CHEST

POINT:

Should Broad-Spectrum Antibiotics Be Routinely Administered to All Patients With Sepsis as Soon as Possible? Yes

Margaret Disselkamp, MD
Angel O. Coz Yataco, MD, FCCP
Lexington, KY
Steven Q. Simpson, MD, FCCP
Kansas City, KS

PODCAST

ABBREVIATIONS: CDI = *Clostridium difficile* infections; MDRO = multidrug-resistant organism; NNT = number-needed-to-treat

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] It affects millions of people worldwide annually, with a mortality ranging from 25% to 50%.[2] Significant improvements in patient outcomes have resulted from early identification and appropriate management in the initial hours following development of sepsis. Evidence-based guidelines currently recommend empiric broad-spectrum antibiotics with one or more antimicrobial agents within 1 h for patients with sepsis or septic shock, a strong recommendation with moderate quality of evidence.[3] However, some have voiced concern that this approach may cause indiscriminate administration of antibiotics, leading to unintended short- and long-term consequences. Despite these concerns, we believe that broad-spectrum antibiotics should be administered as soon as possible to all patients with sepsis and septic shock because withholding appropriate antibiotics is associated with a significant increase in mortality. The benefits of early and appropriate antibiotic administration clearly outweigh the risks of withholding such therapy, and we discuss a few important questions to better illustrate this point.

Why Early Antibiotics?

The diagnosis of sepsis and the attribution of organ dysfunction to infection can be challenging. At its earliest presentation, the signs and symptoms of sepsis are not specific; however, this time is when antibiotics can affect the course of illness the most. Unfortunately, after a patient develops the classic signs of sepsis that are evident even to the untrained eye, the delay while waiting for those signs inevitably leads to increased risk of death. Administration of antibiotics for confirmed or suspected pathogens within 1 h of the onset of hypotension is associated with a survival rate of 79.9%. Moreover, every hour of delay is associated with a mean decrease in survival of 7.6%.[4] These findings have been corroborated by contemporary retrospective studies including approximately 85,000 patients.[5,6] The New York State Department of Health data showed that every hour of delay of antibiotics increased the in-hospital mortality by 4%. Furthermore, patients who received antibiotics after 3 h of presentation had a mortality rate 14% higher than those who received antibiotics within 3 h.[5] The mortality benefit of early antibiotic administration is present across the spectrum of sepsis severity. The OR of death per every hour of antibiotic delay has been reported at 1.09 for sepsis, 1.07 for severe sepsis, and 1.14 for septic shock.[6] The delayed administration of broad-spectrum antibiotics not only increases mortality but is also associated with an 8% per hour increased progression of severe sepsis to septic shock.[7]

Why Broad-Spectrum?

Broad-spectrum antibiotic therapy is defined as the typically empiric use of one or more antimicrobial agents with the specific intent of broadening the range of potential pathogens covered, to ensure adequate antimicrobial coverage.[3] Inappropriate initial antimicrobial therapy occurs in about 20% of patients with septic shock and is associated with a fivefold

AFFILIATIONS: From the Lexington Veterans Affairs Medical Center (Dr Disselkamp), University of Kentucky College of Medicine (Dr Coz Yataco), Lexington Veterans Affairs Medical Center; and the Division of Pulmonary and Critical Care, University of Kansas (Dr Simpson).

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CORRESPONDENCE TO: Angel O. Coz Yataco, MD, 1101 Veterans Dr, B-311A, Lexington, KY 40502; e-mail: angel.coz@uky.edu

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reduction in survival.[8] The OR of mortality attributed to inappropriate antibiotic choice is between 3.4 and 8.99. This relationship is robust to adjustment for severity of illness and other potential risk factors. A study reported that the number-needed-to-treat (NNT) with appropriate antibiotic therapy to prevent one patient death is four.[9] This NNT suggests a high ratio of benefit to risk, significantly higher than thrombolytics for acute myocardial infarction (NNT = 43)[10] or acute ischemic stroke (NNT = 10).[11] This approach should not necessarily translate into administering the same combination of antibiotics to every patient with suspected sepsis. However, the selection of more focused antimicrobial use must reflect a thoughtful choice of drugs to cover most potential pathogens. This is especially important in individuals with a history of multidrug-resistant organisms.[9,12]

If Not Early and Broad, What Are the Alternatives?

