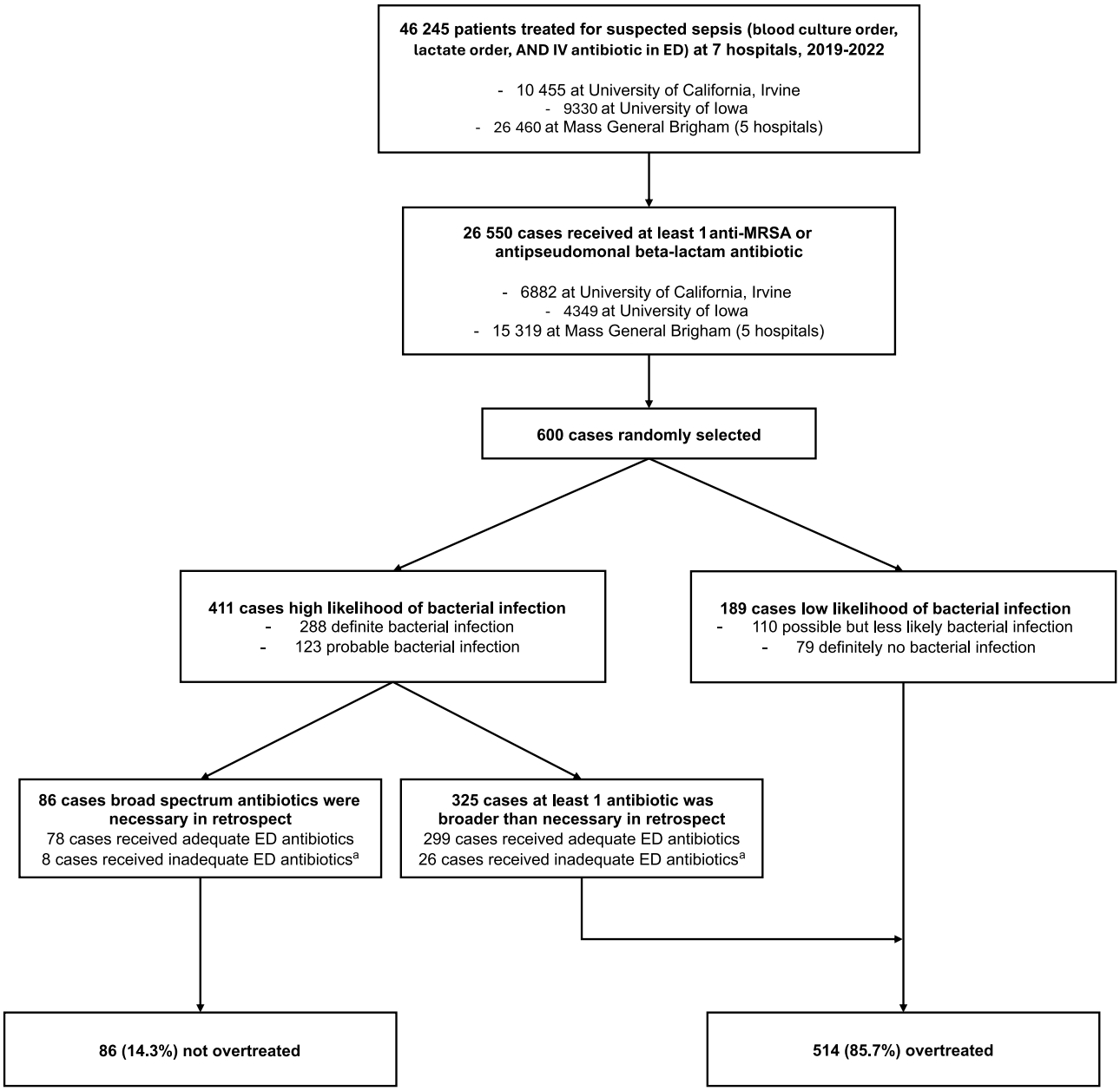

Figure 1. Study flowchart. [a]Antibiotics received in the emergency department either did not have activity against the ultimate causative pathogen in retrospect or, if no causative pathogen was identified, then the antibiotics were judged inadequate based upon presenting syndrome and/or clinical response to prescribed antibiotics; for example, vancomycin and cefepime could be both inadequate and broader than necessary in retrospect in a patient presenting with *Clostridioides difficile* infection (see Supplementary Table 2 for details). Abbreviations: ED, emergency department; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

