Narrowing the Focus:

Optimizing Antibiotic Spectrum to Improve Patient Outcomes

CIDRAP

Acknowledgements

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Executive Summary

Unnecessary broad-spectrum antibiotic (BSA) use is a persistent challenge. However, there are numerous opportunities to enhance prescribing to minimize harm, improve patient outcomes, and combat antimicrobial resistance (AMR). This evidence review highlights the risks associated with BSAs, including microbiome disruption, organ toxicity, increased healthcare costs, longer hospital stays, and higher mortality rates. The summary emphasizes the importance of informed prescribing decisions based on diagnostic testing, patient risk factors, and local epidemiology.

Key Insights

- **Risks of BSAs**: While BSAs are essential in some cases, their use is linked to multiple adverse outcomes such as *Clostridioides difficile* infections, multidrug-resistant organisms (MDROs), and compromised treatment success for primary conditions like cancer and organ transplants.
- **Role of diagnostics**: Rapid molecular diagnostics provide opportunities to reduce unnecessary BSA use by enabling targeted therapy and early de-escalation.
- **Sepsis management**: Empiric narrow-spectrum antibiotics can be appropriate for select patients with community-onset sepsis, particularly those at low risk for resistant organisms, when combined with careful clinical assessment, rapid diagnostics, and ongoing monitoring.
- **Pediatric challenges**: BSAs are frequently overprescribed for upper respiratory infections (URIs) in children, leading to adverse events, microbiome disruption, and potential chronic illness risks. Guideline-concordant prescribing and rapid diagnostics can mitigate these harms.

Recommendations

- **Target high-volume settings**: Focus stewardship efforts on urgent care and direct-to-consumer telemedicine settings where inappropriate BSA prescribing is prevalent.
- **Enhance diagnostics**: Invest in rapid diagnostic tools paired with appropriate stewardship teams to guide prescribing decisions and reduce empiric BSA use.
- **Increase provider education**: Expand clinician training and audit-feedback programs to improve guideline adherence and reduce risk-averse prescribing.
- **Improve public awareness**: Educate patients on the risks of antibiotics to manage expectations and promote informed decision-making.
- **Standardize metrics**: Develop consistent definitions and metrics for antibiotic spectrum activity to improve research and clinical practice.

Conclusion

Judicious use of BSAs is critical to reducing AMR, improving patient outcomes, and lowering healthcare costs. The document calls for strategic interventions, enhanced diagnostics, and education to optimize antibiotic stewardship across diverse clinical settings. Further research is needed to address unique challenges in low-resource environments and refine prescribing practices globally.

Introduction & Background

Overview of Broad-Spectrum Antibiotics

Broad-spectrum antibiotics (BSAs) are a category of therapeutics active against a variety of bacteria. Clinicians often rely on BSAs to cover a wide range of suspected bacterial pathogens, especially when a specific species has not yet been identified. In action, antibiotics do not have the ability to distinguish between pathogenic and commensal bacteria. Therefore, it is critical to administer the most precise antibiotic available to spare the host microbiome. Additionally, exposure to BSAs, especially if given in the incorrect route, dose, or duration, can also drive the development of multidrug-resistant organisms (MDROs) [1].

In some medical contexts where the bacterial species is unknown but urgent treatment is needed, such as septic shock, BSAs may be the most appropriate therapy to quickly address a decompensating patient or severe infection [2]. When faced with such diagnostic uncertainty, practitioners are under significant pressure to prescribe empirically and view BSAs as a safe, attractive solution [3]. However, this approach can also lead to considerable harm. Informed prescribing decisions that rely on diagnostic testing, local epidemiology, patient risk factors, and best practice guidance is the ideal solution to ensure effective treatment and to reduce the negative sequelae of overly broad prescribing.

Harms Associated with BSAs

All antibiotics are associated with potential treatment complications, including the development of *Clostridioides difficile* infection, development of a MDRO, drug toxicity, and dysfunction in various organs and organ systems [10,11]. The overuse and misuse of any antibiotic, from narrow to broad spectrum, can contribute to these adverse outcomes and require further efforts to improve stewardship. However, BSAs have specifically been linked to adverse effects and negative outcomes in published research:

- **Microbiome dysbiosis**: Dysbiosis of the gut microbiome, specifically as a result of BSA use, has been linked to a potential immunological cascade associated with various chronic diseases [12–13]. Among observational studies in children under 12 months of age, BSA exposure has been associated with increased odds of developing asthma and obesity, which was hypothesized to be mediated by an altered microbiome (See Case Study 2) [14,15].

- **Organ toxicity**: Although almost any organ can be affected by antibiotic-induced toxicity, the liver and kidneys are especially susceptible due to their functions as filtering and metabolic centers [16]. One study based on the US Food and Drug Administration (FDA) Adverse Events Reporting System found that critically ill patients receiving longer courses of certain BSAs (meropenem and piperacillin/tazobactam) can suffer substantial liver injury [17]. Another study reviewing post-surgical outcomes found that patients who received BSAs compared with narrow-spectrum antibiotics (NSAs) had almost three times the risk (adjusted odds ratio [aOR], 2.8) of acute kidney injury [18].
- **Longer hospital stays**: One retrospective cohort study of inpatients with aspiration pneumonia found that the use of BSAs was associated with increased hospital stays (101 vs 63.5 hours) [19]. In another study that included pediatric patients hospitalized with urinary tract infections (UTIs), use of BSAs compared to NSAs resulted in an increased length of stay by 13 hours [20].
- **Increased costs**: A review of data from a large US health system found that adult subjects with suspected community-onset pneumonia (COP) who were treated with broader-spectrum therapy, including anti-MRSA and antipseudomonal agents, experienced higher treatment costs than those who did not, with no benefit in patient outcomes [19]. Another study conducted in Japan compared two treatment groups, one administered very broad-spectrum antibiotics and the other administered a narrower spectrum of antibiotics, among subjects with aspiration pneumonia [21]. Researchers found no difference in 30-day mortality or hospital stay duration, but medical costs were 75.6% higher among those in the broadest-spectrum treatment group. In the previously mentioned study of inpatient pediatric patients with UTIs,

Broad or Narrow Spectrum: Is it that simple?

Nomenclature describing the spectrum of antibiotic activity originated in the 1950s and 1960s to categorize new drugs based on their relative effectiveness compared to established antibiotics like streptomycin and penicillin G [4]. As more antibiotics have entered clinical practice, a growing grey area for classifying the spectrum of action has emerged, with the introduction of terms like “moderate,” “extended,” and “ultra-narrow” spectrum. Many experts define BSAs as those that are reliably effective against both gram-positive and gram-negative bacteria, while narrow-spectrum antibiotics (NSAs) are only effective against gram-positive or gram-negative bacteria [5]. The terms “broad” and “narrow” can be more clearly used when comparing two agents, but blanket classification is highly variable by source.

When reviewing literature on the topic of antibiotic spectrum, it is critical to understand that not all researchers rely on standardized definitions of “broad-spectrum”. Across the research, industry, and clinical landscape, the following terms have been used to describe an antibiotic’s spectrum:

- Range of activity by genus/species
- Anti-MRSA (methicillin-resistant *Staphylococcus aureus*) and/or anti-pseudomonal activity
- Anaerobic activity
- “Adequate” empiric coverage for the pathogen eventually identified
- Relative susceptibility [6]
- Intracellular activity
- “Gut-sparing” [7]
- Systemic/nonsystemic activity
- Greater antibiotic “intensity” [8]
- Intrinsic pathogenicity [9]

use of NSAs compared with BSAs in an adjusted model resulted in a 19.8% decrease in treatment costs [20].