The alternative to initiating early broad-spectrum antibiotics is to wait for a worsening clinical course or the results of the cultures obtained.[13] The former approach has the potential to increase mortality; the latter approach is risky because negative cultures are common in sepsis, including lethal sepsis. The Australasian Resuscitation In Sepsis Evaluation (ARISE) trial reported a 35.6% and 36.5% rate of negative cultures in the intervention group and usual care cohorts, respectively.[14] Comparable culture-negative sepsis rates (41%) were found in a prospective cohort of > 1,000 patients. Although the mortality in the culture-negative group (35.9%) was lower than in the culture-positive counterpart (44%), the mortality in both groups was high.[15] Moreover, the rate of positive blood cultures in a retrospective cohort of > 170,000 patients with sepsis was only 17%.[16]

What Are the Consequences of Overtreatment?

We cannot advocate for the empiric use of antibiotics without examining the potential consequences of their use. Risks of antibiotics are incurred by both the patient receiving the antibiotic (in the form of increased risk of other infections, allergic reactions, drug interactions, and antibiotic resistance) and other patients (in the form of potential spread of drug-resistant organisms).[17] In 2011, more than 260 million antibiotic prescriptions were dispensed from outpatient pharmacies in the United States, and approximately 30% of these antibiotic prescriptions were unnecessary.[18] In the inpatient setting, as many as 37% of hospitalized patients have been exposed to unnecessary or inappropriate antibiotics.[17] However, one-third of this overuse of antibiotics involves using them for durations longer than recommended, rather than initiating them inappropriately. Rapidly administering the first dose of broad-spectrum antibiotics does not dictate that those antibiotics should be continued for days without constant reassessment of the need to continue them. If further evaluation reveals no evidence for infection, de-escalation or discontinuation of unnecessary antibiotics is critical to reducing the risk of adverse outcomes related to the exposure to the drugs and potential spread of antibiotic resistance.[19]

Although it is important to use antimicrobial agents in veterinary medicine and livestock production, every effort must be made to curtail inappropriate antibiotic use in humans and overuse of antimicrobials in the non-human settings as well. The latter is an important contributing factor to the emergence and persistence of antimicrobial-resistant bacteria in humans.[20] Although recent regulations have decreased the use for production efforts, in 2016, more than 8 million kilograms of medically important antimicrobial agents were sold and distributed in the United States, and 70% of this amount was used for production or production/therapeutic indications, whereas only 30% was used for therapeutic indications.[21]

Summary

Multiple studies have reported increased mortality associated with a delay in the administration of appropriate antibiotics. Ongoing developments in sepsis research will soon allow clinicians to make a prompt sepsis diagnosis with a higher degree of certainty and avoid unnecessary antibiotic administration to patients whose organ dysfunction is ultimately not related to infection. In addition, curtailing the use of antibiotics in non-human arenas may slow the development of antibiotic resistance. Until these changes occur, the risk to a patient of withholding antibiotics in suspected sepsis while awaiting "confirmation" of infection is substantially greater than the risk of promptly administering broad-spectrum antibiotics. The early antibiotic strategy must be coupled with a full commitment to antibiotic stewardship. If we do not use antibiotics for patients with life-threatening organ dysfunction, who are we saving them for?

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COUNTERPOINT:

Should Broad-Spectrum Antibiotics Be Routinely Administered to All Patients With Sepsis as Soon as Possible? No

Jayshil J. Patel, MD
Paul A. Bergl, MD
Milwaukee, WI

PODCAST

Because sepsis represents a dysregulated immune response to infection, antibiotics are a cornerstone to its management. Clinicians face two key practical questions related to antibiotics in suspected sepsis: When should antibiotic(s) be started; and what antibiotics should be given? Several well-conducted observational studies have reported poorer outcomes with delayed antibiotic administration in sepsis.[1-3] In an early retrospective study of > 2,000 hospitalized patients, survival decreased by 7.6% for every hour delay in antibiotic administration from hypotension onset.[1] Similarly, among ED patients with severe sepsis, time to first antimicrobial agent has been associated with increased risk of progression to septic shock.[3] Finally, using prospectively collected data for the Surviving Sepsis Campaign, investigators showed that the probability of death increased with each hour delay in 17,990 patients across 165 ICUs worldwide, irrespective of the number of organ failures.[2] Definition of time zero has varied across studies; nonetheless, the Surviving Sepsis Campaign gave a strong recommendation based on moderate-quality data to administer IV antimicrobial

