



Published in final edited form as:

Crit Care Med. 2021 November 01; 49(11): e1144–e1150. doi:10.1097/CCM.0000000000005090.

Likelihood of Bacterial Infection in Patients Treated with Broad-Spectrum Intravenous Antibiotics in the Emergency Department

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Abstract

Objectives—Best practice guidelines and quality metrics recommend immediate antibiotic treatment for all patients with suspected sepsis. However, little is known about how many patients given intravenous antibiotics in the Emergency Department (ED) are ultimately confirmed to have bacterial infection.

Design, Setting, and Patients—We performed a retrospective study of adult patients who presented to four Massachusetts EDs between June 2015 and June 2018 with suspected serious bacterial infection, defined as blood cultures drawn and broad-spectrum intravenous antibiotics administered. Structured medical record reviews were performed on a random sample of 300 cases to determine the post-hoc likelihood of bacterial infection, categorized as definite, likely, unlikely, or definitely none.

Interventions—None

Measurements and Main Results—Among the 300 patients with suspected serious bacterial infections, mean age was 68 years (SD 18), median hospital length-of-stay was 5 days (IQR 3–8), 45 (15%) were admitted directly to ICU, and 14 (5%) died in hospital. Overall, 196 (65%) had definite (n=115, 38%) or likely (n=81, 27%) bacterial infection, while 104 (35%) were unlikely (n=55, 18%) or definitely not infected (n=49, 16%). Antibiotic treatment durations differed by likelihood of infection (median 15 days for definite, 9 for likely, 7 for unlikely, and 3 for definitely not infected). The most frequent post-hoc diagnoses in patients with unlikely or definitely no bacterial infection included viral infections (28%), volume overload or cardiac disease (9%), drug effects (9%) and hypovolemia (7%). The likelihoods of infection were similar in the subset of 96 cases in whom ED providers explicitly documented possible or suspected sepsis and in the 45 patients admitted from the ED to the ICU.

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Conflicts of Interest: None of the authors have any conflicts to declare.

Conclusions—One third of patients empirically treated with broad-spectrum antibiotics in the ED are ultimately diagnosed with non-infectious or viral conditions. These findings underscore the difficulty diagnosing serious infections in the ED and have important implications for guidelines and quality measures that compel immediate empiric antibiotics for all patients with possible sepsis.

Keywords

Sepsis; antibiotics; serious infections; likelihood of infection

Current guidelines recommend immediate administration of broad-spectrum antibiotics to all patients with suspected sepsis. The Surviving Sepsis Campaign recommends antibiotics within one hour of sepsis recognition, while the Centers for Medicare and Medicaid Services (CMS) Severe Sepsis/Septic Shock Early Management Bundle (SEP-1) requires antibiotics within three hours of the first clinical signs of sepsis.[1] In practice, however, it is often unclear if an acutely ill patient is infected, particularly early in their clinical course. Many clinicians and professional organizations have therefore expressed concern over the potential for aggressive time-to-antibiotic targets to drive inappropriate broad-spectrum antibiotic overuse, *Clostridioides difficile* infections, and antibiotic resistance.[2, 3]

There are few data, however, on how often patients treated with empiric antibiotics in the Emergency Department (ED) are ultimately confirmed to have bacterial infections. This information is critical to inform the ongoing national debate about risks versus benefits of aggressive time-to-antibiotic measures. We aimed to determine the post-hoc likelihood of bacterial infection in patients treated with broad-spectrum antibiotics in the ED of 4 hospitals using detailed medical record reviews.

Methods

We performed a retrospective study of patients 18 years presenting between June 2015-June 2018 to the EDs at two academic and two community hospitals in Massachusetts: Brigham and Women's Hospital, Massachusetts General Hospital, Faulkner Hospital, and Newton-Wellesley Hospital. During this time, there was a system-wide sepsis education and quality improvement initiative that included ED triage screening, order sets, and electronic best practice alerts. We identified patients with suspected serious bacterial infections in the ED, defined as blood cultures drawn and the administration of at least one intravenous broad-spectrum antibiotic (3rd generation cephalosporin, carbapenem, beta lactam-beta lactamase inhibitor, monobactam, fluoroquinolone, or MRSA/VRE agent; Supplemental Table 1), using the hospitals' Enterprise Data Warehouse.