carbapenems in the ED; in retrospect, these were necessary in 13 of 22 (59.1%) due to isolation of extended-spectrum β-lactamase–type organisms (7/13 [53.8%]), presenting syndrome and prior microbiology (4/13 [30.8%]), or allergies (2/13 [15.4%]). Among patients who received inadequate antibiotics for their presenting pathogen or syndrome, 26 of 34 (76.5%) also received at least 1 antibiotic that was unnecessarily broad in retrospect.

Altogether, 325 of 411 (79.1%) patients adjudicated as definite/probable infection received antibiotics that were unnecessarily broad in retrospect and 189 of 600 patients had less likely or definitely no bacterial infection. Thus, 514 of 600 (86.7%) patients may have been overtreated in retrospect.

Table 2. Demographics and Clinical Characteristics of Included Patients by Post Hoc Likelihood of Bacterial Infection at Time of ED Presentation

Characteristic	All (N = 600 [100%])	Definite/ Probable (n = 411 [68.5%])	Possible but Unlikely/Definitely Not (n = 189 [31.5%])	*P* Value
Age, y, median (IQR)	64 (51.5–75)	64 (50–75)	65 (55–76)	.13
Male sex	329 (54.8)	239 (58.2)	90 (47.6)	.02
Race/ethnicity				.13
Hispanic, any race	89 (14.8)	59 (14.4)	30 (15.9)	
Non-Hispanic Black	35 (5.8)	18 (4.4)	17 (9.0)	
Non-Hispanic White	418 (69.7)	293 (71.3)	125 (66.1)	
Non-Hispanic other (American Indian, Asian, Pacific Islander, ≥2, "other")	58 (9.7)	41 (10.0)	17 (9.0)	
Select comorbidities				
Cancer[a]	167 (27.8)	110 (26.8)	57 (30.2)	.39
Congestive heart failure	101 (16.8)	65 (15.8)	36 (19.1)	.33
Chronic lung disease	120 (20)	78 (19.0)	42 (22.2)	.36
Diabetes[b]	146 (24.3)	96 (23.4)	50 (26.5)	.41
Neurologic disease[c]	93 (15.5)	68 (16.6)	25 (13.2)	.30
Kidney disease[d]	106 (17.7)	70 (17)	36 (19.1)	.55
Obesity	76 (12.7)	52 (12.7)	24 (12.7)	.99
Dementia	39 (6.5)	27 (6.6)	12 (6.4)	.92
Hypertension[e]	280 (46.7)	180 (43.8)	100 (52.9)	.04
Elixhauser 30-d mortality score, median (IQR)	9 (1–18)	8 (0–17)	11 (3–18)	.08
Admission from facility or hospice	83 (13.8)	61 (14.8)	22 (11.6)	.29
Hospitalization last 90 d	265 (44.2)	176 (42.8)	89 (47.1)	.33
Sepsis or bacterial infection leading or most likely diagnosis per ED	521 (86.6)	388 (94.4)	133 (70.4)	<.01
ICU admission (from ED)	133 (22.2)	87 (21.2)	46 (24.3)	.39
Admitting service				.23
Medical	540 (90.0)	364 (88.6)	176 (93.1)	
Surgical	48 (8.0)	38 (9.3)	10 (5.3)	
Other	12 (2.0)	9 (2.1)	3 (1.6)	
Clinical duration, d, median (IQR)				
Length of stay in hospital	6 (4–10)	7 (4–10)	6 (4–9)	<.01
Days of antibiotics in the hospital	5 (3–8)	6 (4–9)	3 (2–6)	<.01
Days of antibiotics in hospital plus discharge	9 (5–16)	12 (8–18)	4 (2–7)	<.01
Days of MRSA antibiotics in the hospital	2 (1–4)	2 (1–4)	1 (0–2)	<.01
Days of antipseudomonal β-lactams in hospital	3 (1–5)	3 (2–5)	2 (1–4)	<.01
Discharge disposition				.14
Home	389 (64.8)	279 (67.9)	110 (58.2)	
In-hospital death	37 (6.2)	20 (4.9)	17 (9.0)	
Hospice	39 (6.5)	25 (6.1)	14 (7.4)	
Non–acute care facility	121 (20.2)	77 (18.7)	44 (23.3)	
Acute care hospital transfer (non-MGB)	10 (1.7)	8 (2)	2 (1.1)	
Patient-directed discharge	4 (0.7)	2 (0.5)	2 (1.1)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ED, emergency department; ICU, intensive care unit; IQR, interquartile range; MGB, Mass General Brigham; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a]Cancer includes codes for leukemia, lymphoma, metastatic cancer, solid tumor without metastasis in situ, solid tumor without metastasis malignant.