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine, Medical College of Wisconsin.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Jayshil J. Patel, MD, Division of Pulmonary and Critical Care Medicine, 8701 W Watertown Plank Rd, 8th Floor, HUB for Collaborative Medicine, Milwaukee, WI 53226; e-mail: jpatel2@mcw.edu

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agents as soon as possible after recognition and within 1 h for both sepsis and septic shock.[4]

Likewise, the Surviving Sepsis Campaign provides a strong recommendation based on moderate-quality evidence for empiric broad-spectrum therapy with one or more antimicrobial agents for patients presenting with sepsis or septic shock to cover all likely pathogens, including bacteria and potentially fungi and viruses.[4] The latter recommendation should give clinicians pause. Here, we argue that the strong recommendation for broad-spectrum antibiotics for all patients with sepsis is rooted in low-quality evidence. Second, we assert that prescribing indiscriminate broad-spectrum antibiotics based on weak evidence produces harm. Finally, we suggest strong recommendations based on low-quality evidence have implications for patients, providers, and policy.

The randomized controlled trial is the ideal study design to show harm; however, for reasons that are self-evident, patients cannot be randomized to appropriate vs inappropriate antibiotics.[5] We are left to draw inferences from observational studies in which patients with and without the exposures of interest (appropriate antibiotics) are observed through time to determine whether they experience outcomes of interest. To support use of broad-spectrum antibiotics in sepsis, one could simply argue the alternative (in this case, inappropriate antibiotics) results in greater harms in observational studies. Indeed, the Surviving Sepsis Campaign uses this approach to reinforce the strong recommendation for broad-spectrum antibiotics, but this approach risks crossing the boundaries of logic using flawed premises.[4]

Undoubtedly, patients with sepsis receiving appropriate antibiotics fare better, a finding supported by numerous observational studies. A systematic review and meta-analysis identified 48 prospective observational studies between 1975 and 2008 that compared inappropriate vs appropriate antibiotics in sepsis.[6] The adjusted OR for mortality with inappropriate antibiotics was 2.05 (95% CI, 1.69-2.49). However, the most common definition for appropriate antibiotic was in vitro activity against the ultimate pathogenic organism, and an inappropriate antibiotic lacked in vitro activity against the organism. Using these definitions, comparing appropriate vs inappropriate antibiotics is akin to comparing an appropriate antibiotic against no therapy. Therefore, studies comparing appropriate vs inappropriate antibiotics are primed to yield better outcomes. More importantly, appropriate antibiotic therapy is not synonymous with broad-spectrum empiric antibiotics. Suggesting broad-spectrum antibiotics are justified based on observational data is a non sequitur, but this leap of logic underlies the Surviving Sepsis Campaign recommendations.[4]

What is the potential for harm with broad-spectrum antibiotics for all patients with sepsis? Despite improving mortality, the incidence of sepsis has been increasing over time.[7,8] A 10-year report across 27 academic medical centers found that the incidence of sepsis increased from 12.8 to 18.6 per 1,000 admissions.[7] In another report, the proportion of sepsis admissions nearly doubled, from 4.9% to 9.4%, between 2010 and 2015.[8] Increasing sepsis incidence coupled with a strong recommendation for broad-spectrum antibiotics opens a pathway for more indiscriminate antibiotic use and a greater risk of antibiotic-associated harm. Up to 20% of patients experience adverse drug effects.[9] Overly broad regimens may include multiple antibiotics, thereby having multiplicative effects for adverse reactions. The incidence of clostridial colitis infection has been increasing, and attributable mortality has doubled.[10] Risk factors include broader spectrum antibacterial use and the postulated "herd effect," which suggests patients not receiving antibiotics in regions where antibiotic use is high are at greater risk for clostridial colitis infection than patients not receiving antibiotics in regions where antibiotic use is low.[10-12] Among critically ill patients, antibiotic use has also been linked to the collapse of the commensal microbiome and development of a pathobiome, which serves to sustain inflammation, immunosuppression, and contribute to multiple organ failure.[13]