- **Impact on outcomes for treatment of cancer and organ transplant**: BSAs can compromise the effectiveness of treatment and health outcomes for patients' primary conditions, such as cancer or organ failure. In a retrospective cohort study of advanced cancer patients, BSAs were associated with reduced cancer treatment efficacy in patients treated with immune checkpoint inhibitors—specifically, lower treatment response rate, longer time to response, and shorter progression-free survival [22]. Notably, NSA use did not decrease immune checkpoint treatment efficacy. Authors suggest the outcomes are related to disturbances in the intestinal microbe community by BSAs. Outcomes for transplant recipients are also impacted by antibiotic use, with data showing that loss of healthy microbial diversity is associated with poor outcomes and increased mortality in transplant recipients [23]. In a retrospective study of allogeneic hematopoietic stem-cell transplantation patients, those who received early BSAs were more likely to experience graft-versus-host disease-related mortality compared with patients receiving narrower agents [24]. Additionally, solid-organ and stem-cell transplant recipients are at higher risk for carbapenemase-producing Enterobacterales (CRE) colonization associated with gut dysbiosis caused by extended courses of BSAs combined with altered immunocompetence [25].
- **Mortality**: Multiple studies support that overly broad antibiotics can be associated with increased mortality. In a study assessing a range of BSA-associated outcomes in COP patients, researchers found that the use of guideline-discordant, overly broad antibiotics (those with anti-MRSA and antipseudomonal activity, specifically) was significantly associated with increased risk of mortality (OR, 3.8) [19]. A retrospective multicenter cohort study of patients hospitalized with pneumonia found that anti-MRSA coverage was typically unnecessary and resulted in significantly increased mortality compared with standard therapy alone (aOR, 1.4) [26]. Even in the case of sepsis, in which BSAs are often touted to have a great benefit, a cohort study of hospitalized patients with culture-proven community-onset sepsis found that unnecessarily broad antibiotics were associated with an increased risk of mortality (OR, 1.22) [27]. More information on this study, including associations between BSAs and sepsis outcomes, can be found below in Case Study 1.

Perception and Use of BSAs: Prescribers and the Public

Research on the knowledge, attitudes, and practices of prescribers and the public regarding BSAs reveals persistent misconceptions and highlights the pressure faced by clinicians when addressing both patient severity of illness and "customer" satisfaction. Prescribers report misconceptions about BSA efficacy, with many believing that BSAs lead to better cure rates [28,29]. Despite awareness of potential adverse events, practitioners often select BSAs during the empiric treatment phase, especially in high-pressure situations like night shifts, or when patients present as particularly ill [30]. These findings point to the complex relationship between prescriber practices, patient satisfaction, and the broader challenge of combating AMR while providing appropriate patient care. The growing concern over rising AMR underscores the tension between perceived immediate benefits and long-term risks.

BSA use in the United States varies by patient demographics and provider characteristics. Patients most likely to receive BSAs include those with comorbidities, those under two years of age or over 65 years of age, those living in the American South, and those with private insurance [31–33]. Although many clinical

guidelines promote the use of narrower-spectrum agents, guideline-discordant prescribing commonly results in unnecessarily broad antibiotics [29,33].

Telemedicine also presents unique barriers to appropriate prescribing, including lack of established provider-patient relationship, inadequate medical record access, limited physical examinations, and reduced diagnostic capability [35]. A review of encounters for acute respiratory tract infections (RTIs) in California compared antibiotic prescribing in telemedicine vs. physician offices. While adjusted rates of prescribing any antibiotic were similar between groups, telemedicine providers were more likely to prescribe a BSA (86% vs. 56%) [34]. Since its widespread adoption during the COVID-19 pandemic, telemedicine quality has improved, including its use of stewardship best practices, but still represents a setting for continued improvement [35]. More work is needed to ensure that the quality of a patient's care is consistent across all clinical settings and diagnoses.

Role of Diagnostics to Improve Care and Outcomes

Timely and reliable diagnostic information is critical for directing patient care, improving clinical outcomes, and reducing medical costs, particularly through targeted antibiotic therapy. Rapid molecular diagnostics, including polymerase chain reaction (PCR)-based assays and syndromic panels, have demonstrated an ability to reduce inappropriate antibiotic use. For example, multiplex PCR systems for respiratory pathogens can distinguish between viral and bacterial pathogens within hours, enabling rapid de-escalation or avoidance of antibiotics altogether [36–38]. In a UK hospital analysis, comprehensive molecular testing was found to provide enough information to allow for a de-escalation in the number and/or spectrum of antibiotics prescribed to 77% of study patients [39]. Improved detection of pathogens leading to early de-escalation from BSAs reduces unnecessary antibiotic use and minimizes the risk of adverse clinical outcomes. Point-of-care (POC) diagnostics can also play an important role in reducing BSA use, especially in outpatient and emergency settings. Biomarker tests such as procalcitonin (PCT) assays may also help to guide initiation of empiric antibiotics and expedite de-escalation across multiple infection types [40,41].

An often-overlooked aspect of the impact of improved diagnostics on antibiotic stewardship is the efficiency of laboratory-to-clinician communication, particularly surrounding the timely relay of positive culture results and antibiotic susceptibility data. Delays in communicating actionable diagnostic results, especially outside of normal laboratory operating hours, can prolong the use of empiric BSAs, increasing resistance selection pressure and potentially worsening patient outcomes. Implementing 24/7 real-time notification platforms has been shown to significantly accelerate the time to de-escalation and appropriate antibiotic coverage [42–44].

Case Studies

The overarching literature underscores that the inappropriate use of BSAs can result in adverse patient outcomes. To explore this issue with greater depth and nuance, the following case studies highlight specific challenges and opportunities for enhancing diagnostic and antibiotic stewardship across different patient populations and clinical settings. Case Study 1: Community-Onset Sepsis in Adults, illustrates the complex balance clinicians must strike between the urgency of initiating treatment and the appropriateness of antibiotic selection in patients with suspected bloodstream infections. Case Study 2: Pediatric Upper Respiratory Infections in Outpatient Settings, provides insights on the volume of BSAs prescribed to children and identifies opportunities to improve stewardship and patient outcomes.

Case Study 1: Community-Onset Sepsis in Adults

Key Insights

- Patients admitted to the hospital with community-onset sepsis are increasingly being prescribed BSAs, often due to Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) guidelines, despite the rarity of resistant organisms.
- Empiric BSA prescribing increases the risk of mortality, length of stay, and subsequent sepsis within 90 days.
- Recent studies support initiating empiric narrow-spectrum versus broad-spectrum antibiotic therapy (including anti-MRSA and antipseudomonal antibiotics) in low-risk infections with clinical and epidemiological monitoring.
- De-escalation is a strategy to narrow antibiotic prescribing and reduce the negative impact of BSAs. While still infrequent among adults with suspected sepsis, de-escalation can be facilitated through assessment of disease severity and rapid microbial diagnostics.

Sepsis: Treating the Unknown Under Pressure

Suspected community-onset sepsis presents a significant challenge to healthcare systems, necessitating rapid clinical decisions in the face of limited diagnostic information. This urgency often leads to the immediate, empiric administration of BSAs. However, this approach is complicated by the fact that a substantial number of individuals presenting with suspected sepsis may ultimately be diagnosed with nonbacterial inflammatory conditions or infections caused by pathogens susceptible to NSAs [45]. This intersection of urgent treatment needs and diagnostic uncertainty has positioned suspected community-onset sepsis as a critical area of study for understanding and optimizing BSA utilization.

The debate surrounding the optimal choice and timing of antibiotics in sepsis is a prominent and ongoing discussion within the medical community, heavily influenced by a complex interplay of epidemiological trends, microbiological data, and individual patient factors. In 2019, the journal *Chest* published a Point / CounterPoint asking, “Should Broad-Spectrum antibiotics be routinely administered to all patients with

sepsis as soon as possible?" [46,47]. Proponents of the affirmative stance argued that the potential benefit of BSAs in reducing mortality, particularly by mitigating the risks of inappropriate initial antibiotic selection or delays in therapy, outweighs the potential harms. They advocated for the careful selection of antibiotics to cover the most likely pathogens, along with a strong commitment to antibiotic stewardship. This approach aims to minimize unnecessary antibiotic use in patients whose organ dysfunction is not infection-related, while awaiting more definitive evidence from ongoing research in sepsis diagnostics and treatment. In contrast, the counterpoint argument proposed that comparing appropriate versus inappropriate antibiotics was an unhelpful characterization of outcomes as BSAs should not be confused with appropriate antibiotics but understood by their overall spectrum of activity. Therefore, the counterpoint authors suggested that antibiotics in sepsis should be specifically prescribed with patient risk factors and microbiologic considerations in mind, rather than choosing therapy that is indiscriminately broad [47].