Of 8,396 ED encounters which met criteria for suspected serious bacterial infection, we randomly selected 75 cases from each hospital for structured medical record reviews using a standardized data abstraction tool on REDCap. Equal numbers of cases were included from each site to maximize generalizability across academic and community centers. All available notes, medication records, laboratory and microbiology test results, radiology reports and images, and pathology records were reviewed to determine the likelihood of bacterial infection at ED presentation using criteria adapted from prior work.

[4] Specifically, we defined *definite bacterial infection* as a compatible clinical syndrome and pathologic diagnosis of infection, operative recovery of pus, positive cultures from a normally sterile site or a non-sterile site via a high quality sample consistent with infection (e.g. positive urine culture and urinalysis showing white blood cells and no squamous cells), or highly suggestive radiography (e.g. abscess, or non-enhancing consolidation on CT chest). *Likely bacterial infection* was defined as not meeting criteria for definite bacterial infection but having a compatible clinical syndrome responsive to antibiotics and no clear alternate etiology or reason for clinical improvement. *Unlikely bacterial infection* was defined as a clinical syndrome potentially consistent with infection, but with a more likely alternate diagnosis in retrospect and not meeting criteria for definite or likely bacterial infection. Finally, *definitely no bacterial infection* was deemed present if there was a clear non-infectious diagnosis that accounted for the clinical syndrome and no evidence of a concurrent bacterial process. Cultures positive for fungal or parasitic organisms were not considered evidence of bacterial infection.

The first 20 cases were reviewed independently by three physician reviewers (C.S., M.K., and C.R.); interrater reliability for classifying the likelihood of infection on an ordinal scale was high (Krippendorff's alpha = 0.89). These 20 cases were then discussed in person to make a final adjudication for any discrepant classifications and ensure a standardized process moving forward. The remaining 280 cases were reviewed by one physician (C.S.); any cases where classifications were unclear at the time of medical record review (n=47) were subsequently discussed by all three reviewers to achieve consensus.

Descriptive statistics were used to calculate the prevalence of each infection category amongst all study patients, in the subset in whom ED providers explicitly documented suspected or possible sepsis, and in those admitted from ED to ICU. We also calculated the prevalence of explicit infectious presenting symptoms (e.g., fevers, chills, productive cough, dysuria, etc.) [5], non-infectious diagnoses for patients with unlikely/definitely no bacterial infection (based on the single best explanation for each patient's presenting syndrome), ED discharge dispositions, and in-hospital mortality rates. Data analysis was done in Microsoft Excel (version 16.43) and R version 4.0.2 (R Core Team 2020). The study was approved by the Mass General Brigham Institutional Review Board.

Results

The study cohort included 300 patients in whom a blood culture was drawn and intravenous antibiotics administered in the ED, most commonly 3rd generation cephalosporins (n=177, 59.0%), anti-MRSA agents (n=144, 48.0%), and beta-lactam/beta-lactamase inhibitors (n=62, 20.7%). At least one explicit infectious symptom was documented in 248 (82.7%) cases, and an ED provider documented possible or suspected sepsis in 96 (32%) cases.

Overall, 196 (65.3%) had definite or likely bacterial infection (115 [38.3%] definite, 81 [27.0%] likely), while 104 (34.7%) had unlikely or definitely no bacterial infection (55 [18.3%] unlikely, 49 [16.3%] definitely no). Of patients with unlikely/definitely no bacterial infection, 29/104 (27.9%) had likely or proven viral infection. Demographic and clinical

characteristics by likelihood category are in Table 1. Representative examples of cases are shown in Supplemental Table 2.