Strength of recommendations have implications for patients, clinicians, and policy. For patients, a strong recommendation implies most individuals would want the course of action. For clinicians, most individuals should perform the recommended course of action. For policy makers, the recommendation can be adapted as policy in most situations, and adherence to a recommendation can be used as a quality performance indicator. Enhancing quality and outcomes and/or reducing costs are fundamental ways to increase the value of an intervention for adoption into policy. Hence, a strong recommendation ought to follow from a valid and sound evidentiary basis. Low-quality evidence using a comparator equivalent to "no therapy" favoring appropriate antibiotics simply does not justify such an illogical recommendation for broad-spectrum antibiotics. Furthermore, haphazard antibiotic use is

associated with significant harm, which may increase financial and patient-centered costs.

Because randomized controlled trials comparing broad-spectrum antibiotics vs inappropriate antibiotics are unlikely to be conducted, antibiotics in sepsis should be tailored to the individual patient to maximize the likelihood of appropriateness. Empiric antibacterial therapy for patients with sepsis ought to first consider the microbiology of infection and the presence of multidrug-resistant risk factors. A 35-year-old man with no medical history who develops septic shock after a nontraumatic necrotizing soft tissue infection may merit therapy directed only against methicillin-resistant *Staphylococcus aureus* and streptococcal species. On the contrary, a 55-year-old woman post-allogeneic bone marrow transplant with hypoxemia, new pulmonary infiltrates, neutropenia, and hypotension warrants broad-spectrum antibiotics, including an empiric antifungal agent, as the potential microbiology of infection is much wider. Furthermore, local organism prevalence and susceptibility patterns and available resources merit consideration. For instance, the Center for Disease Dynamics, Economics, and Policy data for antibacterial resistance reported a 45% rate of methicillin-resistant *S aureus* among 15,126 isolates tested in the United States, compared with 17% in Canada, 11% in the United Kingdom, and virtually nonexistent in the Netherlands.[14] Implementing a policy to provide broad-spectrum antibiotics for all patients, even in regions of low multidrug-resistant pathogen prevalence, undermines the epidemiologic foundation from which such crucial data are generated.

In conclusion, comparing appropriate vs inappropriate antibiotics is probably the same as comparing appropriate vs no antibiotic at all. Substituting empiric broad-spectrum antibiotics for appropriate antibiotics, which are supported by an imprecise premise, increases the risk for patient harm. Antibiotics in sepsis should be tailored to the patient with consideration given to epidemiologic, microbiologic, and host factors.

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Rebuttal From Drs Disselkamp, Coz Yataco, and Simpson

Margaret Disselkamp, MD
Angel O. Coz Yataco, MD, FCCP
Lexington, KY
Steven Q. Simpson, MD, FCCP
Kansas City, KS

As our colleagues pointed out, the incidence of sepsis has increased and mortality has decreased over time.[1] However, we believe that the timely administration of broad-spectrum antibiotics is largely responsible for the

AFFILIATIONS: From the Lexington Veterans Affairs Medical Center (Dr Disselkamp), University of Kentucky College of Medicine (Dr Coz Yataco), Lexington Veterans Affairs Medical Center; and the Division of Pulmonary and Critical Care, University of Kansas (Dr Simpson).

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CORRESPONDENCE TO: Angel O. Coz Yataco, MD, 1101 Veterans Dr, B-311A, Lexington, KY 40502; e-mail: angel.coz@uky.edu

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progress made thus far, and we do not think it endorses indiscriminate antibiotic use. We agree that comparing appropriate antibiotic therapy vs inappropriate therapy is essentially comparing appropriate antibiotics vs no antibiotics at all, and such study is not possible. However, the evidence presented in the Counterpoint may not fully reflect the benefit of timely appropriate antibiotics, as several of the studies in the meta-analysis[2] included patients who received antibiotics up to 24 h following the diagnosis of sepsis[3,4] or even following microbiologic confirmation.[5] These studies precede the era when prompt administration of antibiotics became the cornerstone of sepsis management, an era when sepsis mortality was much higher.

