Clinical Infectious Diseases Advance Access published April 13, 2016

Clinical Infectious Diseases

IDSA FEATURES

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

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Evidence-based guidelines for implementation and measurement of antibiotic stewardship interventions in inpatient populations including long-term care were prepared by a multidisciplinary expert panel of the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. The panel included clinicians and investigators representing internal medicine, emergency medicine, microbiology, critical care, surgery, epidemiology, pharmacy, and adult and pediatric infectious diseases specialties. These recommendations address the best approaches for antibiotic stewardship programs to influence the optimal use of antibiotics.

Keywords. antibiotic stewardship; antibiotic stewardship programs; antibiotics; implementation.

EXECUTIVE SUMMARY

Antibiotic stewardship has been defined in a consensus statement from the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) as "coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration" [1]. The benefits of antibiotic stewardship include improved patient outcomes, reduced adverse events including *Clostridium difficile* infection (CDI), improvement in rates of antibiotic susceptibilities to targeted antibiotics, and optimization of resource utilization across the continuum of care. IDSA and SHEA strongly believe that antibiotic stewardship programs (ASPs) are best led by infectious disease physicians with additional stewardship training.

Summarized below are the IDSA/SHEA recommendations for implementing an ASP. The expert panel followed a process used in the development of other IDSA guidelines, which included a systematic weighting of the strength of recommendation and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (Figure 1) [2–5]. A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found online in the full text of the guidelines. For the purposes of this guideline, the term antibiotic will be used instead of antimicrobial and should be considered synonymous.

RECOMMENDATIONS FOR IMPLEMENTING AN ANTIBIOTIC STEWARDSHIP PROGRAM

Interventions

I. Does the Use of Preauthorization and/or Prospective Audit and Feedback Interventions by ASPs Improve Antibiotic Utilization and Patient Outcomes?

Recommendation

1. We recommend preauthorization and/or prospective audit and feedback over no such interventions *(strong recommendation, moderate-quality evidence)*.

Received 22 February 2016; accepted 23 February 2016.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant clinician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the clinician in the light of each patient's individual circumstances.

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Clinical Infectious Diseases®

DOI: 10.1093/cid/ciw118

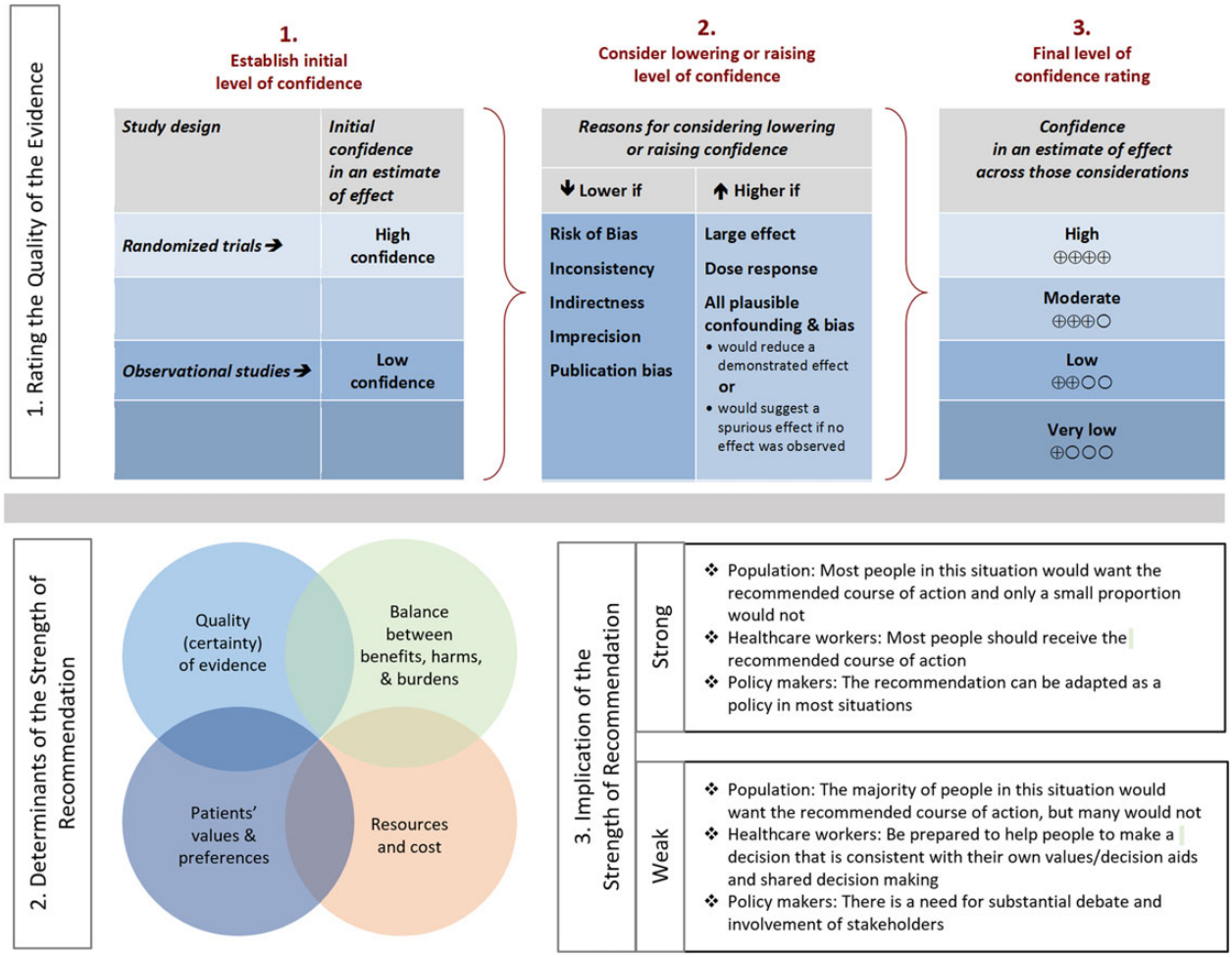

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (unrestricted use of this figure granted by the US GRADE Network).

Comment: Preauthorization and/or prospective audit and feedback improve antibiotic use and are a core component of any stewardship program. Programs should decide whether to include one strategy or a combination of both strategies based on the availability of facility-specific resources for consistent implementation, but some implementation is essential.

II. Is Didactic Education a Useful Antibiotic Stewardship Intervention for Reducing Inappropriate Antibiotic Use?

Recommendation

2. We suggest against relying solely on didactic educational materials for stewardship *(weak recommendation, low-quality evidence)*.

Comment: Passive educational activities, such as lectures or informational pamphlets, should be used to complement other stewardship activities. Academic medical centers and teaching hospitals should integrate education on fundamental antibiotic stewardship principles into their preclinical and clinical curricula.

III. Should ASPs Develop and Implement Facility-Specic Clinical Practice Guidelines for Common Infectious Diseases Syndromes to Improve Antibiotic Utilization and Patient Outcomes?

Recommendation

3. We suggest ASPs develop facility-specific clinical practice guidelines coupled with a dissemination and implementation strategy *(weak recommendation, low-quality evidence)*.

Comment: Facility-specific clinical practice guidelines and algorithms can be an effective way to standardize prescribing practices based on local epidemiology. ASPs should develop those guidelines, when feasible, for common infectious diseases syndromes. In addition, ASPs should be involved in writing clinical pathways, guidelines, and order sets that address antibiotic use and are developed within other departments at their facility.

IV. Should ASPs Implement Interventions to Improve Antibiotic Use and Clinical Outcomes That Target Patients With Specic Infectious Diseases Syndromes?

Recommendation

4. We suggest ASPs implement interventions to improve antibiotic use and clinical outcomes that target patients with specific infectious diseases syndromes *(weak recommendation, low-quality evidence)*.

   Comment: ASP interventions for patients with specific infectious diseases syndromes can be an effective way to improve prescribing because the message can be focused, clinical guidelines and algorithms reinforced, and sustainability improved. ASPs should regularly evaluate areas for which targeted interventions are needed and adapt their activities accordingly. This approach is most useful if the ASP has a reliable way to identify patients appropriate for review.

V. Should ASPs Implement Interventions Designed to Reduce the Use of Antibiotics Associated With a High Risk of CDI?

Recommendation

5. We recommend antibiotic stewardship interventions designed to reduce the use of antibiotics associated with a high risk of CDI compared with no such intervention *(strong recommendation, moderate-quality evidence)*.

   Comment: The goal of reducing CDI is a high priority for all ASPs and should be taken into consideration when crafting stewardship interventions.

VI. Do Strategies to Encourage Prescriber-Led Review of Appropriateness of Antibiotic Regimens, in the Absence of Direct Input From an Antibiotic Stewardship Team, Improve Antibiotic Prescribing?

Recommendation

6. We suggest the use of strategies (eg, antibiotic time-outs, stop orders) to encourage prescribers to perform routine review of antibiotic regimens to improve antibiotic prescribing *(weak recommendation, low-quality evidence)*.

   Comment: Published data on prescriber-led antibiotic review are limited, but successful programs appear to require a methodology that includes persuasive or enforced prompting. Without such a mechanism, these interventions are likely to have minimal impact.

VII. Should Computerized Clinical Decision Support Systems Integrated Into the Electronic Health Record at the Time of Prescribing be Incorporated as Part of ASPs to Improve Antibiotic Prescribing?

Recommendation

7. We suggest incorporation of computerized clinical decision support at the time of prescribing into ASPs *(weak recommendation, moderate-quality evidence)*.

   Comment: Computerized clinical decision support for prescribers should only be implemented if information technology resources are readily available. However, computerized surveillance systems that synthesize data from the electronic health record and other data sources can streamline the work of ASPs by identifying opportunities for interventions.

VIII. Should ASPs Implement Strategies That Promote Cycling or Mixing in Antibiotic Selection to Reduce Antibiotic Resistance?

Recommendation

8. We suggest against the use of antibiotic cycling as a stewardship strategy *(weak recommendation, low-quality evidence)*.

   Comment: Available data do not support the use of antibiotic cycling as an ASP strategy, and further research is unlikely to change that conclusion. Because clinical data are sparse for antibiotic mixing, we cannot give any recommendation about its utility.

Optimization

IX. In Hospitalized Patients Requiring Intravenous (IV) Antibiotics, Does a Dedicated Pharmacokinetic (PK) Monitoring and Adjustment Program Lead to Improved Clinical Outcomes and Reduced Costs?

Recommendations

9. We recommend that hospitals implement PK monitoring and adjustment programs for aminoglycosides *(strong recommendation, moderate-quality evidence)*.
10. We suggest that hospitals implement PK monitoring and adjustment programs for vancomycin *(weak recommendation, low-quality evidence)*.

    Comment: PK monitoring and adjustment programs can reduce costs and decrease adverse effects. The ASP should encourage implementation and provide support for training and assessment of competencies. The conduct of those programs should be integrated into routine pharmacy activities.

X. In Hospitalized Patients, Should ASPs Advocate for Alternative Dosing Strategies Based on PK/Pharmacodynamic Principles to Improve Outcomes and Decrease Costs for Broad-Spectrum ß-Lactams and Vancomycin?

Recommendation

11. In hospitalized patients, we suggest ASPs advocate for the use of alternative dosing strategies vs standard dosing for broad-spectrum β-lactams to decrease costs *(weak recommendation, low-quality evidence)*.

    Comment: Although data for improved outcomes for broad-spectrum β-lactam dosing with this approach are still limited, these interventions are associated with antibiotic cost savings. ASPs should consider implementation but must take into account logistical issues such as nursing and pharmacy education and need for dedicated IV access. Considering the limited evidence, we cannot give any

recommendation about the utility of alternative dosing strategies for vancomycin.

XI. Should ASPs Implement Interventions to Increase Use of Oral Antibiotics as a Strategy to Improve Outcomes or Decrease Costs?

Recommendation

12. We recommend ASPs implement programs to increase both appropriate use of oral antibiotics for initial therapy and the timely transition of patients from IV to oral antibiotics *(strong recommendation, moderate-quality evidence)*.

Comment: Programs to increase the appropriate use of oral antibiotics can reduce costs and length of hospital stay. IV-to-oral conversion of the same antibiotic is less complicated than other strategies and is applicable to many healthcare settings. The conduct of those programs should be integrated into routine pharmacy activities. ASPs should implement strategies to assess patients who can safely complete therapy with an oral regimen to reduce the need for IV catheters and to avoid outpatient parenteral therapy.

XII. In Patients With a Reported History of ß-Lactam Allergy, Should ASPs Facilitate Initiatives to Implement Allergy Assessments With the Goal of Improved Use of Frst-Line Antibiotics?