[b]Diabetes includes codes for diabetes with chronic complications and diabetes without chronic complications.

[c]Neurologic disease includes codes for neurologic disorders affecting movement, seizures and epilepsy, and other neurologic disorders.

[d]Kidney disease includes codes for renal failure moderate and renal failure severe.

[e]Hypertension includes codes for hypertension complicated and hypertension uncomplicated.

Alternative Etiologies in Patients With Lower Likelihood of Bacterial Infection in Retrospect

Among patients with less likely or definitely no bacterial infection, the most common etiologies were viral, fungal, or parasitic infections (39/189 [20.6%]), hematologic/oncologic disease (25/189 [13.2%]), and gastrointestinal disease (eg, acute liver failure [n = 4], gastrointestinal bleed [n = 4], and acute pancreatitis [n = 3]; 23/189 [12.2%]) (Supplementary Table 4). Twenty-seven of 189 (14.3%) had tests positive for a specific viral, fungal, or parasitic infection without evidence of bacterial coinfection, most commonly severe acute respiratory syndrome coronavirus 2 (n = 10) and influenza (n = 6). Twelve patients had presumed viral infection without positive viral polymerase chain reaction or antigen testing.

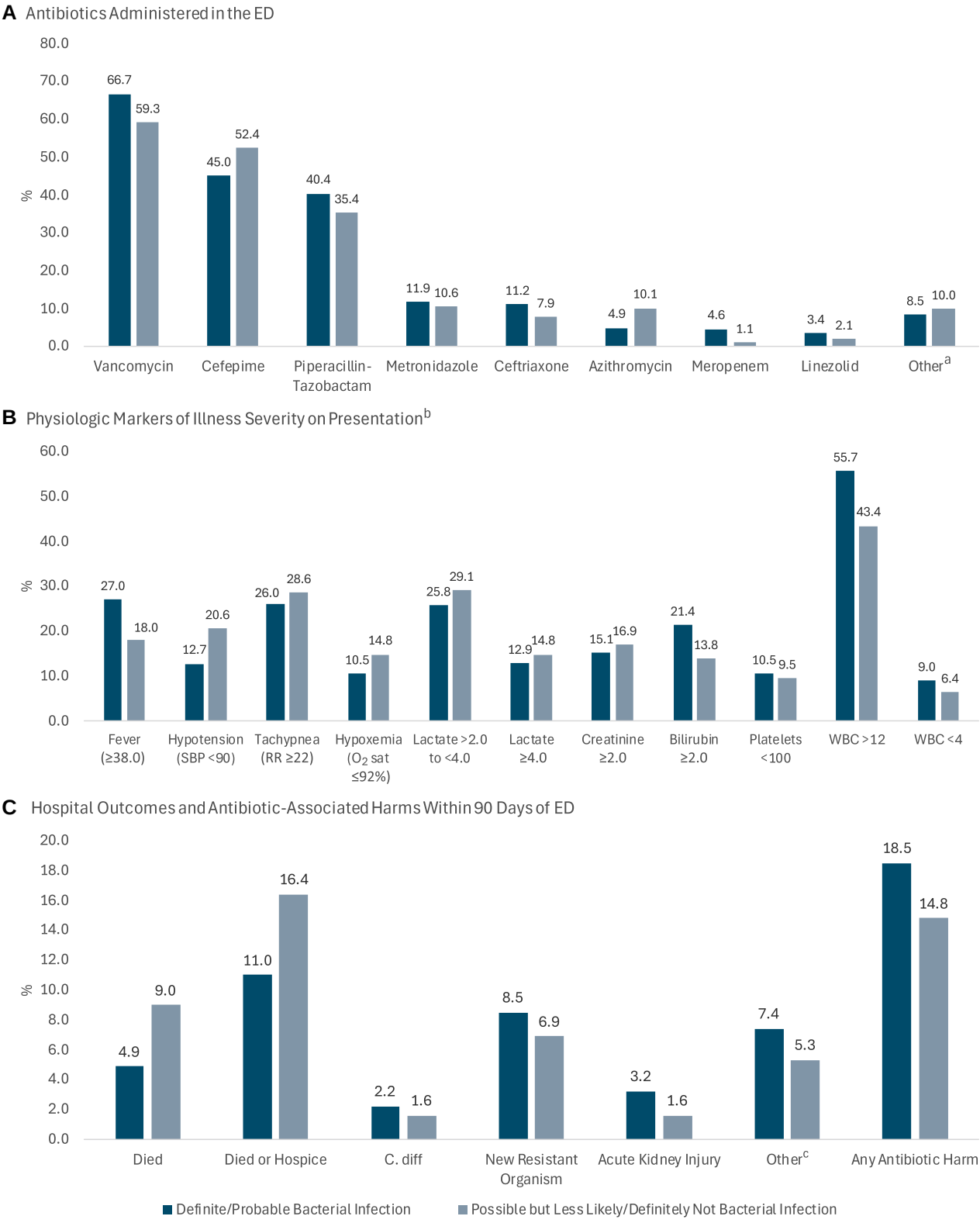

Figure 2. Comparison of antibiotics received in the emergency department (ED) (*A*), severity of illness (*B*), and outcomes by post hoc infection likelihood category (*C*). [a]Other antibiotics administered in the ED: ceftazidime (9), aztreonam (6), clindamycin (6), ampicillin-sulbactam (5), doxycycline (5), levofloxacin (4), ciprofloxacin (3), ertapenem (3), tobramycin (3), cefazolin (2), cefotetan (2), acyclovir (1), ampicillin (1), daptomycin (1), meropenem-vaborbactam (1), rifampin (1), and trimethoprim-sulfamethoxazole (1). [b]Units of measurement: fever (°C), hypotension (mm Hg), tachypnea (breaths/min), hypoxemia (percentage oxygen saturation), lactate (mmol/L), creatinine (mg/dL), bilirubin (mg/dL), platelets (platelets/μL), white blood cell count (cells/μL). [c]Other antibiotic-associated harms within 90 days of ED visit: unspecified other (19), non–*Clostridioides difficile* diarrhea (8), uncomplicated rash (6), cytopenias (4), elevated liver function tests (2), and delirium (2). Abbreviations: C. diff, *Clostridioides difficile*; O_2, oxygen; RR, respiratory rate; SBP, systolic blood pressure; WBC, white blood cell count.