The duration of antibiotic treatment courses decreased across likelihoods of infection: median 15 days (IQR 8.5–22.5) for definite, 9 (7–14) for likely, 7 (4–9) for unlikely, and 3 (1–7) for definitely no bacterial infection. Age, sex, location prior to ED presentation, and care at academic versus community hospital were similar between patients with definite/likely vs unlikely/definitely no bacterial infections. For patients with definite/likely bacterial infection, sources were genitourinary in 69 (35.0%), respiratory in 48 (24.4%), skin or soft tissue in 45 (22.8%), bacteremia or endovascular in 42 (21.3%), abdominal in 24 (12.2%) and other in 19 (9.6%). The most common non-infectious diagnoses that triggered empiric antibiotics in patients with unlikely/definitely no bacterial infection are shown in Figure 1.

45 of 300 patients (15.0%) were admitted from the ED to ICU and 14 (4.7%) died in-hospital. There was no association between post-hoc likelihood of bacterial infection and in-hospital death ($p=0.74$). Likelihood of infection was similar in the subset of 96 cases with documented suspicion of sepsis compared to the rest of the cohort (definite 42.7%, likely 29.2%, unlikely 16.7%, definitely no bacterial infection 11.5%, $p=.36$) and in those who required ICU admission from the ED (definite 16.5%, likely 8.6%, unlikely 16.4%, definitely no bacterial infection 20.4%, $p=.26$).

Discussion

Approximately one third of patients treated in the ED in whom blood cultures were drawn and broad-spectrum intravenous antibiotics administered were found in retrospect to have a low likelihood of bacterial infection. The most common diagnoses for these patients included viral infections; exacerbations or progression of known chronic illnesses such as cardiac disease, malignancies, or neurocognitive disorders; drug effects; hypovolemia, and acute inflammatory conditions. Patients with explicit infectious symptoms were more likely to have bacterial infections, but bacterial infection was also present in many patients without explicit symptoms. The likelihood of bacterial infection was similar in patients with and without documented suspicion of sepsis and those requiring vs not requiring ICU admission.

Our results are concordant with prior studies that have suggested that 20–40% of patients treated empirically for suspected sepsis are unlikely to have infection.[6–8] Notably, though, most patients in these prior studies were critically ill. Our analysis included a broader range of illness severity and provides updated estimates of the rates of antibiotic overtreatment in the current era of sepsis quality measures.

Our findings that many patients receive unnecessary antibiotics in retrospect should not be viewed as criticism of ED providers' decision-making. All clinicians must make determinations of the necessity for antibiotics with limited available information, particularly in the ED.[9] Furthermore, it is now ingrained in medical culture that some degree of overtreatment is preferable to undertreatment given the potential harms of delayed antibiotics in patients with serious infections, particularly in septic shock. Nonetheless, quantifying rates of overtreatment is an important step in weighing the societal risks and

benefits of this culture, particularly as more data emerge on the deleterious consequences of overtreatment.[10, 11]

The median duration of antibiotics was long for patients with definite or likely infection (15 and 9 days, respectively), but only 20% had bloodstream or endovascular infections. This implies that many infected patients may have received longer courses than indicated. Patients with unlikely or definitely no bacterial infection also received non-trivial antibiotic courses (median 7 and 3 days, respectively). This demonstrates the reality that empiric antibiotics are rarely stopped expeditiously and highlights the potential unintended consequences of overemphasizing immediate treatment for any possibility of serious bacterial infection, particularly when patients are reasonably stable.