The Shifting Landscape of Sepsis Prescribing Guidelines

Because of the significant costs and complications of treating sepsis, the US Centers for Medicare & Medicaid Services (CMS) implemented the SEP-1 in 2015. The SEP-1 bundle required BSAs to be administered within 3 hours of onset, and the Surviving Sepsis Campaign's Hour-1 Bundle within 1 hour of onset [48,49]. Current guidelines recommend early empiric treatment with BSAs in suspected sepsis cases because the condition can progress rapidly, leading to tissue damage, organ failure, and death [50]. Observational studies, however, have not found an association between the introduction of the SEP-1 program and a reduction in sepsis-related mortality [51].

Newer research supports that narrower-spectrum prescribing in the empiric period for suspected sepsis can be implemented safely in some patients. Professional organizations are following the literature and are increasingly wary of overly cautious and broad guidelines as more information emerges about their association with limited improvement in patient outcomes. A joint IDSA/ACEP/PIDS/SHEA/SHM/SIPD position paper published in 2023 described concerns with CMS requiring SEP-1 be incorporated into the Hospital Value-Based Purchasing Program [52]. Their concerns were based on multiple studies reporting that SEP-1 implementation since 2015 has led to increased BSA use but not decreased mortality rates. The authors recommend retiring SEP-1 and shifting to sepsis metrics focused on patient outcomes like the electronic clinical quality measure (eCQM) for community-onset sepsis: 30-day mortality. In addition, they suggested coordinating eCQM with the CDC Adult Sepsis Event surveillance to improve patient care outcomes overall.

Like US organizations, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Critically Ill Patients (ESGCIP) also published a clinically oriented review focused on the antimicrobial management of bloodstream infections (BSIs), a common cause of sepsis [53]. They recommended that, for patients with septic shock, antibiotics be administered within the first hour. They acknowledged, however, that antibiotic administration might be able to wait until microbial confirmation of sepsis is identified, as long as the patients are not in shock. The review referenced a study by Hranjec et al. comparing antibiotics started as soon as sepsis was recognized (aggressive approach: median 6 hours from fever to start of antibiotics) versus waiting until microbiological cultures confirmed infection in patients not in shock (conservative approach: median 24 hours from fever to start of antibiotics) [54]. The conservative approach was associated with more appropriate, targeted initial therapy, shorter duration of antibiotics, and lower mortality. The risk of mortality in

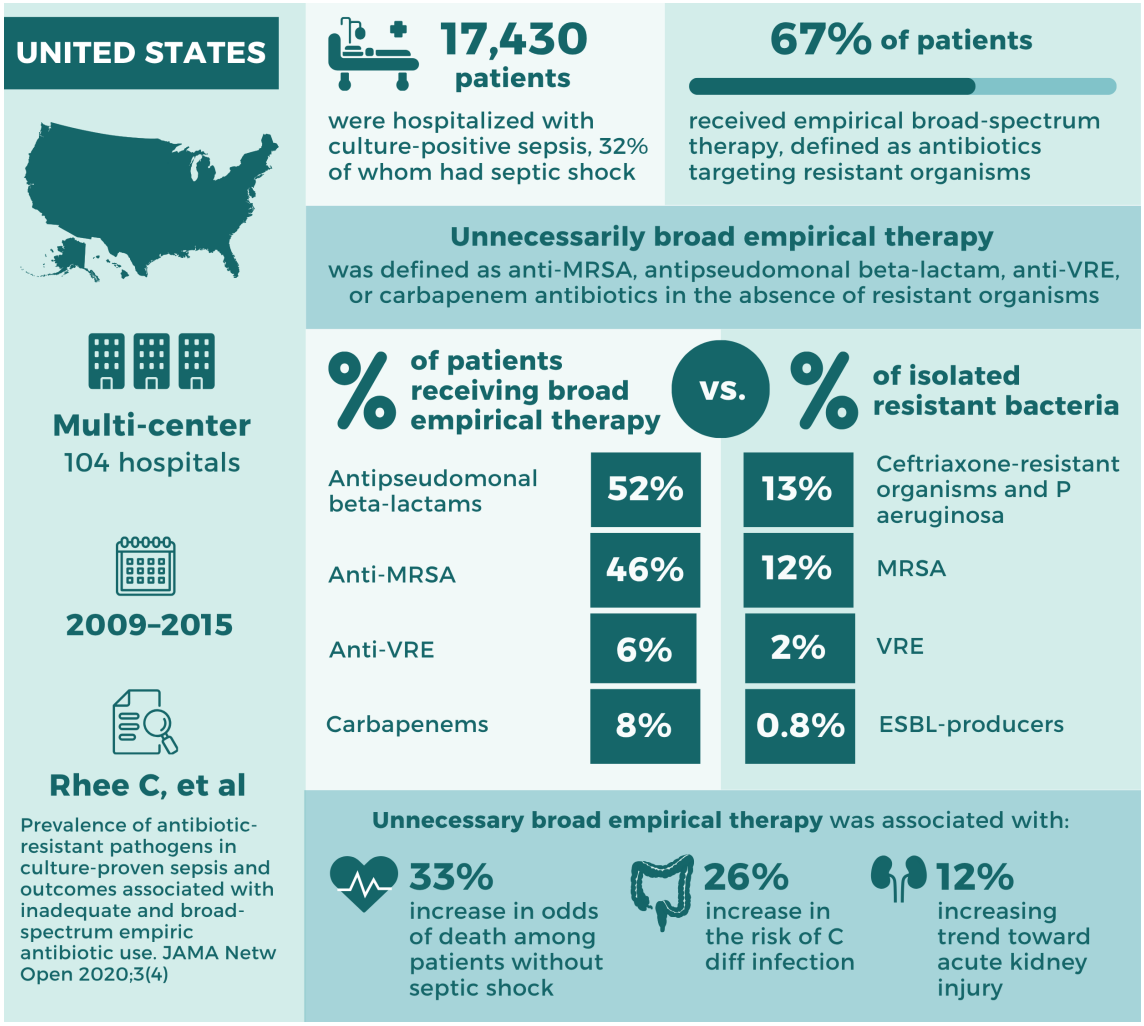
the aggressive therapy group compared to the conservative therapy group was 2.5 fold higher (OR 2.5, 95% confidence interval [CI], 1.5 to 4.0).

ESGCIP recommended that empiric treatment should be targeted to the most likely pathogens with considerations for risk factors such as antibiotic resistance, including epidemiology. They continued with recommending that blood cultures and other specimens be collected without delay before antibiotic administration, so as not to jeopardize microbiological diagnosis and subsequent opportunities for antibiotic stewardship. They also highlighted rapid molecular diagnostic testing to provide timely identification of pathogens and specify resistance patterns from the initial positive blood culture. Finally, they proposed aggressive antibiotic de-escalation and shorter treatments whenever possible to decrease antibiotic-associated harms [54].

Harms Associated with BSAs for Sepsis

While empiric antibiotic management of suspected BSIs and related sepsis is essential, evidence suggests that inappropriately broad empiric therapy can cause harm. These harms can contribute to higher mortality and morbidity, along with increased healthcare costs.

Empiric use of BSAs has been associated with higher mortality among patients with suspected BSIs. Multiple studies have shown that empirical antibiotic use of agents that are either too broad or too narrow can lead to worsened patient outcomes, including mortality [19,26–27,55,56]. A large, multicenter cohort study by Rhee et al. found that in 17,430 patients with culture-positive, community-onset sepsis in US hospitals, unnecessarily broad empiric BSA use led to an increased risk



of in-hospital patient mortality (aOR, 1.22) [27]. Culture-positive sites were primarily urine (52%), blood (40%), and the respiratory tract (17%). The authors found that these patients were frequently "over-covered" by the use of empiric BSAs. Although 67% of cohort patients received coverage for resistant organisms, only 13% of cases had resistant organisms cultured. The most commonly used empirical agents against resistant organisms, namely vancomycin and antipseudomonal beta-lactams, were often unnecessary and did not improve patient outcomes. These findings suggest that overtreatment may paradoxically increase the risk of death, possibly through microbiome disruption, acute drug toxicity, or altered host responses. In the same cohort study, Rhee et al. also found that failure to provide timely, adequate empiric coverage was associated with a similarly increased risk of in-hospital death (aOR, 1.19), highlighting that unnecessary BSAs can cause as much harm as a delay in effective therapy.