Patient Outcomes

Mortality

In-hospital mortality for patients with less likely/definitely no bacterial infection was 17 of 189 (9.0%) versus 20 of 411 (4.9%) for patients with definite/likely bacterial infection, for a crude odds ratio of 1.93 (95% CI, 1.26–2.95). In adjusted analysis, patients with less likely/definitely no bacterial infection had an aOR for death of 2.25 (95% CI, 1.70–2.98) versus those with definite/likely bacterial infections. Results were similar for the combined outcome of in-hospital death or discharge to hospice (aOR, 1.66 [95% CI, 1.22–2.26]) (see Supplementary Tables 5 and 6 for model results).

Antibiotic-Associated Complications

Overall, 104 of 600 patients (17.3%) developed potential antibiotic-associated complications, most commonly colonization or infection with new resistant organisms (48/600 [8.0%]), acute kidney injury (16/600 [2.7%]), and *C. difficile* infection (12/600 [2.0%]). The overall incidence of potential antibiotic-associated harm was similar in patients with definite/likely bacterial infection (76/411 [18.5%]) versus less likely/definitely no bacterial infection (28/189 [14.8%]; see Supplementary Table 7), for an aOR of 0.79 (95% CI, .60–1.05). The overall incidence of antibiotic-associated harm was also similar in patients deemed in retrospect to have been overtreated (ie infection unlikely or antibiotics overly broad) versus not overtreated (86/514 [16.7%] vs 18/86 [20.9%]), for an aOR 0.70 (95% CI, .37–1.32).

DISCUSSION

Among 600 patients treated with anti-MRSA and/or antipseudomonal antibiotics for suspected sepsis in the EDs of 7 hospitals across 3 states, approximately 1 in 3 were retrospectively adjudicated as unlikely to have had a bacterial infection on presentation (ie, unnecessary coverage). Among the two-thirds who likely did have bacterial infections, antibiotics were broader than necessary in retrospect for 4 of 5 patients (ie, overly broad coverage). All told, 86% of patients may have been overtreated in retrospect. This far outnumbers the 8% of patients who were undertreated with inadequate empiric regimens, most of whom also received unnecessarily broad antibiotics in retrospect.

Our findings support the concern that in the setting of sepsis policies that require rapid administration of broad-spectrum antibiotics, empiric antibiotics for suspected sepsis are often unnecessary or broader than necessary in retrospect. Previous studies have also found that substantial proportions (18%–43%) of patients treated for sepsis in the ED or intensive care unit have low post hoc likelihoods of bacterial infection [19–22]. Others have also reported that 70%–90% of patients treated with broad-spectrum regimens could have been managed with narrower-spectrum regimens [23, 24]. Our study extends these investigations, however, by using detailed chart reviews conducted by experienced clinicians to consider factors that might have influenced antibiotic necessity beyond microbiology results alone, including patients' presenting syndromes, allergies to narrower-spectrum agents, and prior history of multidrug-resistant organisms.

We also found that 17% of patients experienced at least 1 adverse effect potentially attributable to their antibiotics, regardless of whether they were subsequently deemed to have had a bacterial infection, and regardless of whether treatment was overly broad. Our estimate is similar to a previous single-center study that reported 20% of general medical ward patients treated with antibiotics suffered potential antibiotic-related adverse effects [28]. We did note fewer antibiotic adverse effects in patients with unlikely bacterial infections versus those with likely bacterial infections, perhaps because the former were treated with shorter courses. Future interventions to encourage rapid de-escalation may further reduce the risk of antibiotic-associated harms, including development of new multidrug-resistant organisms [29, 30].

Our observation that patients with less likely/no definite bacterial infection were more likely to die than those with definite/likely bacterial infection, even after adjusting for other risk factors, contributes to the mixed literature on this topic [20, 21]. Poor outcomes in this cohort most likely reflect the severe irreversible nature of some of these patients' noninfectious conditions (eg, progressive cancer), but the initial suspicion for sepsis and decision to prioritize antibiotics may also have contributed to delays in diagnosing and/or treating patients' true causative conditions. Antibiotic-associated harms were similar in both groups.