Recommendation

13. In patients with a history of β-lactam allergy, we suggest that ASPs promote allergy assessments and penicillin (PCN) skin testing when appropriate *(weak recommendation, low-quality evidence)*.

Comment: Allergy assessments and PCN skin testing can enhance use of first-line agents, but it is largely unstudied as a primary ASP intervention; however, ASPs should promote such assessments with providers. In facilities with appropriate resources for skin testing, the ASPs should actively work to develop testing and treatment strategies with allergists.

XIII. Should ASPs Implement Interventions to Reduce Antibiotic Therapy to the Shortest Effective Duration?

Recommendation

14. We recommend that ASPs implement guidelines and strategies to reduce antibiotic therapy to the shortest effective duration *(strong recommendation, moderate-quality evidence)*.

Comment: Recommending a duration of therapy based on patient-specific factors is an important activity for ASPs. Suitable approaches include developing written guidelines with specific suggestions for duration, including duration of therapy recommendations as part of the preauthorization or prospective audit and feedback process, or specifying duration at the time of antibiotic ordering (eg, through an electronic order entry system).

Microbiology and Laboratory Diagnostics

XIV. Should ASPs Work With the Microbiology Laboratory to Develop Stratified Antibiograms, Compared With Nonstratified Antibiograms?

Recommendation

15. We suggest development of stratified antibiograms over solely relying on nonstratified antibiograms to assist ASPs in developing guidelines for empiric therapy *(weak recommendation, low-quality evidence)*.

Comment: Although there is limited evidence at this time that stratified antibiograms (eg, by location or age) lead to improved empiric antibiotic therapy, stratification can expose important differences in susceptibility, which can help ASPs develop optimized treatment recommendations and guidelines.

XV. Should ASPs Work With the Microbiology Laboratory to Perform Selective or Cascade Reporting of Antibiotic Susceptibility Test Results?

Recommendation

16. We suggest selective and cascade reporting of antibiotics over reporting of all tested antibiotics *(weak recommendation, low-quality evidence)*.

Comment: Although data are limited that demonstrate direct impact of those strategies on prescribing, some form of selective or cascaded reporting is reasonable. After implementation, ASPs should review prescribing to ensure there are no unintended consequences.

XVI. Should ASPs Advocate for Use of Rapid Viral Testing for Respiratory Pathogens to Reduce the Use of Inappropriate Antibiotics?

Recommendation

17. We suggest the use of rapid viral testing for respiratory pathogens to reduce the use of inappropriate antibiotics *(weak recommendation, low-quality evidence)*.

Comment: Although rapid viral testing has the potential to reduce inappropriate use of antibiotics, results have been inconsistent. Few studies have been performed to assess whether active ASP intervention would improve those results.

XVII. Should ASPs Advocate for Rapid Diagnostic Testing on Blood Specimens to Optimize Antibiotic Therapy and Improve Clinical Outcomes?

Recommendation

18. We suggest rapid diagnostic testing in addition to conventional culture and routine reporting on blood specimens if combined with active ASP support and interpretation *(weak recommendation, moderate-quality evidence)*.

Comment: Availability of rapid diagnostic tests is expected to increase; thus, ASPs must develop processes and interventions to assist clinicians in interpreting and responding appropriately to results.

XVIII. In Adults in Intensive Care Units (ICUs) With Suspected Infection, Should ASPs Advocate Procalcitonin (PCT) Testing as an Intervention to Decrease Antibiotic Use?

Recommendation

19. In adults in ICUs with suspected infection, we suggest the use of serial PCT measurements as an ASP intervention to decrease antibiotic use *(weak recommendation, moderate-quality evidence)*.

    Comment: Although randomized trials, primarily in Europe, have shown reduction in antibiotic use through implementation of PCT algorithms in the ICU, similar data are lacking for other regions including the United States where the patterns of antibiotic prescribing and approach to stewardship may differ. If implemented, each ASP must develop processes and guidelines to assist clinicians in interpreting and responding appropriately to results, and must determine if this intervention is the best use of its time and resources.

XIX. In Patients With Hematologic Malignancy, Should ASPs Advocate for Incorporation of Nonculture-Based Fungal Markers in Interventions to Optimize Antifungal Use?

Recommendation

20. In patients with hematologic malignancy at risk of contracting invasive fungal disease (IFD), we suggest incorporating nonculture-based fungal markers in ASP interventions to optimize antifungal use *(weak recommendation, low-quality evidence)*.

    Comment: ASPs with an existing intervention to optimize antifungal use in patients with hematologic malignancy can consider algorithms incorporating nonculture-based fungal markers. Those interventions must be done in close collaboration with the primary teams (eg, hematology-oncology). Antibiotic stewards must develop expertise in antifungal therapy and fungal diagnostics for the programs to be successful. The value of those markers for interventions in other populations has not been demonstrated.

Measurement

XX. Which Overall Measures Best Reflect the Impact of ASPs and Their Interventions?

Recommendation

21. We suggest monitoring antibiotic use as measured by days of therapy (DOTs) in preference to defined daily dose (DDD) *(weak recommendation, low-quality evidence)*.

    Comment: Every ASP must measure antibiotic use, stratified by antibiotic. DOTs are preferred, but DDDs remain an alternative for sites that cannot obtain patient-level antibiotic use data. ASPs should consider measurement of appropriate antibiotic use within their own institutions by examining compliance with local or national guidelines, particularly when assessing results of a targeted intervention, and share that data with clinicians to help inform their practice. Although rates of CDI or antibiotic resistance may not reflect ASP impact (because those outcomes are affected by patient population, infection control, and other factors), those outcomes may also be used for measurement of targeted interventions.

XXI. What is the Best Measure of Expenditures on Antibiotics to Assess the Impact of ASPs and Interventions?

Recommendation

22. We recommend measuring antibiotic costs based on prescriptions or administrations instead of purchasing data *(good practice recommendation)*.

XXII. What Measures Best Reflect the Impact of Interventions to Improve Antibiotic Use and Clinical Outcomes in Patients With Specific Infectious Diseases Syndromes?

Recommendation

23. Measures that consider the goals and size of the syndrome-specific intervention should be used *(good practice recommendation)*.

Special Populations

XXIII. Should ASPs Develop Facility-Specific Clinical Guidelines for Management of Fever and Neutropenia (F&N) in Hematology-Oncology Patients to Reduce Unnecessary Antibiotic Use and Improve Outcomes?

Recommendation

24. We suggest ASPs develop facility-specific guidelines for F&N management in hematology-oncology patients over no such approach *(weak recommendation, low-quality evidence)*.

    Comment: Clinical guidelines with an implementation and dissemination strategy can be successfully used in the care of cancer patients with F&N and are strongly encouraged.

XXIV. In Immunocompromised Patients Receiving Antifungal Therapy, do Interventions by ASPs Improve Utilization and Outcomes?

Recommendation

25. We suggest implementation of ASP interventions to improve the appropriate prescribing of antifungal treatment in immunocompromised patients *(weak recommendation, low-quality evidence)*.

    Comment: In facilities with large immunocompromised patient populations, ASP interventions targeting antifungal therapy can show benefit. Those interventions must be done in close collaboration with the primary teams (eg hematology-oncology, solid organ transplant providers). Antibiotic stewards must develop expertise in antifungal therapy and fungal diagnostics for the programs to be successful.

XXV. In Residents of Nursing Homes and Skilled Nursing Facilities, do Antibiotic Stewardship Strategies Decrease Unnecessary Use of Antibiotics and Improve Clinical Outcomes?

Recommendation

26. In nursing homes and skilled nursing facilities, we suggest implementation of antibiotic stewardship strategies to decrease unnecessary use of antibiotics *(good practice recommendation)*.

    Comment: Implementing ASPs at nursing homes and skilled nursing facilities is important and must involve point-of-care providers to be successful. The traditional physician–pharmacist team may not be available on-site, and facilities might need to investigate other approaches to review and optimize antibiotic use, such as obtaining infectious diseases expertise through telemedicine consultation.

XXVI. In Neonatal Intensive Care Units (NICUs), do Antibiotic Stewardship Interventions Reduce Inappropriate Antibiotic Use and/or Resistance?

Recommendation

27. We suggest implementation of antibiotic stewardship interventions to reduce inappropriate antibiotic use and/or resistance in the NICU *(good practice recommendation)*.

XXVII. Should ASPs Implement Interventions to Reduce Antibiotic Therapy in Terminally Ill Patients?

Recommendation

28. In terminally ill patients, we suggest ASPs provide support to clinical care providers in decisions related to antibiotic treatment *(good practice recommendation)*.

INTRODUCTION

The discovery of antibiotics in the early 20th century transformed healthcare, dramatically reducing morbidity and mortality from infectious diseases and allowing for major advancements in medicine. The increase in organisms with resistance to antibiotics in our armamentarium, however, combined with the slow pace of development of new antibiotics threatens those gains. Approaches to optimize the use of both existing antibiotics and newly developed antibiotics are of critical importance to ensure that we continue to reap their benefits and provide the best care to patients.

The need for antibiotic stewardship across the spectrum of healthcare has been recognized in the National Action Plan for Combating Antibiotic-Resistant Bacteria issued by the White House in March 2015 [6]. This plan calls for establishment of ASPs in all acute care hospitals by 2020 and for the Centers for Medicare and Medicaid Services to issue a Condition of Participation that participating hospitals develop programs based on recommendations from the Centers for Disease Control and Prevention's (CDC) Core Elements of Hospital Antibiotic Stewardship Programs [7]. Expansion of stewardship activities to ambulatory surgery centers, dialysis centers, nursing homes and other long-term care facilities, and emergency departments and outpatient settings is also recommended.

The purpose of this guideline is to comprehensively evaluate the wide range of interventions that can be implemented by ASPs in emergency department, acute inpatient, and long-term care settings as they determine the best approaches to influence the optimal use of antibiotics within their own institutional environments. In addition, this guideline addresses approaches to measure the success of these interventions. This guideline does not specifically address the structure of an ASP, which has been well outlined in a previous guideline [8] and in the CDC's Core Elements of Hospital Antibiotic Stewardship Programs and Core Elements of Antibiotic Stewardship for Nursing Homes [7, 9]. These documents emphasize the importance of physician and pharmacist leadership for an ASP, the need for infectious diseases expertise, and the role of measurement and feedback as critical components of ASPs. This guideline does not address antibiotic stewardship in outpatient settings.

Although not all of the antibiotic stewardship interventions, optimization measures, diagnostic approaches, and program measurements described in this guideline have been implemented or evaluated in all populations or clinical settings, the majority could be considered for use in pediatrics, oncology, community hospitals, small hospitals, and nursing home and long-term care environments, and not limited to acute care facilities. Any antibiotic stewardship intervention must be customized based on local needs, prescriber behaviors, barriers, and resources. In contrast to other guidelines, this guideline provides comments that supplement the formal recommendations and contain practical input from the expert panel to better guide ASPs in determining which interventions to implement.

METHODS

Panel Composition

Led by Co-chairs Tamar Barlam and Sara Cosgrove, a panel of 18 multidisciplinary experts in the management of ASPs was convened per the IDSA Handbook on Clinical Practice Guideline Development [10] in 2012. In addition to members of IDSA and the SHEA, representatives from diverse geographic areas, pediatric and adult practitioners, and a wide breadth of specialties representing major medical societies were included among the panel's membership (American College of Emergency Physicians [ACEP], American Society of Health-System Pharmacists [ASHP], American Society for Microbiology [ASM], PIDS, Society for Academic Emergency Medicine [SAEM], Society of Infectious Diseases Pharmacists [SIDP], and the Surgical Infection Society [SIS]). A guideline

methodologist and member of the GRADE Working Group and a medical writer were added to assist the panel.

Literature Review and Analysis

PubMed, which includes Medline (1946 to present), was searched to identify relevant studies for each of the antibiotic stewardship guideline PICO (population/patient, intervention/indicator, comparator/control, outcome) questions. Search strategies were developed and built by 2 independent health sciences librarians from the Health Sciences Library System, University of Pittsburgh. For each PICO question, the librarians developed the search strategies using PubMed's command language and appropriate search fields. Medical Subject Headings terms and keywords were used for the main search concepts of each PICO question. A data supplement that includes search strings can be found following publication on the IDSA website [11]. Articles in all languages and all publication years were included. Initial searches were created and confirmed with input from the guideline committee chairs and group leaders from February through mid-July 2013. The searches were finalized and delivered between late July and September 2013. After the literature searches were performed, authors continued to review the literature and added relevant articles as needed.