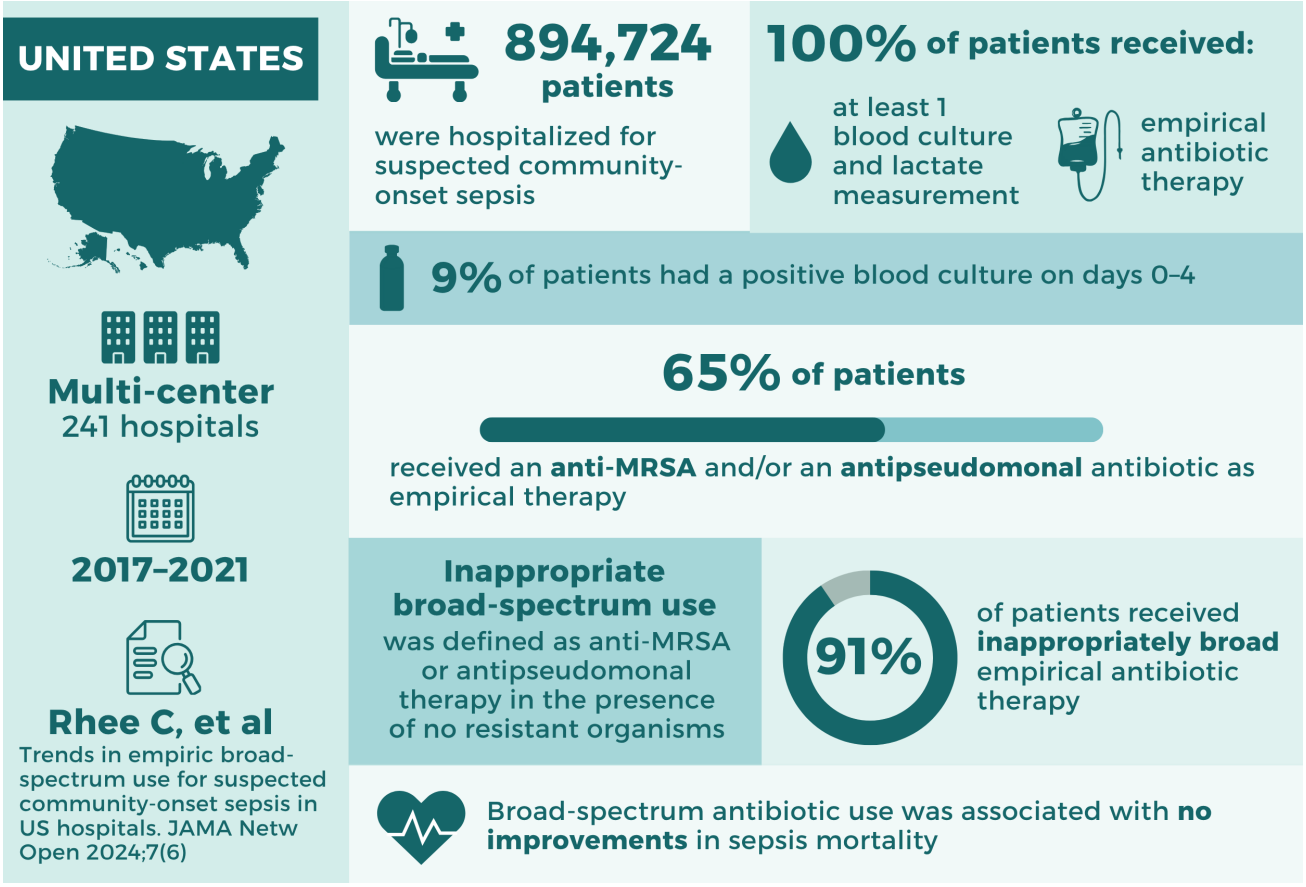
Even short exposures to BSAs in intensive care can result in increased risk of MDROs. In a multicenter cohort study in Japan by Yoshida et al, the authors compared the empiric use of BSAs vs. NSAs on patient outcomes in the ICU. Administering BSAs for 72 hours or longer was associated with an increased risk of detecting a new MDRO (OR, 3.09) compared with NSAs [57]. Additionally, patients in the BSA group had significantly longer duration of antibiotics overall compared with the NSA group (12 vs. 7 days). These results demonstrate the issue of empirically treating patients with suspected sepsis due to traditional cultures and diagnostics requiring 72 hours or more of turnaround time for reliable pathogen identification.

Taking into account local epidemiological data as a companion to diagnostics can guide appropriate empiric antibiotic use, improving patient outcomes and reducing operational costs.

In the Era of Resistance: Is Broader Better?

The threat of resistant infections adds another dimension to empiric antibiotic management of suspected sepsis. However, research suggests that employing a narrower spectrum of empiric antibiotics can be achieved without impacting mortality rates in many cases. In a large cross-sectional study of adults admitted to 241 US hospitals between 2017 and 2021, only 9.6% of patients with suspected community-onset sepsis were identified to have resistant organisms [51]. However, 65% of these patients received anti-MRSA or antipseudomonal therapy, and 34.8% received both, accounting for 50% of all anti-MRSA or antipseudomonal antibiotic prescribing across hospitals. The number of patients with suspected sepsis who were prescribed anti-MRSA or antipseudomonal antibiotics when no resistant organisms were detected increased from 88.0% in 2017 to 91.6% in 2021. This indicates a growing tendency to use BSAs for community-onset sepsis, despite the low prevalence of resistance, highlighting a critical area for antimicrobial stewardship.

Patients admitted to the ICU also present unique prescribing challenges, leading to unnecessarily broad antibiotics during the empiric period. In critically ill patients admitted to a single ICU in Japan, MDROs were unlikely to be detected in the absence of identifiable risk factors such as recent antibiotic exposure (90 days), prolonged hospitalization (> 5 days), invasive procedures (e.g., ventilation, catheterization), and/or a history of MDRO infection or colonization [58]. Patients without these risk factors had only susceptible organisms detected on blood culture, whereas 11% of those in the at-risk group had an MDRO detected on blood culture. Identification of a MDRO was more closely associated with predetermined risk factors than severity of illness alone—a key



consideration for clinicians who may be inclined to prescribe broader therapy based solely on clinical presentation. Despite the lack of MDROs in the patient population without these known risk factors, there were no statistically significant differences in empiric prescribing: anti-MRSA agents were used in 23% of at-risk patients versus 27% in controls, and antipseudomonal agents in 47% versus 36%, respectively. Based on these data, the authors suggested starting empiric narrow-spectrum instead of broad-spectrum antibiotic therapy with clinical and epidemiological monitoring. Together, these data demonstrate the tendency to use BSAs for community-onset sepsis and other critically ill patients, despite the low prevalence of resistance, highlighting a critical area for antimicrobial stewardship.

Delay, Duration, and De-escalation

Evidence suggests that while timely initiation of antimicrobials in sepsis is critical, the belief that faster is always better can be misleading; achieving optimal outcomes requires balancing prompt treatment with careful diagnostic evaluation and antimicrobial stewardship to avoid unnecessary broad-spectrum use.[59,60,61] Delaying or de-escalating BSAs are useful strategies to reduce days of broad-spectrum activity and adverse events. In some clinical subgroups, such as patients with pneumonia and uncomplicated urinary tract infections (uUTIs), treatment with broad-spectrum therapy can be safely delayed while waiting on diagnostic results or changes in clinical status [46]. Delaying BSAs in certain circumstances can effectively reduce the risk of harm, including the potential development of resistant pathogens [46]. Even if a BSA was prescribed empirically, once a pathogen and susceptibilities are identified, de-escalation can protect patient outcomes.