Our study has several limitations. First, post-hoc determination of the likelihood of bacterial infection can be subjective. We mitigated this by using a structured approach to medical record review, *a priori* definitions for each likelihood category, and discussion and consensus building for challenging cases. Second, our study was conducted in hospitals with active sepsis quality improvement efforts, potentially limiting the generalizability of our results. However, many U.S. hospitals have implemented similar initiatives in response to the CMS SEP-1 measure. Third, our study does not address whether overtreatment with antibiotics has become more common over time in response to external pressures like SEP-1 and the Surviving Sepsis Campaign Guidelines.[1] It is also unclear to what degree the local and global focus on sepsis has affected clinicians' thresholds to initiate intravenous antibiotics in patients with suspected serious infections but not necessarily explicit signs of sepsis. This is an important topic for future research. Fourth, our study was not designed to assess the consequences of unnecessary treatment for these patients. Numerous other studies, however, have documented the potential adverse effects associated with antibiotic overtreatment.[12] Fifth, we examined patients for whom suspected sepsis was explicitly documented in ED notes, but this may not fully capture all providers' working diagnoses. Finally, severity of illness was relatively low in our study compared to previous investigations but is indicative of the population receiving intravenous antibiotics in contemporary EDs. Notably, however, the likelihood of bacterial infection was similar amongst patients admitted from the ED to the ICU.

Conclusions

One third of patients empirically treated with broad-spectrum antibiotics in the ED are ultimately diagnosed with non-infectious or viral conditions. These findings underscore the difficulty diagnosing serious infections in the ED and have important implications for guidelines and quality measures that require immediate empiric antibiotics for all patients with possible sepsis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Financial Support: This work was funded by the Centers for Disease Control and Prevention (U54CK000484) and National Institutes of Health (T32 Award HL007633-29). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Centers for Disease Control and Prevention or the National Institutes of Health.

Copyright Form Disclosure: Dr. Shappell received funding from a T32 from the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) (HL007633-29); she received support for article research from the NIH. Drs. Klompas, Ochoa, and Rhee's institutions received funding from the Centers for Disease Control and Prevention (CDC), the Agency for Healthcare Research and Quality, and the Massachusetts Department of Public Health. Drs. Klompas and Rhee received funding from UpToDate. Dr. Ochoa disclosed work for hire. Dr. Rhee received support for article research from the CDC.

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ETIOLOGY OF PRESENTATION FOR PATIENTS WITH POST-HOC DETERMINATION OF UNLIKELY OR DEFINITELY NO BACTERIAL INFECTION

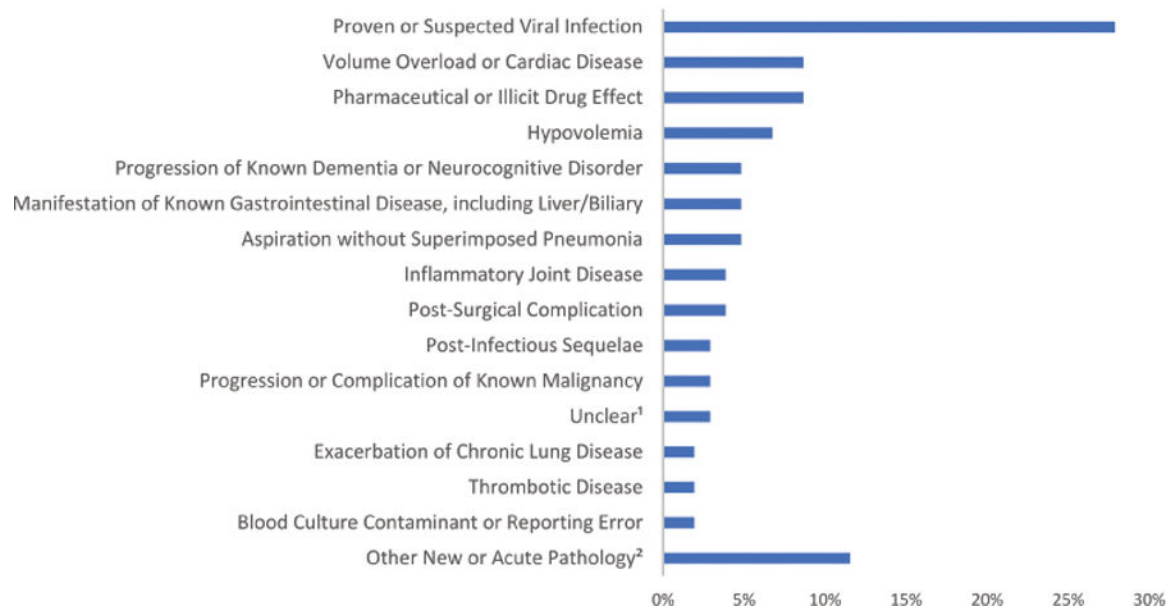


Figure 1. Etiology of Presentation for Patients with Post-Hoc Determination of Unlikely or Definitely No Bacterial Infection