Importantly, by distinguishing between antibiotic coverage that is unnecessary versus overly broad in retrospect, our study helps to disentangle the concept of antibiotic overtreatment and identify actionable responses. Given the adverse consequences of antibiotic delays in true sepsis (particularly septic shock) and the difficulty rapidly ruling out sepsis in some patients, some unnecessary antibiotic administration for potential sepsis in the ED setting is likely unavoidable [7, 31–33]. Future studies may support modified clinical guidelines or the use of rapid diagnostic testing to aid in identifying patients in whom antibiotics may be safely withheld. However, there is likely an immediate opportunity to reduce overly broad antibiotic coverage by refining guidelines for the use of extended-spectrum coverage in the setting of potential sepsis. Computerized clinical decision support tools may prove useful in helping clinicians to prescribe more narrowly by estimating the probability that infection is caused by a multidrug-resistant pathogen, similar to those that have been shown to reduce antibiotic overtreatment in hospitalized patients with urinary tract infection and pneumonia [34, 35].

Our data may also help inform ongoing discussions of the potential risks and benefits of guidelines and policies that incentivize early broad-spectrum antibiotics for all patients with possible sepsis.

Our study has limitations. First, determining the likelihood of bacterial infection can be subjective, especially in patients who have no objective evidence of infection. To mitigate this, we used a structured approach to medical record review with a priori definitions, actively discussed challenging cases, and made final determinations by consensus. Second, we may have undercounted antibiotic-resistant infections that merited broad-spectrum regimens because we focused on recovered pathogens and identifiable syndromes; some patients with negative or pan-susceptible cultures may have had antibiotic-resistant infections at uncultured sites. Conversely, some culture-negative patients adjudicated as requiring anti-MRSA or antipseudomonal therapy based on presenting syndromes or prior history of multidrug-resistant organisms may not actually have been infected with resistant organisms requiring those agents. Third, because our inclusion criteria required receipt of anti-MRSA and/or antipseudomonal β-lactam antibiotics (57.4% of the total population of patients treated for suspected sepsis), our estimates of antibiotic appropriateness and safety are specific to patients treated with extended-spectrum agents and cannot be extrapolated to patients treated with narrower agents. Fourth, it is impossible to be certain whether the adverse events we abstracted were due to patients' initial empiric antibiotics versus subsequent antibiotics or other causes. Fifth, although our study included 7 hospitals (including 3 academic and 4 community hospitals) from 3 geographic regions, our findings may not be generalizable to all hospitals, particularly institutions with higher rates of antimicrobial resistance.

CONCLUSIONS

In retrospect, nearly 1 in 3 patients treated with anti-MRSA and/or antipseudomonal β-lactams in the ED for suspected sepsis were unlikely to have had a bacterial infection, 4 of 5 patients with likely or definite bacterial infections received antibiotics that were overly broad in retrospect based upon their antibiotic sensitivities (in culture-positive infection) or presenting syndrome (in culture-negative infection), and 1 in 6 patients developed antibiotic-associated complications. Cases with low post hoc likelihood of infection were more likely to die compared to those with definite/probable bacterial infection but suffered similar rates of antibiotic-associated harms. These findings have important implications for antibiotic stewardship efforts in the face of ongoing quality improvement and policy initiatives that seek to speed delivery of broad-spectrum antibiotics for patients with suspected sepsis.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The Centers for Disease Control and Prevention (CDC) and the Agency for Healthcare Research and Quality (AHRQ) had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the CDC or AHRQ.

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Potential conflicts of interest. C. R. and M. K. report royalties from UpToDate. D. R. reports consulting fees from Dynamed and Carb-X, unrelated to this research. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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