While early empiric BSA treatment may be reasonable in some cases when a bacterial cause of sepsis is unknown, the clinical presentation is more severe, and the patient meets certain risk factors, treatment can be optimized (narrowing, or in some cases broadening, the spectrum of treatment)

Time to targeted, adequate antibiotics is a critical metric for sepsis, rather than relying solely on time to initiate any antibiotic.

by identifying the causative pathogen and associated resistance markers as quickly as possible. Furthermore, a substantial proportion of patients with suspected sepsis are ultimately diagnosed with a viral infection or a non-infectious condition [45,62]. These findings support the idea that rapid empiric prescribing can be safely balanced with a more measured, targeted approach reinforcing the value of diagnostic stewardship and careful risk assessment in guiding initial antibiotic therapy. Providers should take care to regularly reassess the need for BSAs for suspected sepsis.

Similarly, in a retrospective study of 124,577 adults with suspected sepsis across 236 hospitals over 5 years, antibiotic de-escalation was more likely in patients with positive cultures for non-resistant organisms and lower disease severity [63]. These patients were initially treated with anti-MRSA and antipseudomonal antibiotics, but had no resistant bacteria detected. De-escalation was defined as stopping these antibiotics or switching to a narrower-spectrum antibiotic by day four. Antibiotics were de-escalated in 29.5% of patients overall, with therapy narrowed in 21.8% and stopped in 7.7% of patients. De-escalation by day four was associated with lower risk for acute kidney injury, ICU admissions, and in-hospital mortality. These findings underscore the potential benefits of timely de-escalation in improving patient outcomes and reducing unnecessary BSA exposure.

Diagnostic Challenges & Opportunities

While prompt diagnosis and treatment of sepsis are essential to improve outcomes, there remains no single diagnostic tool to reliably identify or exclude bacterial infection, which likely has led to under-recognition (and over-treatment) of viral infections and non-infectious inflammatory states [64]. This contributes to unnecessary and overly broad antibiotic use that is harmful to individuals and populations. The timeframe for traditional diagnostic blood cultures to identify an organism (>72 h) is not acceptable in sepsis treatment timelines and contributes to overly broad empiric prescribing based on diagnostic uncertainty. However, more rapid phenotypic and molecular tests are shifting that diagnostic landscape and opening the possibility of selecting narrower and more precise treatment as early as possible. Additionally, matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (MS) is a rapid diagnostic that is being used to identify bacteria, yeast, and fungi and can reduce the identification of pathogens in less than 24 hours [65].

Although the timely initiation of treatment for sepsis is critical, administering antibiotics, often BSAs, before taking a diagnostic sample can introduce harm by limiting pathogen identification. For example, a prospective study of a clinical cohort of septic patients between 2010 and 2017 compared blood cultures obtained before and during antibiotic therapy [66]. Those who had a blood culture drawn before the onset of antibiotic therapy had a 50.6% positivity rate compared with 27.7% of those who had already begun antibiotics. Furthermore, gram-positive and gram-negative organisms were more frequent by greater than 2.4- and 1.8-fold in blood cultures obtained prior to antibiotics, respectively.

While rapid diagnostic tests (RDTs) are shortening the time to pathogen identification in BSIs, these tools must be combined with

an infectious diseases (ID) consult and antimicrobial stewardship to facilitate the prescribing of targeted therapy. In a study of adult ICU patients with positive blood cultures, a control group (routine laboratory testing) was compared to an intervention group (RDT and immediate ID consultation) [67]. In the intervention group, the pathogen was identified in 84.6% of the patients, and overall adherence to the local antibiotic therapy guidance for sepsis (relying primarily on NSAs) was significantly higher (89.3%) than in the control group (27.8%). Incorporation of RDTs along with ID consultation in the workflow for suspected sepsis ICU patients led to a significantly higher percentage of pathogen-directed therapy and reduced BSAs.

Improvement Opportunities

Improving outcomes in BSI and suspected sepsis patients is dependent on an understanding of epidemiological patterns, host risk factors, and timely and accurate data on causative pathogens and their susceptibilities. Recent advances in diagnostics, AI, and clinical decision-making frameworks can potentially direct empirical therapy, reduce unnecessary BSA use, and improve patient outcomes.

- **Rapid diagnostics play a critical role in the early identification of pathogens and selection of appropriate therapy, reducing the use of unnecessarily broad antibiotics.** Traditional blood cultures remain the diagnostic standard for BSIs, but are limited by low sensitivity, potential for contamination, and long turnaround times, leading to empiric overuse of BSAs. While sensitivity and contamination challenges still remain, rapid diagnostics, including multiplex PCR panels and MALDI-TOF, can offer same-day identification of common BSI pathogens and their resistance genes [70]. These technologies improve not only pathogen identification rates but also support early de-escalation of therapy. For example, rapid molecular tests can rule out MRSA or *Pseudomonas*

Opportunities to Prevent Invasive Infection: *E coli* bacteremia in older adults with UTI

High-burden community-acquired pathogens such as *Escherichia coli*, especially in vulnerable populations (e.g., adults over 65 years of age), present a targeted, high-impact opportunity for optimizing care with prevention and more targeted antibiotics. A systematic review found that *E coli* accounts for 27% of all bacteremia cases in high-income countries, with incidence rising sharply in individuals over the age of 65 (100 to 300 cases per 100,000 person-years) [68]. The most common source of origin of *E coli* bacteremia was the urinary tract (53%), providing preventable or predictable infection pathways in many cases. A recent prospective study similarly found that over 60% of invasive *E coli* cases in hospitalized older adults originated in the urinary tract, with 50% of those cases being community-acquired [69]. Optimization of case identification criteria, combined with timely culture data, allowed for rapid diagnosis and early infection source control. Additionally, up to 30% of the *E coli* isolates collected in the study were resistant to TMP/SMX or fluoroquinolones, reinforcing the need for risk-based empiric therapy and local surveillance. Given the consistent epidemiology of *E coli* bacteremia in these cases, this represents an opportunity for more focused, risk-based empiric treatment.

aeruginosa within hours, allowing for the discontinuation or avoidance of vancomycin and daptomycin or antipseudomonal agents. Emerging metagenomic platforms and host-response biomarkers are also being evaluated for culture-negative sepsis and for early recognition of sepsis. Integrating these tools into early management protocols has the potential to significantly improve the accuracy and timeliness of antibiotic interventions.

- **De-escalation and discontinuation of BSAs are protective for patient outcomes and can be informed by diagnostics.** Antibiotic de-escalation, once pathogen susceptibilities are known, is associated with lower mortality and reduced adverse effects [71]. In a prospective cohort of 628 ICU patients with severe sepsis or septic shock, those who underwent antibiotic de-escalation had significantly lower in-hospital (27.4% vs. 32.5%) and 90-day mortality (28.3% vs. 34.1%) compared with patients whose regimens were unchanged [72]. De-escalation was more common with culture positivity, and when initial therapy was broad, emphasizing the importance of utilizing diagnostics to de-escalate BSA use. These findings were confirmed in a recent meta-analysis of 25 prospective and retrospective studies [73]. The authors found that overall, antibiotic de-escalation was associated with reduced mortality (relative risk [RR], 0.67), shortened hospital length of stay (approximately four days), and lowered antibiotic use. To realize the benefits of de-escalation and discontinuation, quality improvement efforts must consider the post-prescription period, particularly the timing between a prescriber's change in order and a patient receiving adjusted therapy. Efforts should be made to ensure that care is adjusted in a timely manner to spare unnecessary hours or days of antibiotics, especially those that are overly broad-spectrum [74].
- **Healthcare facilities would benefit from strategic programming and quality improvement efforts that target patient outcomes for suspected sepsis, including updating diagnostic workflows.** Sepsis management should balance the urgency of antibiotic initiation with the harms of overuse, as not all patients benefit from immediate BSA therapy. As emphasized by Striche et al., healthcare facilities should stratify patients by case severity, collect diagnostic specimens as early as possible, and reassess therapy within 48 to 72 hours of implementation [75]. Protocols should also include automated electronic health record prompts for de-escalation when supported by susceptibility data or biomarker levels. Incorporating these operational principles can guide care and improve antibiotic stewardship.