Process Overview

To evaluate evidence, the panel followed a process consistent with other IDSA guidelines. The process for evaluating the evidence was based on the IDSA Handbook on Clinical Practice Guideline Development [10] and involved a systematic weighting of the quality of the evidence and the grade of recommendation using the GRADE system (Figure 1) [2–5]. Unless otherwise stated, each PICO comparator was usual practice.

For recommendations in the category of good practice statements, we followed published principles by the GRADE working group on how to identify such recommendations and use appropriate wording choices. Accordingly, a formal GRADE rating was not pursued for those statements [12].

Panel members were divided into 5 subgroups: (1) interventions, (2) optimization of antibiotic administration, (3) microbiology and laboratory diagnostics, (4) measurement and analysis, and (5) antibiotic stewardship in special populations. Each author was asked to review the literature, evaluate the evidence, and determine the initial strength of the recommendations along with an evidence summary supporting each recommendation in his/her assigned subgroup. The evidence was graded based on the effectiveness of the antibiotic stewardship intervention, not the underlying data that provided the groundwork for the intervention. The panel reviewed all recommendations, along with their strength and the quality of the evidence. Discrepancies were discussed and resolved, and all panel members are in agreement with the final recommendations.

Consensus Development Based on Evidence

The panel met face to face on 3 occasions and conducted numerous teleconferences to complete the work of the guideline. The purpose of the meetings and teleconferences was to develop and discuss the clinical questions to be addressed, assign topics for review and writing of the initial draft, and develop recommendations. The whole panel reviewed all sections. The guideline was reviewed and approved by the IDSA Standards and Practice Guidelines Committee (SPGC), the IDSA Board of Directors, the SHEA Guidelines Committee, and the SHEA Board of Directors, and was endorsed by ACEP, ASHP, ASM, PIDS, SAEM, SIDP, and SIS.

Guidelines and Conflicts of Interest

The expert panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that may be construed as constituting an actual, potential, or apparent conflict. Panel members were provided IDSA's conflicts of interest disclosure statement and were asked to identify ties to companies developing products that may be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. Decisions were made on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. Potential conflicts of interests are listed in the Notes section at the end of the guideline.

Revision Dates

At annual intervals, the panel chair, the SPGC liaison advisor, and the chair of the SPGC will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the entire panel will reconvene to discuss potential changes. When appropriate, the panel will recommend revision of the guideline to the IDSA SPGC and SHEA guidelines committees.

RECOMMENDATIONS FOR IMPLEMENTING AN ANTIBIOTIC STEWARDSHIP PROGRAM

Interventions

I. Does the Use of Preauthorization and/or Prospective Audit and Feedback Interventions by ASPs Improve Antibiotic Utilization and Patient Outcomes?

Recommendation

1. We recommend preauthorization and/or prospective audit and feedback over no such interventions *(strong recommendation, moderate-quality evidence)*.

   Comment: Preauthorization and/or prospective audit and feedback improve antibiotic use and are a core component of any stewardship program. Programs should decide whether to include one strategy or a combination of both strategies

based on the availability of facility-specific resources for consistent implementation, but some implementation is essential.

Evidence Summary

Preauthorization is a strategy to improve antibiotic use by requiring clinicians to get approval for certain antibiotics before they are prescribed. Prospective audit and feedback (PAF) is an intervention that engages the provider after an antibiotic is prescribed. Each type is associated with unique advantages and disadvantages (Table 1).

Preauthorization has been associated with a significant reduction in the use of the restricted agents and of associated costs [13–16]. Outcome studies with preauthorization have shown decreased antibiotic use and decreased antibiotic resistance, particularly among gram-negative pathogens [13–15, 17]. Preauthorization studies have demonstrated no adverse effects for patients [13, 14]. White et al [13] reported that initiation of a preauthorization requirement for selected antibiotics at a county teaching hospital was associated with a 32% decrease in total parenteral antibiotic expenditures ($P < .01$) and increased percentages of susceptible gram-negative isolates—all without changes in hospital length of stay and survival. For example, *Pseudomonas aeruginosa* susceptibility to imipenem increased for isolates recovered in the ICU (percentage of susceptible isolates before vs after preauthorization: 65% vs 83%; $P \leq .01$) and other inpatient settings (83% vs 95%; $P \leq .01$). Overall 30-day survival rates were unchanged in patients with gram-negative bacteremia (79% vs 75%; $P = .49$) [13]. In addition, restrictive policies such as preauthorization have been shown to be more effective than persuasive strategies in reducing CDI, according to a meta-analysis evaluating antibiotic stewardship and CDI [18].

There are several factors to consider when implementing a preauthorization intervention. The skills of the person providing approval are important. Antibiotic approval by an antibiotic stewardship team consisting of a clinical pharmacist and an infectious diseases attending physician was more effective than off-hour approval by infectious diseases fellows in recommendation appropriateness (87% vs 47%; $P < .001$), cure rate (64% vs 42%; $P = .007$), and treatment failures (15% vs 28%; $P = .03$) [19]. Inaccuracy in communication of the clinical scenario by the requesting prescriber to the antibiotic stewardship team increases the likelihood of inappropriate recommendations [20]. Direct chart review optimizes preauthorization. It is also important to consider the alternative treatments that clinicians may choose when antibiotics are restricted and monitor changes in usage patterns. Rahal et al [21] implemented a preauthorization requirement for cephalosporins. This was associated with a reduction in the incidence of ceftazidime-resistant *Klebsiella*, but imipenem use increased and a 69% increase in the incidence of imipenem-resistant *P. aeruginosa* was seen. Preauthorization requires real-time availability of the person providing approval. Institutions that use preauthorization often allow administration of the restricted antibiotic overnight until approval can be obtained the next day. To provide 24-hour availability and to facilitate communication without impeding provider workflow, Buising et al [14] developed a computerized approval system based on defined indications for restricted agents, demonstrating reduced antibiotic consumption and increased *Pseudomonas* susceptibility rates over a 2-year period.

PAF interventions also have been shown to improve antibiotic use, reduce antibiotic resistance, and reduce CDI rates [22–27], without a negative impact on patient outcomes [26, 28–30]. For instance, PAF conducted by a clinical pharmacist and infectious diseases physician at a community hospital led to a 22% reduction in the use of parenteral broad-spectrum antibiotics as well as a reduction in rates of CDI and nosocomial infections due to antibiotic-resistant Enterobacteriaceae over a 7-year period of time [22]. PAF has also been effective in the ICU [24, 25]. For example, a PAF intervention in multiple ICUs at a large academic institution demonstrated decreased meropenem resistance and decreased CDIs ($P = .04$) without adversely affecting mortality [25]. PAF has been effective in children's hospitals by significantly reducing antibiotic use and dosing errors while limiting the development of antibiotic resistance [26, 27]. PAF can also be a strategy to improve

Table 1. Comparison of Preauthorization and Prospective Audit and Feedback Strategies for Antibiotic Stewardship

Preauthorization	Prospective Audit and Feedback
Advantages	
• Reduces initiation of unnecessary/ inappropriate antibiotics • Optimizes empiric choices and influences downstream use • Prompts review of clinical data/ prior cultures at the time of initiation of therapy • Decreases antibiotic costs, including those due to high-cost agents • Provides mechanism for rapid response to antibiotic shortages • Direct control over antibiotic use	• Can increase visibility of antimicrobial stewardship program and build collegial relationships • More clinical data available for recommendations, enhancing uptake by prescribers • Greater flexibility in timing of recommendations • Can be done on less than daily basis if resources are limited • Provides educational benefit to clinicians • Prescriber autonomy maintained • Can address de-escalation of antibiotics and duration of therapy
Disadvantages	
• Impacts use of restricted agents only • Addresses empiric use to a much greater degree than downstream use • Loss of prescriber autonomy • May delay therapy • Effectiveness depends on skill of approver • Real-time resource intensive • Potential for manipulation of system (eg, presenting request in a biased manner to gain approval) • May simply shift to other antibiotic agents and select for different antibiotic-resistance patterns	• Compliance voluntary • Typically labor-intensive • Success depends on delivery method of feedback to prescribers • Prescribers may be reluctant to change therapy if patient is doing well • Identification of interventions may require information technology support and/or purchase of computerized surveillance systems • May take longer to achieve reductions in targeted antibiotic use

antibiotic use in hematology-oncology patients. In one study, the addition of PAF led to a significant decrease in the use of restricted antibiotics during the intervention period from 574.4 to 533.8 study-antibiotic days per 1000 patient-days (incidence rate ratio, 0.93; 95% confidence interval [CI], .88–.97; $P = .002$), although neutropenic patients and those undergoing hematopoietic stem cell transplant were excluded [31].

The effectiveness of PAF may depend on the infrastructure in place at an institution. A multicenter study of a PAF program added to existing ASPs found overall that 27.3% of antibiotic courses were determined to be unjustified, and clinicians accepted recommendations to change or stop the antibiotics in 66.7% of these. In the 2 sites with established ASPs and dedicated personnel, the addition of PAF led to significant reductions in antibiotic usage; however, among the 3 centers without established resources, no impact was identified [31].

PAF can be very labor intensive, and identification of appropriate patients for intervention can be challenging and require computerized surveillance systems; however, where daily review or preauthorization is not feasible, limited PAF can still have an impact [32]. A pharmacist-driven PAF intervention conducted 3 days a week at a 253-bed community hospital demonstrated a 64% decline in DOTs per 1000 patient-days after implementation, a 37% reduction in total antibiotic expenditures, and a decrease in use of carbapenems, vancomycin, and levofloxacin [33].

The benefit of preauthorization compared with PAF has had limited study. Restrictive measures such as preauthorization were compared with persuasive measures such as PAF in a meta-analysis of 52 interrupted time series in a Cochrane review [34]. Persuasive interventions included PAF, dissemination of educational resources, reminders, and educational outreach. Although equivalent to persuasive measures at 12 or 24 months, restrictive interventions had statistically greater effect size on prescribing outcomes at 1 month (+32%; 95% CI, 2%–61%; $P = .03$) and on colonization or infection with *C. difficile* or antibiotic-resistant bacteria at 6 months (+53%; 95% CI, 31%–75%; $P = .001$). The authors concluded that restrictive interventions are preferred when the need is urgent [34]. Another study [35] at an academic institution demonstrated that when a preauthorization strategy was switched to a PAF strategy, overall antibiotic use increased (preauthorization vs PAF: −9.75 vs +9.65 DOTs per 1000 patient-days per month; $P < .001$), as did hospital length of stay (−1.57 vs +1.94 days per 1000 patient-days; $P = .016$).

Whether one chooses preauthorization, PAF, or a combination of those strategies, implementation should serve as the foundation of a comprehensive ASP. Effective implementation requires the support of hospital administration, allocation of necessary resources for a persistent effort by dedicated, well-trained personnel, and ongoing communication with clinicians.

II. Is Didactic Education a Useful Antibiotic Stewardship Intervention for Reducing Inappropriate Antibiotic Use?

Recommendation

2. We suggest against relying solely on didactic educational materials for stewardship *(weak recommendation, low-quality evidence)*.

   Comment: Passive educational activities, such as lectures or informational pamphlets, should be used to complement other stewardship activities. Academic medical centers and teaching hospitals should integrate education on fundamental antibiotic stewardship principles into their preclinical and clinical curricula.

Evidence Summary

Education is a common tool for ASPs. Strategies include educational meetings with didactic lectures and distribution of educational pamphlets and materials. No comparative studies are available to determine which educational strategy is most effective.

Dissemination of educational materials in the context of a focused stewardship goal can be successful. For example, in a Cochrane review published in 2013 [34], dissemination of educational materials via printed forms or meetings was associated with improved antibiotic use in 5 of 6 studies; the median effect size based on the type of study ranged from 10.6% to 42.5%. Education alone, however, can result in nonsustainable improvements in antibiotic prescribing. Landgren et al [36] performed a crossover study with an educational marketing campaign that targeted perioperative prophylaxis. Prescribing improved during the intervention period but was not sustained over the next 12 months [36]. Educational strategies are likely most effective when combined with other stewardship strategies such as PAF [34].

Educational strategies should include medical, pharmacy, physician assistant, nurse practitioner, and nursing students and trainees. In a survey of fourth-year medical students at 3 schools in the United States [37], 90% of respondents confirmed that they would like more education on appropriate antibiotic use. In addition, they had low mean knowledge scores on this topic, suggesting the need for instruction in fundamental antibiotic stewardship principles. The Accreditation Council for Graduate Medical Education announced its commitment to antibiotic stewardship in 2015 and will provide resources and materials to postgraduate training hospitals [38].

III. Should ASPs Develop and Implement Facility-Specific Clinical Practice Guidelines for Common Infectious Diseases Syndromes to Improve Antibiotic Utilization and Patient Outcomes?