We advocate early broad-spectrum therapy to cover all likely pathogens, and we are not supporting indiscriminate antibiotic use or the same combination of antibiotics for every patient. This entails a thoughtful approach directed by the patient's history, clinical status, local epidemiologic factors, and other patient characteristics, including chronic underlying diseases, chronic organ failure, medications, indwelling devices, immunosuppression, and recent infections or exposure to other antimicrobial agents.[6] The goal of administering broad-spectrum antibiotics is to give at least one "appropriate" antibiotic before the delay increases the risk of death and to de-escalate as necessary as information becomes available. Until the findings of ongoing research provide clinicians with the ability to promptly diagnose sepsis and promptly identify the causative organisms with higher certainty, we must administer timely broad-spectrum antibiotics to patients with suspected sepsis. The risks of withholding antibiotics clearly outweigh the potential risks of an unnecessary first dose to patients whose organ dysfunction is ultimately not related to infection.

We acknowledge that *Clostridium difficile* infections (CDI) are reason for concern, but we believe that withholding antibiotics in patients with suspected sepsis is not the best strategy to address the problem. Increasing cumulative antibiotic doses raise the risk of CDI, and antibiotic duration > 8 days is associated with a threefold risk of CDI.[7] As we mentioned in our initial argument, durations longer than recommended account for 33% of the antibiotic overuse. Effective antibiotic stewardship should successfully decrease the number and duration of administered antibiotics. The postulated "herd effect" is an interesting concept, and although we agree it is important to curtail antibiotic use, we emphasize that most of the unnecessary antibiotic use can be decreased in the outpatient setting,[8] not in patients with suspected sepsis. Moreover, decreasing antibiotic overuse in the livestock industry can reduce the population's antibiotic exposure.

All microbes have the potential to induce sepsis, depending on their virulence and the host's response to it. However, we underscore that we are not advocating rapid broad-spectrum antibiotics for patients without life-threatening organ dysfunction or without a distinguishable source of infection. We are speaking of patients with a clear infection and established organ dysfunction; that is, patients with sepsis, those with the most to gain—or to lose.

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Rebuttal From Drs Patel and Bergl

Jayshil J. Patel, MD
Paul A. Bergl, MD
Milwaukee, WI

In their defense of early broad-spectrum antibiotics in sepsis, Disselkamp et al[1] present literature supporting appropriate antibiotics in sepsis, outline harmful consequences of waiting to start antibiotics more generally, and suggest that harms from early broad-spectrum antibiotics are avoidable with early de-escalation.

First, we agree that sepsis identification warrants timely, appropriate antibiosis. However, we believe that conflating antibiotic appropriateness with "broad-spectrum" represents a non sequitur, a prevalent example of faulty logic (Table 1) in this contemporary debate. Antibiotic correctness in the cited studies[2-4] was largely determined by in vitro antibiotic activity against recovered pathogens. Disselkamp et al[1] invoke a strawman argument by comparing patients who received appropriate antibiotics vs those who received incorrect antibiotics known ex post facto. Furthermore, the authors cite a retrospective analysis of patients with sepsis and positive blood cultures that reported a number-needed-to-treat of 4 (95% CI, 3.7-4.3) to prevent one death with appropriate antibiotics.[2] Because observational studies determine association, not causation, use of number-needed-to-treat is misleading, particularly because high-risk patients receiving ineffective therapy comprised the comparator group.