Case Study 2: Pediatric Upper Respiratory Infections in Outpatient Settings

Key Points

- Pediatric URIs in outpatient settings result in large amounts of BSA prescribing, often against established guidelines.
- Diagnostics for URIs provide an opportunity to improve targeted prescribing; however, multiple barriers, such as timing, cost, and telemedicine use, remain a challenge.
- Expanding clinician education and audit-and-feedback programs can be effective in reducing the use of BSAs and should be targeted for the settings with the highest volume of inappropriate prescribing, such as urgent care and direct-to-consumer (DTC) telemedicine.

Broad-Spectrum Antibiotics in Outpatient Pediatrics

Outpatient pediatrics is a challenging setting for providers to ensure appropriate prescribing of antibiotics. National data indicate that 21% of outpatient pediatric encounters result in an antibiotic prescription, half of which are broad-spectrum [76]. Prescriptions for BSAs vary by patient characteristics. Compared with those who receive NSAs, subgroups of patients who receive disproportionately high amounts of BSAs include children under 6 years of age, those living in the American South, and patients with private insurance [77]. The considerable volume of antibiotic prescriptions given in these settings is not always warranted. In a national analysis of pediatric data, BSAs were inappropriately prescribed in more than 6 million visits per year [76].

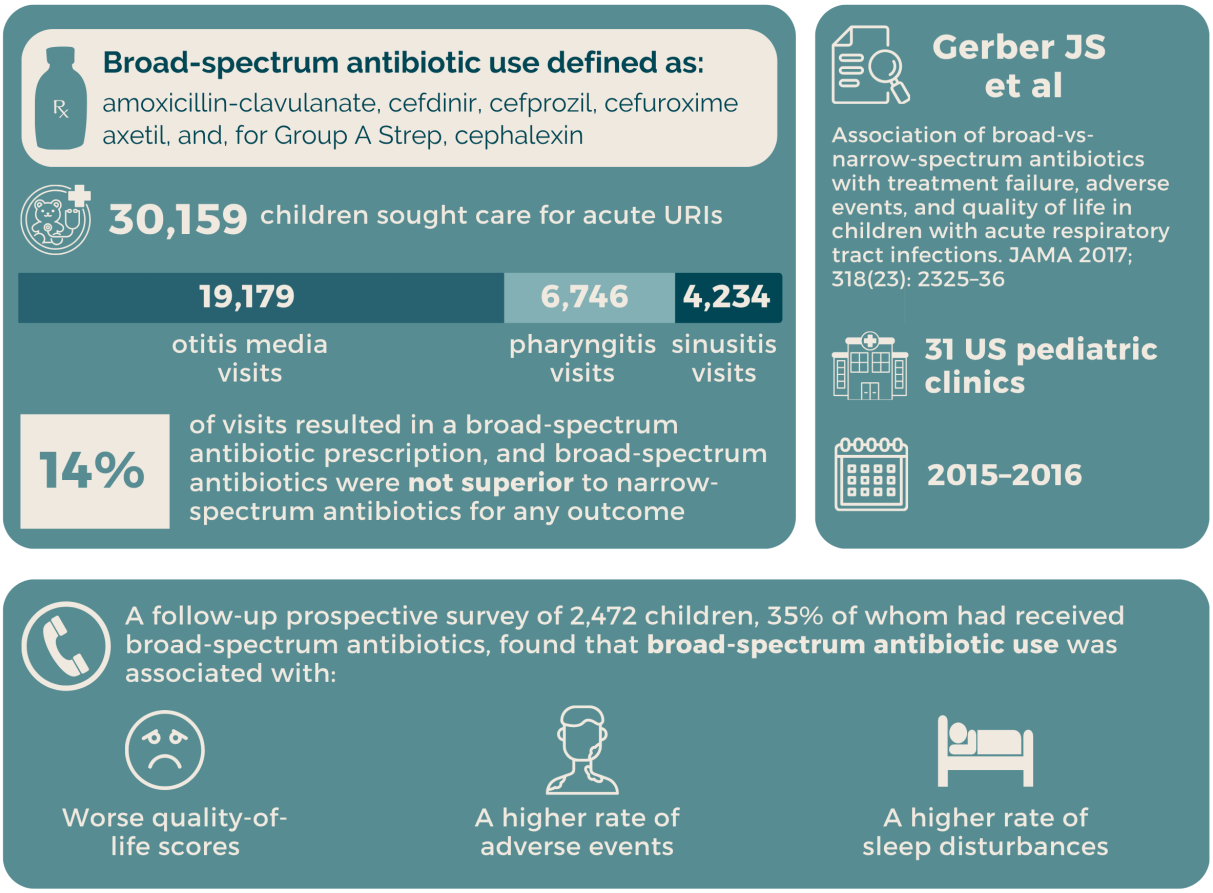
Harms of Broad-Spectrum Antibiotics in Pediatric Patients

Antibiotics are not harmless, especially in young children. Pediatric patients face acute and chronic risks from unwarranted antibiotics:

- **Increased adverse events and emergency department (ED) visits**: BSAs are highly associated with adverse events in children, including diarrhea, vomiting, candidiasis, rash, and allergic reactions,

which may result in a cascade of additional interventions [78]. One study based on nationally representative US surveillance data found that antibiotic-associated adverse events result in significant numbers of ED visits, predominantly in young children [79].

- **Reduced quality of life**: Children receiving BSAs for URIs experienced reduced Pediatric Quality of Life Inventory scores (a standardized tool to describe a child's physical, emotional, social, and school functioning) compared with those who received NSAs [80].
- **Microbiome disruption and chronic illness risk**: Antibiotics, especially BSAs, are known to disrupt the microbiome, potentially leading to a ripple effect of immunological consequences. Research demonstrates that early and repeated exposure to antibiotics in childhood is associated with an increased risk of chronic diseases, including irritable bowel disease, juvenile idiopathic arthritis, asthma, and obesity [81–83]. The risk for developing these chronic conditions was highest for children exposed before one year of age and demonstrated a dose-response relationship. BSAs, in particular, were associated with a higher risk of developing asthma (OR, 1.10) compared with NSAs and were most closely implicated in increased risk for early-persistent asthma [84,85].
- **Increased hospitalization**: BSAs are often used with the assumption that they will cover a wider range of potential pathogens and, therefore, are more likely to resolve infections that could progress in severity. However, BSAs are not a superior alternative to an appropriately targeted antibiotic. In a retrospective cohort of pediatric outpatient visits for pneumonia, the odds of subsequent hospitalization were higher in children (aOR, 1.34) who received BSAs compared with NSAs [86].

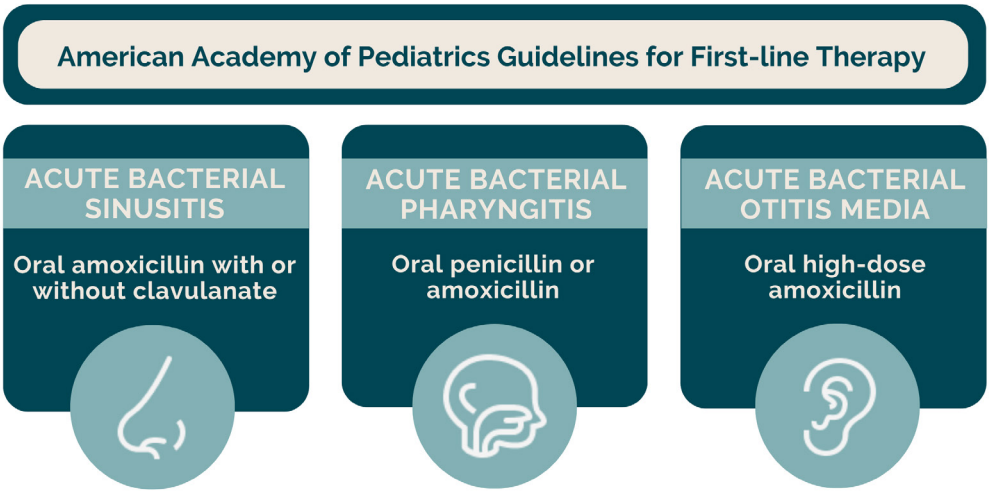


Upper Respiratory Infections: A Diagnostic and Prescribing Challenge

The majority (>70%) of antibiotic prescriptions for children in outpatient settings are for suspected URIs [76]. The three most common bacterial URI diagnoses resulting in BSA prescriptions for children in outpatient settings are acute otitis media (AOM), acute bacterial sinusitis, and group A streptococcal (GAS) pharyngitis [87]. These conditions are a prime target for stewardship interventions to have the highest impact on patient outcomes. Healthcare providers, and increasingly the public, are aware that antibiotics are not an effective therapy for viral infections. Efforts to reduce unnecessary use of antibiotics for viral infections have reduced excess prescribing overall, although more work is needed to close the gap entirely [88]. Similar efforts to improve guideline-concordant prescribing of first-line antibiotics, which typically favor NSAs over BSAs for bacterial infections, could continue the drive toward appropriate and safe care for pediatric patients.