Recommendation

3. We suggest ASPs develop facility-specific clinical practice guidelines coupled with a dissemination and implementation strategy *(weak recommendation, low-quality evidence)*.

   Comment: Facility-specific clinical practice guidelines and algorithms can be an effective way to standardize prescribing

practices based on local epidemiology. ASPs should develop those guidelines, when feasible, for common infectious diseases syndromes. In addition, ASPs should be involved in writing clinical pathways, guidelines, and order sets that address antibiotic use and are developed within other departments at their facility.

Evidence Summary

Implementation of facility-specific clinical practice guidelines can lead to substantial changes in antibiotic use for infections commonly treated in hospitals. Most published studies of clinical practice guidelines have involved pneumonia, including community-acquired pneumonia (CAP) in adults [39–41] and children [42], and healthcare-associated pneumonia [43–46]. One study involved cellulitis and cutaneous abscesses [47]. Several of these studies described a process of interdisciplinary guideline development along with a multifaceted dissemination and implementation strategy to increase awareness and uptake of the guideline [40, 43, 45, 47]. Such strategies included guideline dissemination in electronic or hard-copy formats, provider education, engagement of peer champion advocates, audit and feedback of prescribing practices to providers, checklists, and incorporation of recommendations into electronic order sets.

Specific improvements in antibiotic use associated with implementation of facility-specific guidelines have included statistically significant increases in likelihood of adequate initial therapy [40, 46], use of narrower-spectrum antibiotic regimens [41, 42, 47], earlier switch from IV to oral therapy [39], and shorter duration of treatment [39, 41, 45–47]—all without adverse effects on other clinical outcomes. For those studies powered to detect differences in clinical outcomes, reductions in mortality [40], length of hospital stay [39–41, 43, 44], adverse events [39, 48], recurrence or readmission [46], and treatment costs [40, 44] have been demonstrated.

The sustainability of the effects of guideline implementation has not been well established. In one study, changes in prescribing and outcomes were sustained 3 years after guideline implementation [43]; however, in another study, removal of measures to promote guideline adherence after 1 year was associated with a reduction in adherence [49]. Therefore, interventions to maintain guideline adherence over time may be necessary, and intended outcomes should be monitored.

IV. Should ASPs Implement Interventions to Improve Antibiotic Use and Clinical Outcomes That Target Patients With Specific Infectious Diseases Syndromes?

Recommendation

4. We suggest ASPs implement interventions to improve antibiotic use and clinical outcomes that target patients with specific infectious diseases syndromes *(weak recommendation, low-quality evidence)*.

   Comment: ASP interventions for patients with specific infectious diseases syndromes can be an effective way to improve prescribing because the message can be focused, clinical guidelines and algorithms reinforced, and sustainability improved. ASPs should regularly evaluate areas for which targeted interventions are needed and adapt their activities accordingly. This approach is most useful if the ASP has a reliable way to identify patients appropriate for review.

Evidence Summary

In addition to hospital-wide activities, such as preauthorization or development of clinical guidelines, a strategy for targeted efforts to improve antibiotic use and clinical outcomes for a specific infectious diseases issue has been shown to be effective. Studies have involved skin and soft tissue infections (SSTIs), asymptomatic bacteriuria (ASB), or CAP.

For example, to reduce the use of broad-spectrum therapy and shorten the duration of treatment for adults with uncomplicated SSTIs, an intervention was developed that included dissemination of a treatment algorithm, electronic order sets, recruitment of physician champions, and quarterly feedback to providers of compliance with the guideline. This study of 169 adults demonstrated a 3-day reduction in the length of therapy, 30% reduction in broad-spectrum antibiotic prescribing, and 0.3% reduction in clinical failure [47].

Interventions to reduce inappropriate treatment of ASB at geriatric or long-term care institutions have resulted in significant decreases in antibiotic use [50, 51]. For example, Zabarsky et al [50] developed an intervention that discouraged both nurses from collecting urine cultures from asymptomatic patients and primary care providers from treating ASB. After the intervention, urine cultures decreased from 2.6 to 0.9 per 1000 patient-days ($P < .0001$), ASB overall rate of treatment declined from 1.7 to 0.6 per 1000 patient-days ($P = .0017$), and total days of antibiotic therapy were reduced from 167.7 to 117.4 per 1000 patient-days ($P < .001$). The improvements were sustained for 30 months of follow-up.

ASP interventions for CAP have increased the proportion of patients receiving appropriate therapy (54.9% to 93.4% in one hospital and 64.6% to 91.3% in a second hospital) [52]. In a pediatric population, a CAP intervention resulted in an increase in the proportion of patients receiving empiric ampicillin from 13% to 63% and a decrease in the proportion of patients receiving empiric ceftriaxone from 72% to 21%, without an increased risk of treatment failure. [42]. Other studies have demonstrated optimization of antibiotic use, such as reduced time to oral antibiotic conversion by 1–2 days [39, 53], decreased duration of therapy from a median of 10 to 7 days [54] with 148 days of antibiotic therapy avoided in the 6-month study period, and improved appropriate narrowing of antibiotic therapy from 19% to 67%. There was no difference between the baseline and intervention periods in the proportions of patients who were readmitted within 30 days (14.5% vs 7.7%; $P = .22$) or who developed CDI (4.8% vs 1.5%; $P = .28$). In a study involving 5

hospitals, implementation of a guideline that included criteria for oral conversion and hospital discharge reduced length of stay from 7.3 to 5.7 days ($P < .001$); 30-day readmission proportions did not differ (1.9% vs 2.4%; $P = .6$) [53].

An alternative approach is assessing patients with blood cultures growing specific pathogens. Patients with bacteria or yeast in their blood can usually be identified through communication with the microbiology laboratory or through alerts from computerized surveillance systems. For example, Antworth et al [55] described the impact of a candidemia-care bundle in which patients were identified by electronic medical records and clinical microbiology reports. Implementation of this bundle was associated with improved care related to both drug therapy (eg, appropriate antifungal therapy selection rates for bundle vs historic control: 100% vs 86.5%; $P < .05$) and nondrug therapy (eg, ophthalmologic examination rates: 97.6% vs 75.7%; $P = .01$). Similarly, Borde et al [56] observed improvements in both drug therapy (appropriate initial anti-infective therapy: 85% vs 4%; $P < .001$) and nondrug therapy (follow-up cultures: 65% vs 33%; $P < .001$)—as well as decreased mortality (10% vs 44%; $P < .001$) after implementing an ASP bundle targeting *Staphylococcus aureus* bacteremia. In a study targeting gram-negative bacteremia, Pogue et al [57] combined active alerting of positive blood cultures with ASP intervention. In the subgroup of patients not on appropriate antibiotic therapy at the time of the initial positive blood culture, the intervention was associated with reduced mortality (odds ratio [OR], 0.24; 95% CI, .08–.76) and length of stay (OR, 0.76; 95% CI, .66–.86). In all patients, the intervention group had shorter time to appropriate therapy (8 vs 14 hours; $P = .01$) and length of stay (7 vs 8 days; $P < .001$).

V. Should ASPs Implement Interventions Designed to Reduce the Use of Antibiotics Associated With a High Risk of CDI?

Recommendation

5. We recommend antibiotic stewardship interventions designed to reduce the use of antibiotics associated with a high risk of CDI compared with no such intervention *(strong recommendation, moderate-quality evidence)*.

   Comment: The goal of reducing CDI is a high priority for all ASPs and should be taken into consideration when crafting stewardship interventions.

Evidence Summary

ASPs have been shown to reduce hospital-onset CDI. The primary ASP interventions were restriction of high-risk antibiotics such as clindamycin [58–61] and/or broad-spectrum antibiotics, especially cephalosporins [59–64] and fluoroquinolones [59–63, 65]. Climo et al [58] were among the first to report that restriction of clindamycin was associated with decreased clindamycin use, decreased CDI ($P < .001$), increased clindamycin susceptibility ($P < .001$), and overall cost savings attributable to fewer cases of CDI [58]. More recent studies have been conducted in a variety of hospital settings. Some have been prompted by outbreaks [59, 65], whereas others were performed in endemic situations [22, 63].

Implementation of ASPs has been associated with statistically significant sudden or linear-trend decreases in nosocomial CDI rates [22, 58–61, 63–65], which have been sustained for up to 7 years [22]. A meta-analysis [18] highlights the effectiveness of stewardship for CDI prevention and outlines ASP intervention strategies. Other studies support that antibiotic restriction can further reduce CDI rates when added to previous infection control measures [58, 59]. In fact, Valiquette et al [59] reported that simply strengthening basic infection control measures did not reduce the CDI rate. CDI rates, however, declined ($P < .007$) with antibiotic stewardship interventions to reduce the use of second- and third-generation cephalosporins, clindamycin, macrolides, and fluoroquinolones through dissemination of local treatment guidelines, PAF, and reduction in duration of therapy.

VI. Do Strategies to Encourage Prescriber-Led Review of Appropriateness of Antibiotic Regimens, in the Absence of Direct Input From an Antibiotic Stewardship Team, Improve Antibiotic Prescribing?

Recommendation

6. We suggest the use of strategies (eg, antibiotic time-outs, stop orders) to encourage prescribers to perform routine review of antibiotic regimens to improve antibiotic prescribing *(weak recommendation, low-quality evidence)*.

   Comment: Published data on prescriber-led antibiotic review are limited, but successful programs appear to require a methodology that includes persuasive or enforced prompting. Without such a mechanism, these interventions are likely to have minimal impact.

Evidence Summary

Strategies to prompt prescribers to assess antibiotic therapy without formal ASP intervention have undergone only limited evaluation. Lee et al [66] developed a structured electronic checklist for antibiotic time-out audit to be performed twice weekly by a senior resident on the medical care team (referred to as "self-stewardship"). Unit pharmacists reminded residents to complete the checklist and compliance was 80%. Initially, the time-outs resulted in changes in antibiotic therapy in 15% of cases; however, the magnitude of change diminished over the 18-month study period. CDI rates decreased by 19% and annual antibiotic costs decreased by 46% (from $149 743 to $80 319), but overall antibiotic use did not [66]. Checklists to guide process of care in a medical ICU have been studied [67, 68]. In one study [67], physicians received face-to-face prompting if they overlooked the antibiotic review on the checklist. Prompting improved compliance with the checklist and was associated with a reduced duration of antibiotic therapy and a lower risk-adjusted mortality than no prompting in patients receiving

empiric antibiotics (OR, 0.41; 95% CI, .18–.92; $P = .03$) [67]. Even with prompting, prescribers may have difficulty performing self-stewardship. For example, in a study by Lesprit et al [69], clinicians were prompted to review IV therapy at 72 hours. There was no significant change in the frequency of antibiotic regimen modification compared with the control group; however, requests for infectious diseases input increased.

Antibiotic stop orders are another approach to requiring physicians to review their antibiotic use. This has been best studied for 3-day stop orders for vancomycin [70, 71]. Guglielmo et al [70] reported that the stop order was associated with less continuation of vancomycin in the absence of documented gram-positive infection (33/133 [25%] vs 15/142 [11%]; $P = .002$) and less use of vancomycin in febrile neutropenia (37/133 [28%] vs 22/142 [15%]; $P < .013$). Hospital-wide vancomycin use decreased as well (160 g vs 100–120 g per 1000 patient-days; P not stated) [70]. A safety mechanism should be paired with stop orders to avoid unintended interruptions and to prevent alienating prescribers against antibiotic stewardship interventions.

Collectively, these findings suggest that antibiotic review by the prescriber can have an important stewardship impact if done with appropriate reminders or prompting, but available data do not confirm feasibility or sustainability.

VII. Should Computerized Clinical Decision Support Systems Integrated Into the Electronic Health Record at the Time of Prescribing be Incorporated as Part of ASPs to Improve Antibiotic Prescribing?

Recommendation

7. We suggest incorporation of computerized clinical decision support at the time of prescribing into ASPs *(weak recommendation, moderate-quality evidence)*.

   Comment: Computerized clinical decision support for prescribers should only be implemented if information technology resources are readily available. However, computerized surveillance systems that synthesize data from the electronic health record and other data sources can streamline the work of ASPs by identifying opportunities for interventions.

Evidence Summary

Computerized decision support systems are designed to improve antibiotic use by providing treatment recommendations to clinicians at the time of prescribing [72–77].