Second, Disselkamp et al[1] suggest that awaiting culture results before starting broad-spectrum antibiotics can potentially increase mortality by citing culture-negative sepsis rates in a randomized controlled trial of early goal-directed therapy[3] and two observational studies.[4,5] Culture-negative patients in these studies, however, did not necessarily receive broad-spectrum antibiotics,[3-5] a finding that buttresses the argument for targeted antibiosis. Kumar et al[4] found that culture-negative sepsis comprised 29.0% of their cohort; for these patients, appropriate antibiotics reflected "broadly accepted norms…of the typical pathogens for the clinical syndrome." Patients with culture-negative sepsis actually had decreased odds of inappropriate antibiosis (OR, 0.4233; 95% CI, 0.3578-0.5007) and comparable mortality to all patients with culture-positive sepsis (OR, 0.86; 95% CI, 0.71-1.03). Similarly, Phua et al[5] presumed antibiotic appropriateness in all culture-negative sepsis cases, representing 41.5% of their cohort. Again, mortality was similar between culture-negative cases and culture-positive cases with appropriate therapy (35.9% vs 41.9%; $P = .11$). Although none of these studies detailed antibiotic choices, the findings support antibiotics tailored to the clinical syndrome, at least in patients with culture-negative sepsis.

Finally, we must consider how recommendations for early empiric broad-spectrum antibiotics, which are ostensibly harmless because of rapid de-escalation, contribute to population-level health. Contemporary population-based studies suggest clinicians are choosing broader antibiotic regimens upfront,[6,7] and these trends are associated with increasing multidrug-resistant organism (MDRO) infections.[7] Indication creep and therapeutic inertia may be unintended consequences of early broad-spectrum antibiosis. Furthermore, widespread use of broad-spectrum therapy creates a vicious cycle in which increasingly resistant MDROs prompt clinicians to use even broader agents.

In summary, we cannot justify broad-spectrum therapy for all patients with sepsis. Broad-spectrum antibiotics should be reserved for the patients at risk for antibiotic inappropriateness, such as those susceptible to MDROs.[2] Judging antibiotic appropriateness and sepsis outcomes in retrospect does not reflect the reality of daily practice, nor does it suggest that all patients should receive broad-spectrum agents empirically. Instead, antibiotics targeted to the clinical syndrome, context, and patient characteristics would best balance benefits and risks.

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine, Medical College of Wisconsin.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Jayshil J. Patel, MD, Division of Pulmonary and Critical Care Medicine, 8701 W Watertown Plank Rd, HUB, 8th Floor, Milwaukee, WI 53226; e-mail: jpatel2@mcw.edu

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TABLE 1] Logical Fallacies Invoked in Contemporary Debates About Empiric Antibiotic Spectra

Common Arguments for Early Empiric Broad-Spectrum Antibiotics	Logical Fallacy/Fallacies Invoked With Incorrect Conclusion(s)	Our Words of Caution
Studies show that early appropriate antibiotics are associated with lower mortality in sepsis; ergo, we should prescribe broad-spectrum antibiotics to all patients	Non sequitur: *Appropriate* and *broad-spectrum* can be used interchangeably	These two descriptors are not synonymous. *Appropriate empiric therapy* should consist of targeted antibiosis that considers the unique factors and context of the patient
Multiple studies have confirmed that inappropriate antibiotics increase the risk of death in sepsis	Post hoc (false cause): Incorrectly prescribing antibiotics directly causes deaths from sepsis	Even well-designed retrospective studies may not account for all confounders and thus cannot prove causality. Prospective, randomized controlled trials are required to test the benefits and harms of targeted vs empiric broad-spectrum antibiotics for sepsis
The guidelines recommend broad empiric therapy	Appealing to authority and band-wagoning: Because experts and many clinicians are prescribing broad-spectrum antibiotics, this approach is correct	Clinicians should consider the concordance between the strength of recommendation and level of evidence and the implications of guideline recommendations for patients, providers, and policy
The only alternative to empiric broad-spectrum therapy is to await cultures and other diagnostic data	Strawman and false dilemma: Advocates for more rational antibiotic prescribing do not believe in empiric therapy and/or cannot settle for a middle ground	Clinicians should choose empiric antibiotic spectra based on factors such as likely infectious site, pathogen, local epidemiology, and the balance of benefits and potential harms of therapy
Short courses of broad-spectrum therapy do not incur harm, and the empiric regimen can always be narrowed later	Anecdote and argument to moderation: Clinicians routinely consider and feel comfortable narrowing therapy when patients clinically improve. Starting broad and narrowing later is a fair compromise in the face of uncertainty	Population-based data suggest clinicians are opting for broader spectrum antibiotics.[6,7] No study has addressed how often empiric broad-spectrum therapy is narrowed in actual practice

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