BSAs present an increased risk for adverse events, without consistent evidence of benefit for URIs. Despite the risks to individual patients and the population, BSAs are frequently prescribed for URIs despite the potential harms and the lack of consistent evidence for benefit. A cohort study of pediatric practices by Alzahrani et al. compared the efficacy and safety of broad- vs. narrow-spectrum antibiotics for common URIs. The study found no increase in treatment failure for those receiving NSAs, while the prospective cohort who received BSAs demonstrated a 10-fold increase in patient-reported adverse events [32]. Other studies have demonstrated non-inferiority with NSAs and found increased rates of adverse events for BSAs for pediatric URIs [77].

Antibiotic choice and duration in pediatric outpatient settings are frequently noncompliant with guidelines [89]. Current American Academy of Pediatrics guidelines for URIs in pediatrics do not heavily favor BSA use, but instead promote watchful waiting, use of NSAs like amoxicillin, reserving BSAs only for when they are needed, and prescribing the shortest duration that remains effective [90]. Unfortunately, compliance with these guidelines is inadequate, leading to unnecessary use of BSAs and antibiotics overall. In a cross-sectional study of outpatient pediatric encounters, only 31% of antibiotics were the optimal choice and duration based on current guidelines [91]. URIs, particularly pharyngitis, were the most common culprits resulting in unnecessary antibiotic prescriptions. Cefdinir, a BSA, was the most common sub-optimal choice prescribed for AOM, pharyngitis, and sinusitis. While there is some evidence that the epidemiology of upper respiratory pathogens in children has shifted after the introduction of pneumococcal conjugate vaccines in children,



evidence suggests that first-line NSAs are still appropriate for AOM and do not result in increased treatment failure [92].

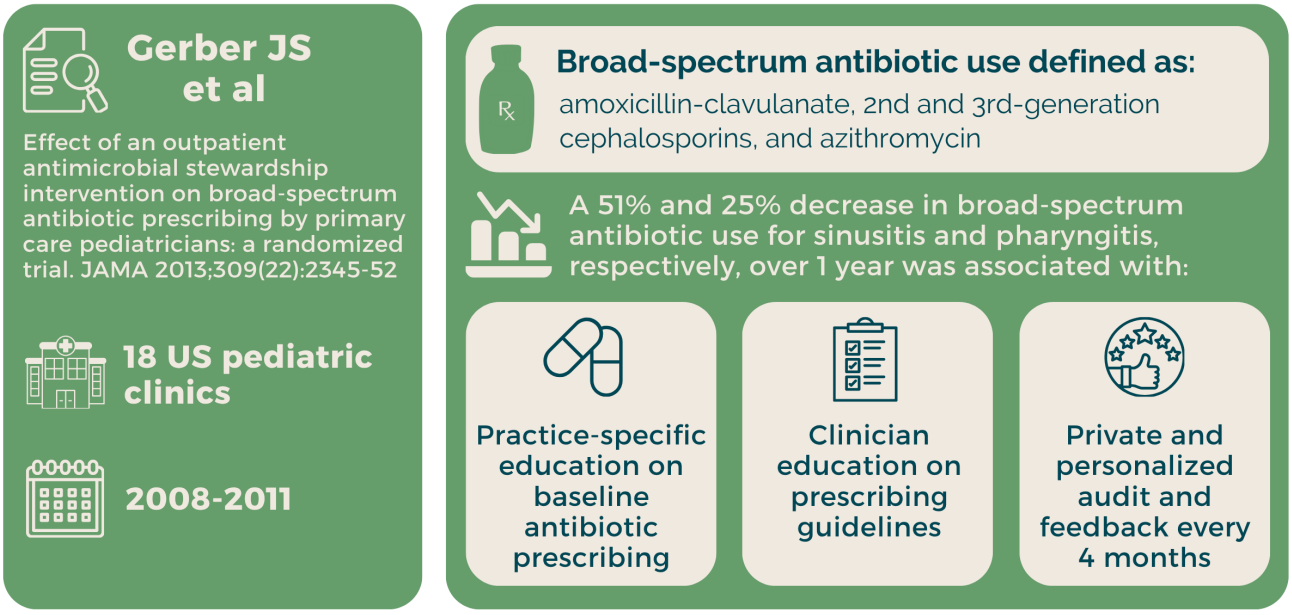
Diagnostic Challenges

Rapid diagnostics have the potential to play a critical role in identifying the presence or absence of viral and bacterial infections. Pathogen identification through diagnostic tools allows prescribers to act on reliable information rather than empiric, "cautious" prescribing, which often results in use of BSAs. However, numerous studies have assessed the impact of implementing various POC diagnostic tools for pediatric outpatient URIs and found little to no benefit in patient outcomes or judicious prescribing behaviors compared with usual care [93–95]. Outpatient pediatric visits for URIs face a unique set of challenges in implementing diagnostic tools to reduce BSA prescribing:

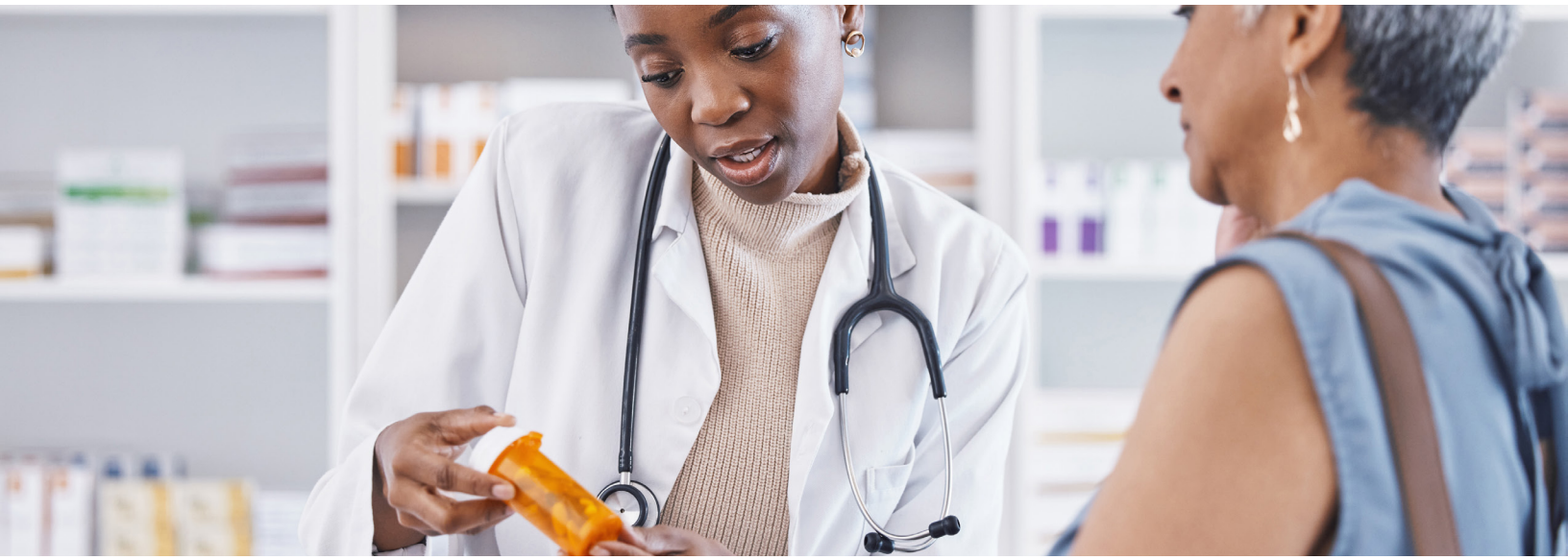
- **Balancing cost, accuracy, and speed**: Outpatient settings rely on rapid turnaround times and POC technologies whose results are expected quickly by patients and providers. Rapid antigen detection tests (RADTs) for acute pharyngitis meet the need for a relatively quick turnaround time; however, the results are far less sensitive and specific compared to PCR testing [96]. Systematic reviews show that POC testing for pediatric URIs can be cost-effective when implemented in concert with stewardship interventions [97]. Included studies demonstrated that if POC diagnostics result in more judicious prescribing, then they are cost-effective overall. However, many of the tests used still surpassed a willingness-to-pay threshold.