Implementation of computerized decision support systems for prescribers has been associated with reduced use of broad-spectrum antibiotics [73, 74], improved antibiotic dosing [75], reduced antibiotic resistance [74], more appropriate antibiotic selection [73, 77], fewer prescribing errors [72, 75, 78], reduced adverse events [72, 76], reduced antibiotic costs [72, 73, 75, 76], reduced length of stay [72], and reduced mortality [76]. Computerized surveillance systems for ASPs may improve efficiency by facilitating more PAF interventions and reducing the time for such interventions [79–81]. Use of those systems by ASPs has been associated with reduced use of broad-spectrum antibiotics [81] and reduced antibiotic costs [79].

Among the potential disadvantages of computer decision support and surveillance systems are the time and financial resources required for implementation and maintenance, and the potential for a high proportion of nonactionable alerts that may lead to "alert fatigue" [80, 81].

VIII. Should ASPs Implement Strategies That Promote Cycling or Mixing in Antibiotic Selection to Reduce Antibiotic Resistance?

Recommendation

8. We suggest against the use of antibiotic cycling as a stewardship strategy *(weak recommendation, low-quality evidence)*.

   Comment: Available data do not support the use of antibiotic cycling as an ASP strategy, and further research is unlikely to change that conclusion. Because clinical data are sparse for antibiotic mixing, we cannot give any recommendation about its utility.

Evidence Summary

Antibiotic cycling involves withdrawal of an antibiotic or antibiotic class from general use (within a ward or an institution) for a designated period of time and substitution with antibiotics from a different class having a comparable spectrum of activity but for which bacteria may have different resistance mechanisms. Antibiotic cycling is difficult to achieve, labor intensive, and impractical for most inpatient facilities.

Many studies have been performed, but they fail to provide compelling evidence of the benefit of antibiotic cycling, partly because of methodologic shortcomings. Common weaknesses include single-center setting (usually in ICUs), before-and-after time-series analysis, lack of adherence to prescribing protocols, multiple simultaneous interventions (including infection prevention and guideline implementation), and lack of long-term follow-up. Brown and Nathwani [82] performed a systematic review of antibiotic cycling in 2005 and concluded that available study results did not permit conclusions regarding the efficacy of cycling.

In contrast to cycling that is performed at the level of the medical facility or patient care ward, a strategy known as antibiotic mixing is performed at the level of the individual patient, in which consecutive patients with the same diagnosis receive an antibiotic from a different class in rotation. Mathematical modeling suggests that antibiotic mixing is a more promising strategy for limiting emergence of resistance than cycling, but few clinical studies validate these models [83, 84]. Comprehensive reviews published in 2010 [85, 86] concluded that more work is needed to demonstrate the usefulness of antibiotic mixing.

Optimization

IX. In Hospitalized Patients IV Intravenous Antibiotics, Does a Dedicated PK Monitoring and Adjustment Program Lead to Improved Clinical Outcomes and Reduced Costs?

Recommendations

9. We recommend that hospitals implement PK monitoring and adjustment programs for aminoglycosides *(strong recommendation, moderate-quality evidence)*.
10. We suggest that hospitals implement PK monitoring and adjustment programs for vancomycin *(weak recommendation, low-quality evidence)*.

    Comment: PK monitoring and adjustment programs can reduce costs and decrease adverse effects. The ASP should encourage implementation and provide support for training and assessment of competencies. The conduct of those programs should be integrated into routine pharmacy activities.

Evidence Summary

In randomized studies, individualized PK monitoring and adjustment of aminoglycoside dosing compared with standard dosing is associated with increased likelihood of obtaining serum concentrations within therapeutic range [87, 88] and reduced institutional costs [87, 89]. Reductions in nephrotoxicity, hospital length of stay, and mortality [87, 90–92] have been observed in some studies. Leehey et al [88] randomized patients receiving aminoglycosides to dosing directed by one of 3 groups: (1) physicians with PK monitoring input from a pharmacist; (2) physician–pharmacist PK monitoring team; or (3) physicians with no external input (control group). The PK monitoring groups achieved higher peak and marginally lower trough concentrations; however, there was no statistically significant difference in the likelihood of nephrotoxicity among groups 1, 2, and 3 (27%, 16%, and 16%, respectively; $P = .31$). Clinical failure was less common in the PK-monitored groups across all patients (1%, 0%, and 11%, respectively; $P = .004$), but not among patients with microbiologically proven infection. Bartal et al [90] compared the outcomes of usual care vs an intensive PK monitoring program among patients receiving initial high-dose extended-interval gentamicin dosing. Nephrotoxicity was lower in the PK monitoring group (5% vs 21%; $P = .03$), with similar proportions of patients experiencing cure of infection or death at 28 days between the groups.

Only one randomized controlled study [93] has been performed assessing the impact of a PK monitoring and adjustment program for vancomycin; no difference in efficacy in the concentration-monitoring arm was demonstrated, but there was a lower incidence of nephrotoxicity (adjusted OR, 0.04; 95% CI, .006–.30) at a cost per case of nephrotoxicity avoided of $435. Observational studies [93–96] of vancomycin dose individualization showed similar effects, with costs stable or lower.

Broader interventions directed at antibiotic dosing, usually involving integration of dosing support into computerized physician order-entry systems, have shown improved adherence to dosing guidelines as well as fewer adverse effects, but no difference in effectiveness (eg, clinical cure, hospital mortality, or length of stay) [97–99]. No studies have examined the relationship between PK monitoring and adjustment programs and institutional antibiotic resistance prevalence.

X. In Hospitalized Patients, Should ASPs Advocate for Alternative Dosing Strategies Based on PK/Pharmacodynamic Principles to Improve Outcomes and Decrease Costs for Broad-Spectrum ß-Lactams and Vancomycin?

Recommendation

11. In hospitalized patients, we suggest ASPs advocate for the use of alternative dosing strategies vs standard dosing for broad-spectrum β-lactams to decrease costs *(weak recommendation, low-quality evidence)*.

    Comment: Although data for improved outcomes for broad-spectrum β-lactam dosing with this approach are still limited, these interventions are associated with antibiotic cost savings. ASPs should consider implementation but must take into account logistical issues such as nursing and pharmacy education and need for dedicated IV access. Considering the limited evidence, we cannot give any recommendation about the utility of alternative dosing strategies for vancomycin.

Evidence Summary

Dosing strategies based on PK/pharmacodynamic (PK/PD) principles for aminoglycosides, such as once-daily dosing, have been shown to be effective in reducing nephrotoxicity and, in some studies, improve clinical outcomes [100, 101]. The effectiveness of alternative dosing schemes for β-lactam antibiotics and vancomycin based on PK/PD principles is unclear.

For β–lactam antibiotics, one meta-analysis showed decreased mortality (risk ratio, 0.59; 95% CI, .41–.83) among patients receiving continuous infusions of carbapenems or piperacillin-tazobactam vs standard infusions. This meta-analysis included 3 randomized controlled trials (RCTs) that comprised only 25% of the patient outcomes analyzed [102]. In contrast, another meta-analysis that included 14 RCTs did not support improved outcomes using prolonged infusions of broad-spectrum β-lactam antibiotics (either extended or continuous infusion) [103]. A Cochrane review [104] and a recent randomized trial [105] in critically ill patients of continuous infusions of β-lactam antibiotics compared with standard intermittent dosing also did not demonstrate benefits in outcome.

For vancomycin, continuous infusion has not been shown to improve clinical outcomes in adults but has been associated with decreased nephrotoxicity in a meta-analysis [106]. Similarly, continuous-infusion vancomycin has been associated with few adverse effects and no nephrotoxicity in children [107].

Alternative dosing strategies for β-lactam antibiotics [108] and vancomycin [109] were associated with significantly lower costs than intermittent infusions in randomized studies. Savings

were attributable to lower acquisition costs of β-lactam antibiotics but not overall hospital expenses [108], and lower costs of vancomycin acquisition and monitoring [109].

XI. Should ASPs Implement Interventions to Increase Use of Oral Antibiotics as a Strategy to Improve Outcomes or Decrease Costs?

Recommendation

12. We recommend ASPs implement programs to increase both appropriate use of oral antibiotics for initial therapy and the timely transition of patients from IV to oral antibiotics *(strong recommendation, moderate-quality evidence)*.

    Comment: Programs to increase the appropriate use of oral antibiotics can reduce costs and length of hospital stay. IV-to-oral conversion of the same antibiotic is less complicated than other strategies and is applicable to many healthcare settings. The conduct of those programs should be integrated into routine pharmacy activities. ASPs should implement strategies to assess patients who can safely complete therapy with an oral regimen to reduce the need for IV catheters and to avoid outpatient parenteral therapy.

Evidence Summary

The findings of many studies [110–116] have shown that programs aimed to increase the use of oral antibiotics are associated with reduced drug costs and length of hospital stay without compromising efficacy or safety. For example, Omidvari et al [115] reported that patients with CAP randomized to receive an abbreviated course of IV cephalosporin followed by oral cephalosporin had a lower total cost of care ($5002 vs $2953; $P < .05$) and shorter hospital stay (10 vs 7 days; $P = .01$) than those treated with conventional IV cephalosporin therapy. There were no differences in clinical course, cure rate, survival, or resolution of chest radiographs [115]. Laing et al [116] reported that the incidence of line complications was lower in patients who were switched to oral therapy than in those who remained on IV therapy (17/81 vs 26/81), but this difference was not significant ($P = .077$).

Unlike automatic conversion from IV to oral formulations of the same antibiotic, switching from IV antibiotics without an equivalent oral formulation needs more advanced assistance. Mertz et al [114] reported that early switching on medical wards was associated with a shorter duration of IV antibiotic treatment (reduction in median days, 19%; 95% CI, 9%–29%; $P = .001$), a trend toward a decreased overall duration of antibiotic treatment, and economic savings—all without significant changes in mortality or readmissions; however, only 151 of 246 (61.1%) of potential cases were switched. This might have been partly attributable to the lack of precise recommendations for switching when an oral equivalent was not available (eg, piperacillin-tazobactam or meropenem) as switching occurred less often in such patients. In contrast, Sevinç et al [112] reported an increased percentage of eligible patients being converted from IV to oral antibiotics (52/97 [54%] vs 66/80 [83%]; difference, 29%; 95% CI, 16%–42%; $P < .001$) after implementation of guidelines for switching therapy. They directed providers to seek infectious diseases consultation for patients on IV formulations without an oral equivalent. ASPs can have an important role with more complicated IV-to-oral transitions.

Another example of the potential benefit of IV-to-oral transition is reduction in the need for outpatient parenteral antibiotic therapy (OPAT). For example, Conant et al [117] reported outcomes in 56 patients who received oral (n = 50) or no additional antibiotics (n = 6) after mandatory infectious diseases approval of OPAT. Denial of OPAT was associated with true clinical failure in only 1 of 56 patients and a per-patient cost savings of $3847.

XII. In Patients With a Reported History of ß-Lactam Allergy, Should ASPs Facilitate Initiatives to Implement Allergy Assessments With the Goal of Improved Use of First-Line Antibiotics?

Recommendation

13. In patients with a history of β-lactam allergy, we suggest that ASPs promote allergy assessments and PCN skin testing when appropriate *(weak recommendation, low-quality evidence)*.

    Comment: Allergy assessments and PCN skin testing can enhance use of first-line agents, but it is largely unstudied as a primary ASP intervention; however, ASPs should promote such assessments with providers. In facilities with appropriate resources for skin testing, the ASPs should actively work to develop testing and treatment strategies with allergists.

Evidence Summary

PCN is the most common drug "allergy" noted at hospital admission, and is reported in 10%–15% of patients and 15%–24% of those requiring antibiotic therapy [118, 119]. Compared with nonallergic patients, patients labeled as having a PCN allergy are exposed to more alternative antibiotics; have increased prevalence of *C. difficile*, methicillin-resistant *S. aureus*, and vancomycin-resistant enterococcal infections; and have longer hospital stays [118].

Properly performed skin testing using major and minor PCN determinant reagents has a negative predictive value of 97%–99% and a positive predictive value of 50%. Studies demonstrate that PCN and other β-lactam antibiotics can be safely given to patients with a putative PCN allergy who have had an allergy assessment and negative PCN skin testing [119, 120]. Rimawi et al [121] reported that all but one of 146 patients with a history of PCN allergy who had a negative skin test tolerated β-lactam therapy, resulting in a negative predictive value of >99%. They also found that the use of skin testing to guide antibiotic therapy yielded an annual savings of $82 000 at a university teaching hospital.

Using structured drug allergy assessments has been associated with improved antibiotic stewardship as demonstrated by antibiotic selection, reduced alternative antibiotic use, decreased length of hospital stay and costs, and increased guideline

adherence [119, 120]. For example, Park et al [122] reported that collaboration between trained pharmacists and allergists was associated with increased β-lactam prescriptions in patients with a history of PCN allergy. ASPs should encourage mechanisms that ensure allergy assessments are performed.