¹**Unclear:** work-up without evidence of bacterial infection and patient made Comfort Measures Only (n=2) or left against medical advice (n=1) before definitive diagnosis could be established.

²**Other New or Acute Pathology (n=1 for each of the following):** angioedema, constipation, dermatitis, gastrointestinal bleeding, hernia, inflammatory pericarditis, new presentation of interstitial lung disease, new presentation of Wilson's Disease, pancreatitis, post-traumatic rhabdomyolysis, renal stones, vasovagal episode.

Table 1.

Characteristics of Study Participants Grouped by Post-Hoc Likelihood of Bacterial Infection

	Definite or Likely	Unlikely or None	Total
Demographics			
Age, years, mean (SD)	67.9 (17.9)	69.4 (17.9)	68.4 (17.9)
Female sex, n (%)	101 (52)	56 (54)	157 (52)
White Race, n (%)	147 (75)	73 (70)	220 (73)
Elixhauser Comorbidities, n (%)			
Cancer	70 (36)	38 (37)	108 (36)
Diabetes	35 (18)	17 (16)	52 (17)
Chronic Lung Disease	25 (13)	12 (12)	37 (12)
Congestive Heart Failure	20 (10)	13 (13)	33 (11)
Renal Failure	23 (12)	10 (10)	33 (11)
Academic (vs Community) Hospital, n (%)	91 (46)	59 (57)	150 (50)
Location Prior to ED, n (%)			
Home	142 (72)	80 (77)	222 (74)
Subacute or Chronic Facility	32 (16)	15 (14)	47 (16)
Clinic	22 (11)	9 (9)	31 (10)
Presence of Explicit Infectious Symptoms¹, n (%)	174 (89)	74 (71)	248 (83)
Chief Complaint, n (%)			
Fever, Chills	45 (23)	14 (13)	59 (20)
Respiratory	27 (14)	30 (29)	57 (19)
Skin or Extremity	31 (16)	10 (10)	41 (14)
Gastrointestinal	23 (12)	15 (14)	38 (13)
Neurologic, including Altered Mental Status	19 (10)	13 (13)	32 (11)
Vague, e.g. fatigue, failure to thrive	18 (9)	11 (11)	29 (10)
Other	20 (10)	9 (9)	29 (10)
Genitourinary	13 (7)	2 (2)	15 (5)
Number of Antimicrobial Classes Administered in ED, n (%)			
1	109 (56)	64 (62)	177 (59)
2	73 (37)	37 (36)	110 (37)
3	14 (7)	3 (3)	17 (6)
Duration of Antibiotics, days, median (IQR)	12 (8, 20)	5.5 (2, 8.25)	9 (5, 16)
ED Discharge Location, n (%)			
Ward	149 (76)	71 (68)	220 (73)
ICU	26 (13)	19 (18)	45 (15)
ED Observation	16 (8)	8 (8)	24 (8)
Home	5 (3)	6 (6)	11 (4)
Positive Blood Culture, n (%) <i>Excluding common contaminant organisms</i>	40 (20)	0 (0)	40 (13)

	Definite or Likely	Unlikely or None	Total
Positive Non-Blood Culture, n (%)	136 (69)	38 (37)	174 (58)
Positive Non-Bacterial Culture, n (%)	4 (2)	9 (9)	13 (4)
Died During Encounter, n (%)	8 (4)	6 (6)	14 (5)

¹Explicit infectious symptoms include objective or subjective fever, chills, or rigors; productive cough; dysuria; skin redness or concern for soft-tissue infection; referral for specific infection diagnosis

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