Opportunities

- **Focus improvement efforts on settings and diagnoses with the highest volume of unnecessary BSAs.** Prescriptions for AOM and pharyngitis account for the highest volume of total antibiotic prescriptions for pediatric outpatient URIs and represent an important target for intervention [91]. Additionally, inappropriately broad prescribing for pediatric URIs is most concentrated in providers who primarily see adults and in DTC telemedicine [36,98,99]. Structural interventions and educational campaigns should target these settings and providers to maximize impact. While non-pediatricians who see children and adolescents for URIs are more likely to prescribe guideline-discordant antibiotics, there is still considerable room for improvement in pediatricians as well [98].



- **Improving access to rapid molecular diagnostics has the potential to reduce overuse and misuse of antibiotics in pediatric outpatients, including BSAs.** RADTs, as well as concurrent cultures for GAS, are commonly used in outpatient pediatric settings to inform care of URIs. Their utility for guiding antimicrobial therapy, however, is limited [100]. Rapid PCR testing for acute pharyngitis in children has been demonstrated to improve appropriate antibiotic use [96]. In contrast to RADT, rapid molecular technologies result in more sensitive and specific results that lead to more actionable insights and positively affect prescribing outcomes [101]. It is critical to note that the diagnostic tools themselves are not sufficient in addressing the challenge of BSA use and misuse but rely on appropriate utilization and interpretation in the clinical context.
- **Clinician education and feedback can be effective in improving guideline concordance and reducing the use of overly broad antibiotics.** Some antimicrobial stewardship programs (ASPs) that use a multidisciplinary approach of education and audit-and-feedback have proven effective in improving prescribing when providers are engaged [102,103]. In a randomized controlled trial of 25 pediatric primary care clinics, a 1-hour educational session and quarterly audit reports for 1 year resulted in significant drops in unnecessary BSA prescriptions. Overall, prescriptions for BSAs decreased by 12.5% more in the intervention group (26.8% to 14.3%). The impact was greatest for patients with acute sinus infections, for whom BSA prescriptions decreased from approximately 39% to 19% [104]. Interventions in clinical settings are most effective when providers recognize a need for improvement and see value for their patients.



Recommendations

The following recommendations highlight some of the evidence-based interventions known to decrease the initiation and duration of unnecessary BSAs and improve patient outcomes across sub-populations and clinical settings.

- **Prioritize quality improvement efforts in high-volume clinical settings**. While there is room for improvement across all settings, targeting interventions to the locations and populations receiving the greatest quantities of unnecessary BSAs will produce the greatest impact. Urgent care settings, particularly those that are DTC and not associated with a patient's primary care provider, are an expanding source of BSAs for the general population [105]. Multifactorial stewardship interventions that discourage antibiotics for suspected viral infections, prompt clinicians to use first-line NSAs, and require justification for BSAs have proven effective in improving stewardship in these settings without sacrificing patient outcomes or satisfaction [106].
- **Maximize the use of diagnostics to guide prescribing decisions**. In the short term, it can be lower cost to prescribe a BSA "out of caution" rather than use a diagnostic tool. However, there are long-term financial and health harms when prescribing is not data-driven. Providers and patients would benefit from appropriately priced and reimbursed diagnostic tools to maximize their use. Diagnostics are most appropriately used, and most cost-effective, when combined with knowledgeable ASP teams [112]. More data are necessary to quantify the benefits and harms of higher-cost technologies to low-income, uninsured, and underinsured patients, as well as payors and policymakers [113].
- **Increase provider education, tools, and support that highlight that appropriate spectrum prescribing.** Literature shows that prescribers are aware of the threat of AMR and the need for improved stewardship; however, challenges remain in implementing initiatives that change behavior. Research suggests that root causes for overprescribing/misprescribing are linked to risk aversion, action bias, and concerns about patient satisfaction [107]. Education and tools, such as standardized, evidence-based clinical practice and dosing guidelines based on age, along with diagnostic technologies to manage uncertainty in the empiric period, can improve the clinician's ability to prescribe appropriately and with confidence [108].

Additionally, computerized order entry prompts can be an effective means of nudging clinicians towards narrower-spectrum agents [109]. Decision-support tools, including emerging AI capabilities, may help evaluate relevant patient characteristics to maximize empiric prescribing and antibiotic stewardship when paired with appropriate diagnostic and epidemiological data [110,111]. AI decision-making tools hold the promise of helping clinicians avoid both under- and over-treatment, particularly in complex or ambiguous presentations.

- **Enhance public awareness that antibiotics are not harmless.** While public awareness of the importance of antibiotic stewardship has improved in recent years, more work is needed to ensure patients and their caregivers have appropriate expectations when seeking medical care and know what questions to ask their providers [114]. Greater awareness of US FDA warnings, such as the black-box warnings on fluoroquinolones, may aid patients in presenting an informed challenge to a prescription that may require a more considered weighing of potential harms [115,116].
- **Standardize research and quality improvement metrics around spectrum activity**. Research and healthcare quality improvement efforts require reliable and comparable metrics and concept definitions that can be used across the field. Metrics like "days of therapy" are insufficient in describing the details behind antibiotic administration. Additionally, the concept of "broad" or "narrow" spectrum antibiotics is variable across the literature and is often collapsed with terms such as "susceptible" or "adequate," confused with antibiotic class, or based solely on the number of total species covered. Researchers and clinicians would benefit from position papers standardizing and defining these key terms and promoting detailed metrics for research, such as "spectrum scores" and "days of antibiotic spectrum coverage" [117]. Additionally, there is a relative lack of studies that clarify whether prescribing is excessively broad in comparison with studies that assess whether prescribing is broad enough. Studies that clearly assess the former metric will be necessary for an informed change in clinical practice guidelines.

Conclusion

While BSAs are a valuable tool in medicine, it is imperative that prescribers use them appropriately to minimize harm. Judicious use of antibiotics is necessary to reduce the growing threat of AMR, promote the best patient outcomes, and lower healthcare costs. While this analysis highlights the key challenges and opportunities to improve appropriate-spectrum prescribing, further work is needed to make a lasting, global impact on this critical issue.

Acronyms

ADE	adverse drug events
AOM	acute otitis media
aOR	adjusted odds ratio
ASP	antibiotic stewardship program
BSI	bloodstream infection
BSA	broad-spectrum antibiotic
CAP	community-acquired pneumonia
CDC	US Centers for Disease Control and Prevention
CI	confidence interval
CMS	US Centers for Medicare & Medicaid Services
DTC	direct-to-consumer
eCQM	electronic clinical quality measure
ED	emergency department
ICU	intensive care unit
GAS	Group A *Streptococcus*
MALDI-TOF	matrix-assisted laser desorption/ionization time-of-flight
MDRO	multidrug-resistant organism
MRSA	methicillin-resistant *Staphylococcus aureus*
NSA	narrow-spectrum antibiotic
OR	odds ratio
PCR	polymerase chain reaction
PCT	procalcitonin
POC	point of care
RADT	rapid antigen detection test
RDT	rapid diagnostic test
SEP-1	Severe Sepsis and Septic Shock Early Management Bundle
UTI	urinary tract infection
URI/URTI	upper respiratory infection/upper respiratory tract infection

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