XIII. Should ASPs Implement Interventions to Reduce Antibiotic Therapy to the Shortest Effective Duration?

Recommendation

14. We recommend that ASPs implement guidelines and strategies to reduce antibiotic therapy to the shortest effective duration *(strong recommendation, moderate-quality evidence)*.

    Comment: Recommending a duration of therapy based on patient-specific factors is an important activity for ASPs. Suitable approaches include developing written guidelines with specific suggestions for duration, including duration of therapy recommendations as part of the preauthorization or prospective audit and feedback process, or specifying duration at the time of antibiotic ordering (eg, through an electronic order entry system).

Evidence Summary

Findings from 2 pre–post investigations suggest that antibiotic stewardship interventions aimed at reducing the duration of antibiotic therapy lead to similar clinical outcomes compared with the preintervention period. Specifically, education and PAF for adult inpatients with CAP led to a median decrease in antibiotic use from 10 to 7 days ($P < .001$), with no significant differences in length of stay or 30-day readmission rates [54]. A second study [47] found reduced antibiotic utilization and duration of therapy (from 13 to 10 days; $P < .001$) after implementation of a guideline for inpatients with SSTIs. There are limited studies specifically evaluating the impact of ASP interventions to reduce duration of antibiotic therapy on clinical outcomes; however, evidence from systematic reviews [123–126] and RCTs [127–136] demonstrated that prescription of shorter courses of antibiotic therapy is associated with outcomes similar to those with longer courses in both adults and children with a variety of infection types (Table 2) and few adverse events.

Microbiology and Laboratory Diagnostics

XIV. Should ASPs Work With the Microbiology Laboratory to Develop Stratified Antibiograms, Compared With Nonstratied Antibiograms?

Recommendation

15. We suggest development of stratified antibiograms over solely relying on nonstratified antibiograms to assist ASPs in developing guidelines for empiric therapy *(weak recommendation, low-quality evidence)*.

    Comment: Although there is limited evidence at this time that stratified antibiograms (eg, by location or age) lead to improved empiric antibiotic therapy, stratification can expose important differences in susceptibility, which can help ASPs develop optimized treatment recommendations and guidelines.

Evidence Summary

Institutional antibiograms are helpful to ASPs for the development of guidelines for empiric therapy. The Clinical and Laboratory Standards Institute [137] provides guidelines for antibiogram construction and reporting, both for routine cumulative antibiograms and for enhanced antibiograms, which may be stratified by various parameters including patient location or population if at least 30 isolates are available for each organism. A single institutional, or hospital-wide, antibiogram may mask important susceptibility differences across units within the institution. For example, certain antibiotic-resistant organisms are often significantly more common in ICU than in non-ICU settings. At one medical center, the percentages of bacterial isolates resistant to antibiotics were significantly higher in medical and surgical ICUs than were those predicted by the hospital-wide antibiogram, whereas the percentage of isolates susceptible to antibiotics was higher in non-ICU units, compared with the hospital overall [138]. Similarly, antibiograms can be stratified by population age group (eg, pediatrics) [139], by infection site (eg, blood or respiratory vs all sources) [140, 141], by patient comorbidities (eg, cystic fibrosis) [142], or by acquisition in the community vs healthcare setting [143].

One institution [144] constructed a pediatric-specific antibiogram for *Escherichia coli* and compared it with antibiograms generated from combined data from both adult and pediatric isolates. There were significant antibiotic susceptibility differences between *E. coli* isolates obtained from pediatric patients vs the hospital-wide antibiogram data [144]. Provision of pediatric-specific data optimized prescribing choice when compared with no antibiogram and also with the hospital-wide antibiogram. Another institution [139] also found age-specific differences with overestimation of resistance in *E. coli* and *S. aureus* for children and underestimation for the elderly.

XV. Should ASPs Work With the Microbiology Laboratory to Perform Selective or Cascade Reporting of Antibiotic Susceptibility Test Results?

Recommendation

16. We suggest selective and cascade reporting of antibiotics over reporting of all tested antibiotics *(weak recommendation, low-quality evidence)*.

    Comment: Although data are limited that demonstrate direct impact of those strategies on prescribing, some form of selective or cascaded reporting is reasonable. After implementation, ASPs should review prescribing to ensure there are no unintended consequences.

Evidence Summary

Selective reporting is the practice of reporting susceptibility results for a limited number of antibiotics instead of all tested

Table 2. Meta-analyses and Examples of Randomized Clinical Studies Comparing Shorter Versus Longer Duration of Antibiotics

Reference	Clinical Condition/Population	Treatment Duration, d	Clinical Outcome[a]
Meta-analyses			
Dimopoulos et al, 2008 [123]	Adults and children with CAP	3–7 vs 5–10	Clinical success, relapse, mortality, adverse events
Pugh et al, 2011 [124]	Adults with VAP	7–8 vs 10–15	Antibiotic-free days[b], recurrence[b]
Dimopoulos et al, 2013 [125]	Adults with VAP	7–8 vs 10–15	Relapse, mortality, antibiotic-free days[c]
Randomized clinical trials			
Chastre et al, 2003 [127]	Adults with VAP	8 vs 15	Mortality, recurrent infections[d]
El Moussaoui et al, 2006 [128]	Adults with CAP	3 vs 5	Clinical and radiological success
Greenberg et al, 2014 [129]	Children with CAP	5 vs 10	Treatment failure[e]
Hepburn et al, 2004 [130]	Adults with cellulitis	5 vs 10	Clinical success
Sandberg et al, 2012 [131]	Adult females with acute pyelonephritis	7 vs 14	Clinical efficacy, adverse events
Talan et al, 2000 [132]	Women with acute uncomplicated pyelonephritis	7 vs 14	Bacteriologic and clinical cure[f]
Runyon et al, 1991 [133]	Adults with spontaneous bacterial peritonitis	5 vs 10	Mortality, bacteriologic cure, recurrence
Saini et al, 2011 [134]	Neonatal septicemia	2–4 vs 7 (with sterile culture)	Treatment failure
Sawyer et al, 2015 [135]	Adults with intra-abdominal infection	4 vs ≤10	Composite of surgical site infection, recurrent intra-abdominal infection, or death
Bernard et al, 2015 [136]	Adults with vertebral osteomyelitis	42 vs 84	Cure at 1 y by independent committee and secondary outcomes

Abbreviations: CAP, community-acquired pneumonia; VAP, ventilator-associated pneumonia.

[a] There were no statistically significant between-group differences in outcomes unless otherwise noted.

[b] Shorter course was associated with more antibiotic-free days (mean difference, 4.02; 95% confidence interval [CI], 2.26–5.78) and fewer VAP recurrences due to multidrug-resistant organisms (odds ratio [OR], 0.44; 95% CI, .21–.95), without adverse effects on other outcomes. For VAP due to nonfermenting gram-negative bacilli, however, shorter course was associated with more recurrences (OR, 2.18; 95% CI, 1.14–4.16).

[c] Shorter course was associated with more antibiotic-free days (mean difference, 3.40 days; 95% CI, 1.43–5.37).

[d] Shorter course was associated with more antibiotic-free days (13.1 v 8.7 days; $P < .001$) and no increase in recurrent infection except in the subset with nonfermenting gram-negative bacilli.

[e] The 5-day, but not the 3-day, course was not inferior to the 10-day course.

[f] Shorter course was associated with higher bacteriologic (99% vs 89%; 95% CI, .04–.16; $P = .004$) and clinical cure rates (96% vs 83%; 95% CI, .06–.22; $P = .002$).

antibiotics. For example, a laboratory that practices selective reporting would routinely release linezolid and daptomycin results only when enterococci are nonsusceptible to ampicillin and vancomycin. In a randomized study for urinary tract infections, Coupat et al [145] used a case-vignette format and randomly assigned residents to an intervention group, which received antibiotic susceptibility results for 2–4 antibiotics, or to a control group, which received full-length results for all 25 antibiotics tested. The increase in appropriateness of antibiotic prescription with the use of selective reporting ranged from 7% to 41%, depending upon the clinical scenario. Similar results have been seen in some prospective surveys [146, 147].

Cascade reporting is one type of selective reporting in which susceptibility results of secondary antibiotics (either more costly or broader spectrum) are only reported if an organism is resistant to the primary antibiotic within the particular antibiotic class (eg, if the organism is cefazolin susceptible, ceftriaxone would not be reported). There are no published guidelines for cascade antibiotic reporting. The Clinical and Laboratory Standards Institute [148] provides guidance for testing and reporting susceptibilities for certain organisms, but does not cover all organism-antibiotic combinations. ASPs should work with the microbiology laboratory to assess the impact these strategies may have on development of the antibiogram (eg, susceptibility data for suppressed results may not be available for inclusion).

XVI. Should ASPs Advocate for Use of Rapid Viral Testing for Respiratory Pathogens to Reduce the Use of Inappropriate Antibiotics?

Recommendation

17. We suggest the use of rapid viral testing for respiratory pathogens to reduce the use of inappropriate antibiotics *(weak recommendation, low-quality evidence)*.

    Comment: Although rapid viral testing has the potential to reduce inappropriate use of antibiotics, results have been inconsistent. Few studies have been performed to assess whether active ASP intervention would improve those results.

Evidence Summary

Studies of the value of ASP interventions based on rapid testing for respiratory viruses are lacking. However, some data are available on decreased inappropriate antibiotic use with rapid viral testing. Those studies have been performed primarily in pediatric populations such as children presenting to physicians' offices [149] or emergency departments [150–152], or children requiring hospitalization [153]. One study focused specifically on immunocompromised children [154] and 2 focused on adults [155, 156].

Findings from some trials showed that rapid diagnostic testing for respiratory viruses by rapid antigen, rapid immunoassay, or direct fluorescent antigen was associated with decreased ancillary test orders (eg, chest radiograph, urinalysis) [150, 157], decreased

antibiotic use [149, 150, 153, 156, 157], and increased antiviral use [149, 150, 157]. For example, Bonner et al [150] reported that physician awareness of positive influenza results by a rapid immunoassay reduced the number of laboratory tests ordered ($P = .01$), the number of radiographs ordered ($P < .001$), and the associated charges ($P < .001$). The authors also noted decreased antibiotic use ($P < .001$), increased antiviral use ($P = .02$), and shortened time to discharge ($P < .001$). There was no impact on the above outcomes for patients with negative rapid test results.

Kadmon et al [154] recently reported that polymerase chain reaction (PCR) test results prompted initiation of specific antiviral therapy and avoidance of unnecessary antibiotics in 17 of 50 episodes (34%). Other studies [152, 155], however, have failed to detect statistically significant benefits in antibiotic use, hospital stays, or hospital admissions when reporting PCR or direct fluorescent antigen results. The lack of an appreciable benefit was attributable in part to the time to reporting of PCR results, which ranged from 12 to 24 hours in one study [152] to a mean of 30 hours in another study [155].

XVII. Should ASPs Advocate for Rapid Diagnostic Testing on Blood Specimens to Optimize Antibiotic Therapy and Improve Clinical Outcomes?

Recommendation

18. We suggest rapid diagnostic testing in addition to conventional culture and routine reporting on blood specimens if combined with active ASP support and interpretation *(weak recommendation, moderate-quality evidence)*.

    Comment: Availability of rapid diagnostic tests is expected to increase; thus, ASPs must develop processes and interventions to assist clinicians in interpreting and responding appropriately to results.

Evidence Summary

The use of rapid molecular assays and mass spectrometry to identify bacterial species and susceptibility in blood cultures has been associated with statistically significant improvements in time to initiation of appropriate antibiotic therapy [158–162], rates of recurrent infection [159], mortality [159, 163], length of stay [159, 161], and hospital costs [160, 161]. For example, Forrest et al [163] described the use of peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) for enterococci. Compared with pre–PNA-FISH, rapid testing coupled with antibiotic stewardship team support was associated with more rapid identification of *Enterococcus faecalis* (1.1 vs 4.1 days) and *Enterococcus faecium* (1.1 vs 3.4 days), faster time to effective therapy (1.3 vs 3.1 days), and decreased 30-day mortality for *E. faecium* (26% vs 45%) (all $P < .05$) [163]. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry can rapidly identify bacteria, including rare species not ordinarily associated with clinical infection or pathogens that are difficult to grow or to identify to the species level [164]. In the study by Huang et al [159], the stewardship team received immediate notification of blood culture Gram stain, MALDI-TOF identification, and susceptibility results, and then gave recommendations. MALDI-TOF was associated with more rapid identification of organisms (55.9 vs 84.0 hours; $P < .001$). Identification of organisms with MALDI-TOF in combination with real-time ASP review and intervention was associated with faster time to initiation of both effective (20.4 vs 30.1 hours; $P = .021$) and optimal antibiotic therapy (47.3 vs 90.3 hours; $P < .001$). A recent RCT [162] compared standard blood culture processing (that included MALDI-TOF for organism identification) with rapid multiplex PCR (rmPCR) with templated comments, and rmPCR with templated comments and real-time ASP audit and feedback (rmPCR/AS). Both interventions were associated with greater use of narrow-spectrum β-lactams (rmPCR 71 hours and rmPCR/AS 85 hours vs control 42 hours; $P = .04$) and faster time to appropriate escalation (rmPCR 6 hours and rmPCR/AS 5 hours vs control 24 hours; $P = .04$). The intervention with ASP involvement was also associated with more rapid appropriate de-escalation (21 hours vs control 34 hours and rmPCR 38 hours; $P < .0001$). These interventions were not, however, associated with improved mortality, length of stay, or cost, possibly because of the use of other rapid tests and ASP support at the institution.

These studies underscore the importance of combining use of rapid testing with 2 strategies to maximize the benefits and likelihood of a favorable impact on outcomes. First, ASP support [159–163] or rapid notification of results [158, 162] was a consistent feature of the studies that found statistically significant associations between rapid testing and outcomes. In contrast, studies lacking these features often did not find evidence of associations between rapid testing and improved antibiotic use [165], time to initiation of appropriate antibiotic therapy [166], or length of stay benefit [165]—despite shortening the time to pathogen identification. Second, rapid testing should be performed continuously (ie, 24/7) or at least in frequent batches [167, 168]. The optimal implementation of rapid testing requires increased laboratory resources and additional costs.

XVIII. In Adults in ICUS With Suspected Infection, Should ASPs Advocate PCT Testing as an Intervention to Decrease Antibiotic Use?

Recommendation

19. In adults in ICUs with suspected infection, we suggest the use of serial PCT measurements as an ASP intervention to decrease antibiotic use *(weak recommendation, moderate-quality evidence)*.

    Comment: Although randomized trials, primarily in Europe, have shown reduction in antibiotic use through implementation of PCT algorithms in the ICU, similar data are lacking for other regions including the United States where the patterns of antibiotic prescribing and approach to

stewardship may differ. If implemented, each ASP must develop processes and guidelines to assist clinicians in interpreting and responding appropriately to results, and must determine if this intervention is the best use of its time and resources.

Evidence Summary

PCT has been assessed for its role in (1) shortening the duration of antibiotic therapy for bacterial infection based on serial measurements of PCT levels, and (2) avoidance of initiation of antibiotic therapy when the PCT level is low. Evidence from several prospective RCTs supports the use of PCT in decisions concerning discontinuation of antibiotic therapy in critically ill patients in ICUs [169–172]. In general, trials assessing PCT-guided discontinuation of antibiotic therapy report significantly more antibiotic-free days (2–4 days) in the PCT arm, without a negative effect on mortality. A meta-analysis focusing exclusively on critically ill ICU patients with severe sepsis or septic shock (including 7 studies and 1075 patients) showed no significant difference in 28-day mortality or hospital mortality and a median reduction of approximately 2 days in the length of antibiotic therapy with PCT guidance [173]. In a European multicenter study, Bouadma et al [172] examined de-escalation of therapy in 621 septic patients and demonstrated 2.7 more antibiotic-free days in the PCT group ($P < .001$), although days of antibiotic exposure per 1000 inpatient-days were high for each group (653 PCT vs 812 control) [172]. Available evidence does not support the use of PCT to avoid initiation of antibiotics in the critically ill ICU population when the PCT result is negative [174, 175].

XIX. In Patients With Hematologic Malignancy, Should ASPs Advocate for Incorporation of Nonculture-Based Fungal Markers in Interventions to Optimize Antifungal Use?

Recommendation

20. In patients with hematologic malignancy at risk of contracting IFD, we suggest incorporating nonculture-based fungal markers in ASP interventions to optimize antifungal use *(weak recommendation, low-quality evidence)*.

    Comment: ASPs with an existing intervention to optimize antifungal use in patients with hematologic malignancy can consider algorithms incorporating nonculture-based fungal markers. Those interventions must be done in close collaboration with the primary teams (eg, hematology-oncology). Antibiotic stewards must develop expertise in antifungal therapy and fungal diagnostics for the programs to be successful. The value of those markers for interventions in other populations has not been demonstrated.

Evidence Summary

Some studies have demonstrated that the use of nonculture-based fungal markers can safely reduce antifungal treatments for patients with hematologic malignancy at high risk for IFD. Although not specifically studied as part of an ASP intervention, incorporation into existing ASPs for antifungal stewardship in that population may be useful. A variety of fungal tests such as galactomannan (GM), (1,3)-β-D-glucan (BDG), or single- or multipathogen fungal PCR have been studied. For example, Cordonnier et al [176] compared a preemptive approach (antifungal treatment initiation using both clinical and GM evidence of IFD) with an empiric strategy (antifungal treatment for any high-risk patient with suggestive clinical signs of IFD). The preemptive approach was associated with decreased antifungal treatment (39.2% vs 61.3%; $P < .001$) and no detrimental effect on mortality.

Few studies assessed utilization of BDG or PCR to target therapy. An RCT [177] of *Aspergillus* and *Candida* PCR compared survival between allogeneic stem cell transplant recipients who received empiric antifungal treatment with those who received empiric plus PCR-based antifungal treatment. The authors demonstrated improved 30-day survival in the group in which treatment decisions were in part based upon PCR, but survival did not differ by day 100.

There are limited data assessing the value of fungal markers in other patient populations. Pediatric data are limited, but studies [178] have shown that GM assay is a useful adjunctive tool when monitored twice weekly in hospitalized children with hematologic malignancies and fever.

Measurement

XX. Which Overall Measures Best Reflect the Impact of ASPs and Their Interventions?

Recommendation

21. We suggest monitoring antibiotic use as measured by DOTs in preference to DDD *(weak recommendation, low-quality evidence)*.

    Comment: Every ASP must measure antibiotic use, stratified by antibiotic. DOTs are preferred, but DDDs remain an alternative for sites that cannot obtain patient-level antibiotic use data. ASPs should consider measurement of appropriate antibiotic use within their own institutions by examining compliance with local or national guidelines, particularly when assessing results of a targeted intervention, and share that data with clinicians to help inform their practice. Although rates of CDI or antibiotic resistance may not reflect ASP impact (because those outcomes are affected by patient population, infection control, and other factors), those outcomes may also be used for measurement of targeted interventions.

Evidence Summary

DOTs and DDDs are standardized methods for measurement of antibiotic use. Both are useful for facility-level monitoring and interfacility comparisons. DOTs have some important advantages. DOTs are not impacted by dose adjustments and can be used in both adult and pediatric populations, whereas DDDs have more limited use in pediatrics due to weight-based dosing. In addition, the Antimicrobial Use and Resistance Module in

the CDC's National Healthcare Safety Network requires reporting of antibiotic use by DOTs [179]. DOTs, however, require patient-level antibiotic use data, which currently may not be feasible at every facility [180–182]. Either method can be used to examine overall use or specific use by unit, provider, or service in the hospital. In addition to measurement of antibiotic use, appropriateness of prescribing can be assessed by determining compliance with facility-specific antibiotic treatment guidelines. This is particularly useful when assessing the success of a targeted intervention.

Measurement of ASP impact on patient outcomes is important but is more challenging than measurement of antibiotic use or guideline compliance. For example, using CDI rates to measure the effectiveness of stewardship interventions has significant limitations. Although implementation of ASPs has been associated with reduced CDI rates in quasi-experimental studies [18], the quantitative relationships between changes in antibiotic use and CDI incidence are largely unknown. Because CDI rates are affected by other practices besides antibiotic use, such as compliance with infection control measures, they may be a relatively insensitive metric for judging the effectiveness of ASPs. Moreover, traditional statistical techniques have significant limitations when applied to nonindependent events such as CDI. Despite this, when implementing ASP interventions directed at reduction of antibiotics considered to be high risk for promoting CDI (eg, cephalosporins, clindamycin, fluoroquinolones), including rates of healthcare-facility-onset CDI as a secondary outcome measure is recommended in that population.

Antibiotic resistance is an even more complex metric than CDI because the development and spread of resistance is impacted by many factors. Implementation of stewardship interventions has been associated with reduced resistance in both gram-positive and gram-negative bacteria [34]; however, observed effects on resistance are unpredictable because of confounding variables and many pathogen and host factors. Still, measurement of resistance may be useful for selected bacterial pathogens and in focused patient populations receiving a targeted ASP intervention.

ASPs have the potential to decrease length of stay, primarily as a consequence of timely switching from IV to oral antibiotics or by stopping unnecessary IV antibiotics; however, the impact depends on the preexisting contribution of prolonged administration of parenteral antibiotics to excess length of stay. Days of hospitalization avoided is a better measure of the effectiveness of ASP. Parenteral therapy and days of central venous access avoided are other metrics that can be useful.

XXI. What is the Best Measure of Expenditures on Antibiotics to Assess the Impact of ASPs and Interventions?

Recommendation

22. We recommend measuring antibiotic costs based on prescriptions or administrations instead of purchasing data *(good practice recommendation)*.

Evidence Summary

ASPs result in cost savings for facilities [183]. It is important to monitor program costs in addition to measuring antibiotic use as one way to justify continued administrative support for ASP activities. Antibiotic costs should be measured based on prescriptions or administrations instead of purchasing data [184] and normalized to account for patient census (eg, antibiotic cost per patient-day) [184]. Program costs (eg, salary for stewardship personnel) [19, 185] and adjustment for inflation or standardizing costs across years [185] should be considered. Analyses that measure the effects of an intervention over time should compare actual costs after the initiation of the intervention vs projected costs in the absence of the intervention, as direct cost reductions tend to plateau [185, 186]. More robust analyses include expenditures beyond drug acquisition such as those for drug administration, therapeutic drug monitoring, and toxicities [187]. If resources are available, programs should analyze broader effects on budgets, such as total hospitalization costs [58, 160, 188].

XXII. What Measures Best Reect the Impact of Interventions to Improve Antibiotic Use and Clinical Outcomes in Patients With Specific Infectious Diseases Syndromes?

Recommendation

23. Measures that consider the goals and size of the syndrome-specific intervention should be used *(good practice recommendation)*.

Evidence Summary

The choice of metrics for syndrome-specific interventions (see Section IV) to improve therapy can measure process or outcome (Table 3) [39, 50–57, 189–191]. For example, interventions designed to increase compliance with a guideline should evaluate the proportion of patients in each period who are compliant. Evidence of unintended negative effects such as hospital readmission or increase in rates of hospital-acquired CDI should also be monitored. The major limitation to these metrics is the availability of reliable data.

Special Populations

XXIII. Should ASPs Develop Facility-Specific Clinical Guidelines for Management of F&N in Hematology-Oncology Patients to Reduce Unnecessary Antibiotic Use and Improve Outcomes?

Recommendation

24. We suggest ASPs develop facility-specific guidelines for F&N management in hematology-oncology patients over no such approach *(weak recommendation, low-quality evidence)*.

    Comment: Clinical guidelines with an implementation and dissemination strategy can be successfully used in the care of cancer patients with F&N and are strongly encouraged.

Table 3. Possible Metrics for Evaluation of Interventions to Improve Antibiotic Use and Clinical Outcomes in Patients With Specific Infectious Diseases Syndromes

Process Measures	Outcome Measures
Excess days of therapy (ie, unnecessary days of therapy avoided based on accepted targets and benchmarks)[a]	Hospital length of stay
Duration of therapy	30-day mortality
Proportion of patients compliant with facility-based guideline or treatment algorithm[a]	Unplanned hospital readmission within 30 d
Proportion of patients with revision of antibiotics based on microbiology data	Proportion of patients diagnosed with hospital-acquired *Clostridium difficile* infection or other adverse event(s) related to antibiotic treatment[a]
Proportion of patients converted to oral therapy	Proportion of patients with clinical failure (eg, need to broaden therapy, recurrence of infection)

Sources: [39, 50–57, 189–191].

[a] These metrics are applicable for antibiotic stewardship program interventions to reduce antibiotic treatment of asymptomatic bacteriuria, which, in most cases, should not be treated; therefore, the other metrics do not apply.

Evidence Summary

Implementing clinical pathways for management of F&N can reduce unnecessary antibiotic use without adverse outcomes in hematology-oncology units, although data are limited. Nucci et al [192] reported that adoption of 1997 IDSA guidelines in patients with hematologic malignancies or who were undergoing hematopoietic stem cell transplant was associated with reductions in empiric glycopeptide use (pre- vs postguidelines: 33% vs 7% of F&N episodes; $P < .0001$) and total glycopeptide use (73% vs 43% of F&N episodes; $P = .0008$). Success rates for empiric regimen, time to defervescence, duration of antibiotic therapy, and death rates were similar before and after guideline adoption. No deaths were attributed to infections due to gram-positive organisms [192].

Studies have shown that adherence to treatment guidelines resulted in improvement in important clinical outcomes. For example, Pakakasama et al [193] demonstrated that implementation of clinical guidelines in pediatric cancer patients resulted in statistically significant reductions in septic shock (intervention vs control: 3.5% vs 10.9%; $P = .011$), ICU admissions (2.9% vs 9.4%; $P = .016$), and death (0% vs 6.5%; $P = .001$). In another study [194], adherence to an ASP protocol for initial antibiotic therapy based on IDSA guidelines was associated with lower mortality (hazard ratio, 0.36; 95% CI, .14–.92) in 169 adult patients with 307 episodes of F&N (79% with hematologic malignancy).

XXIV. In Immunocompromised Patients Receiving Antifungal Therapy, do Interventions by ASPs Improve Utilization and Outcomes?

Recommendation

25. We suggest implementation of ASP interventions to improve the appropriate prescribing of antifungal treatment in immunocompromised patients *(weak recommendation, low-quality evidence)*.

Comment: In facilities with large immunocompromised patient populations, ASP interventions targeting antifungal therapy can show benefit. Those interventions must be done in close collaboration with the primary teams (eg, hematology-oncology, solid organ transplant providers). Antibiotic stewards must develop expertise in antifungal therapy and fungal diagnostics for the programs to be successful.

Evidence Summary

Programs that have successfully implemented antifungal stewardship interventions have used a multipronged approach that included PAF, education, and development of clinical guidelines [195–198]. Published studies have not focused exclusively on immunocompromised patients, but those patients accounted for the largest group in most reports. Patients in the ICU made up the second-largest group. One study [196] reviewed 636 antifungal prescriptions for 6 years after implementing an antifungal ASP, of which 72% were from the adult and pediatric hematology services. That study utilized their ASP to provide feedback to the primary teams regarding fungal diagnosis, serologic and radiographic investigations, drug therapeutic monitoring, and/or starting, stopping, or modifying antifungal therapy. The primary teams had a high compliance rate (88%) with the ASP recommendations. Process of care measures for the management of candidemia and aspergillosis (eg, optimal voriconazole monitoring, use of recommended first-line therapy) improved. Patient outcomes were favorable in 47 of 63 (75%) patients with aspergillosis and 52 of 60 (87%) with candidemia, and did not change significantly during the observation period—although the study was underpowered to demonstrate improvement. The total cost of antifungals was considered to be stable and actually decreased in the year just after the formal study ended.

In a second study [197], the stewardship team focused on high-cost antifungals at a tertiary hospital in 173 patients over a 12-month period. The following antifungal agents were successfully stopped or switched: liposomal amphotericin B (51/125 [41%]), caspofungin (8/11 [73%]), micafungin (33/51 [65%]), and combination therapy (5/10 [50%]). In contrast, voriconazole was stopped or switched in only 16 of 89 (18%) patients. The total annual cost for these 4 antifungal agents fell from £1.835 million before the ASP intervention to £1.656 million during intervention, resulting in a crude savings of £179 000.

XXV. In Residents of Nursing Homes and Skilled Nursing Facilities, do Antibiotic Stewardship Strategies Decrease Unnecessary Use of Antibiotics and Improve Clinical Outcomes?

Recommendation

26. In nursing homes and skilled nursing facilities, we suggest implementation of antibiotic stewardship strategies to decrease unnecessary use of antibiotics *(good practice recommendation)*.

Comment: Implementing ASPs at nursing homes and

skilled nursing facilities is important and must involve point-of-care providers to be successful. The traditional physician–pharmacist team may not be available on-site, and facilities might need to investigate other approaches to review and optimize antibiotic use, such as obtaining infectious diseases expertise through telemedicine consultation.

Evidence Summary

Nursing homes are significant reservoirs for multidrug-resistant organisms [199]. Developing approaches to improve antibiotic use is important; however, few studies have shown an impact on clinical outcomes.

Jump et al [200] reported a decrease in systemic antibiotic use by 30.1% ($P < .001$) and fewer positive *C. difficile* tests ($P = .04$) after initiating an infectious diseases consultation service at a single Veterans Affairs long-term care facility. The intervention included 24/7 consultation availability by telephone, with weekly on-site case review by an infectious diseases physician and a nurse practitioner. This model, however, may not be possible in many US nursing homes given resource restraints such as lack of finances, availability of an infectious diseases physician, and interest.

Schwartz et al [201] conducted an intervention that included physician education, guideline implementation, and presentation of local baseline antibiotic use data in a public long-term care facility with 20 salaried internists. Antibiotic starts decreased by 25.9%, and antibiotic DOTs decreased by 29.7%; those decreases were sustained for a 2-year follow-up period. This level of physician staffing, however, is not typical of most facilities.

Stewardship interventions inclusive of the nursing staff have been successful in reducing antibiotic use, but the effect on clinical outcome is not usually reported. Fleet et al [202] evaluated the impact of the Resident Antimicrobial Management Plan at 30 nursing homes in England. The nursing staff received written educational materials and used this tool to record compliance with good practice points at treatment initiation and 48–72 hours later. Antibiotic consumption over 12 weeks decreased by 4.9% (95% CI, 1.0%–8.6%; $P = .02$) in the intervention group and increased by 5.1% (95% CI, .2%–10.2%; $P = .04$) in the control group. Loeb et al [189] studied a multifaceted educational intervention for urinary tract infections that included a diagnostic and treatment algorithm at 24 nursing homes in Ontario, Canada and Idaho. Antibiotic use for suspected urinary tract infection was lower at intervention than at usual-care nursing homes (1.17 vs 1.59 courses per 1000 resident-days; weighted mean difference, −0.49; 95% CI, −.93 to −.06). Zimmerman et al [203] assessed a quality improvement program at 12 nursing homes in North Carolina. This multifaceted program consisted of guideline education for providers, sensitization to antibiotic prescribing matters for nursing staff and family members, and prescribing feedback for providers and nursing staff. Between baseline and follow-up at 9 months, prescription rates dropped more at intervention homes (13.16 vs 9.51 per 1000 resident-days) than at comparison homes (12.70 vs 11.80 per 1000 resident-days; pooled difference in differences, −2.75; $P = .05$).

XXVI. In NICUs, do Antibiotic Stewardship Interventions Reduce Inappropriate Antibiotic Use and/or Resistance?

Recommendation

27. We suggest implementation of antibiotic stewardship interventions to reduce inappropriate antibiotic use and/or resistance in the NICU *(good practice recommendation)*.

Evidence Summary

Limited evidence is available to determine the most effective ASP strategies in the NICU, but general principles should apply [204].

Antibiotic policy and guidelines have been shown to be effective in the NICU [205]. After implementing a vancomycin guideline, Chiu et al [206] saw a 35% reduction in the initiation of vancomycin and a 65% overall decrease in exposure to vancomycin compared with the preimplementation period. Zingg et al [205] evaluated antibiotic use after initiating a policy to shorten antibiotic therapy for sepsis and coagulase-negative staphylococcal infection, and to stop preemptive treatment if blood cultures were negative. They found an overall 2.8% yearly reduction in antibiotic use ($P < .001$) without increasing mortality. Antibiotic restriction interventions can be successful in the NICU. For example, Murki et al [207] reported that restricting all cephalosporin classes was associated with a 22% decreased incidence of extended-spectrum β-lactamase–producing, gram-negative infections compared with the previous year ($P = .03$). The proportion of ampicillin use increased from 12.8% to 25.7% ($P < .001$) after the intervention, and the proportion of cephalosporin use declined from 15.8% to 3.0% ($P < .001$).

XXVII. Should Antimicrobial Stewardship Programs Implement Interventions to Reduce Antibiotic Therapy in Terminally Ill Patients?

Recommendation

28. In terminally ill patients, we suggest ASPs provide support to clinical care providers in decisions related to antibiotic treatment *(good practice recommendation)*.

Evidence Summary

End of life is defined as the final days or weeks of life in patients under hospice care where the primary goals are managing symptoms, improving comfort, and optimizing quality of life—not prolonging survival. In contrast, palliative care is more general and can be pursued along with curative therapies.

Antibiotic use, frequently with multiple antibiotics, is common in patients with terminal cancer. Therapy is often continued after transition to comfort care and discontinued less than 1 day prior to death [208]. Patients with advanced dementia also have high exposure to antibiotics, especially in the weeks prior

to death [209]. Therefore, older adults with advanced dementia or who are in long-term care facilities [209] and patients receiving end-of-life treatment in the ICU [210] may become reservoirs for resistant bacteria. For example, end-of-life antibiotic treatment in the ICU was independently associated with acquisition of resistant bacteria in a logistic regression analysis [210].

For patients under hospice care, the impact of antibiotic therapy on symptom alleviation should be considered in the context of specific infections [208, 211]. For example, treating urinary tract infection may improve dysuria and treating thrush may improve dysphagia [211, 212], but the impact of antibiotics on the symptoms of respiratory tract infection is less clear [213–216]. Givens et al [213] reported that, compared with no antibiotic therapy, antibiotic treatment of suspected pneumonia in patients with advanced dementia via any route of administration was associated with improved survival but less comfort ($P < .001$ for all comparisons) as measured by the Symptom Management at End of Life Dementia scale. In contrast, antibiotic treatment of pneumonia in nursing home residents with dementia was associated with fewer symptoms in 2 Dutch studies. Van der Steen et al [214] reported that the level of discomfort was generally higher in patients for whom antibiotic therapy was withheld in nonsurvivors compared with surviving patients treated with antibiotics; however, those nonsurvivor patients had more discomfort before pneumonia developed. Subsequently, Van der Steen et al [215] reported fewer symptoms if pneumonia was treated with antibiotics rather than just fluids in patients with dementia even if death was imminent; the majority of patients received oral therapy. If prolonging survival is not a primary goal, withholding antibiotic agents should be considered. If treatment is desired, antibiotic agents should be administered orally whenever possible.

Patients and their surrogates should be engaged in the decision to use antibiotic agents at end of life. Stiel et al [217] reported that families of terminally ill cancer patients are often consulted about stopping antibiotics, but the decision to start therapy is usually made by clinicians without much discussion. Similarly, Givens et al [218] reported that most infectious episodes in nursing home residents with advanced dementia did not involve healthcare proxies in decision making.

Given significant treatment burdens, potential for adverse effects such as CDI, and public health risks, antibiotic therapy should be viewed as aggressive care in the end-of-life setting.

CONCLUSIONS

This guideline discusses a broad range of possible ASP interventions. We have emphasized the need for each site to assess its clinical needs and available resources and individualize its ASP with that assessment in mind.

A powerful way to support antibiotic stewardship is to improve the scientific basis for ASP interventions. As outlined in Section XIII, ASPs can successfully intervene to reduce the duration of therapy for many infections because well-constructed, randomized controlled clinical trials have demonstrated that clinical outcomes are equivalent. Rigorous published evidence is often needed to convince clinicians to alter well-established, albeit suboptimal, practice. For example, ASPs can cite high-quality data to reduce unnecessary antibiotic treatment of uncomplicated diverticulitis [219], or ASB (eg, in women 60 years or younger, diabetic patients, or the elderly) [220]. Additional clinical trials that incorporate consideration of antibiotic stewardship in their design are critically needed.

Another significant gap is the dearth of implementation research in this area [28]. Although the National Action Plan for Combating Antibiotic-Resistant Bacteria [6] will require the institution of ASPs across healthcare facilities, little effort and limited research funding have been allocated to study how best to achieve large-scale implementation. Qualitative assessments that can examine the impact of factors such as organizational culture, prescriber attitudes, and the self- efficacy of the antibiotic steward (ie, the extent to which he/she believes his/her goals can be reached) are lacking and are important to establish the context in which ASP implementation occurs [221, 222]. There is inadequate information on the best model for an ASP. For example, should stewards use the "bundle" approach that has been applied to ventilator-associated pneumonia [223] and central line–associated bloodstream infection with great success [224]? Although ASPs have studied application of a combination of interventions, they are not comparable to existing bundles because they require interpretation, expertise, and persuasion [225]. A new or adapted model for ASP is likely needed and best developed through application of rigorous implementation science.

Despite the recognition that much more research is needed, this guideline identifies core interventions for all ASPs as well as other interventions that can be implemented based on facility-specific assessments of need and resources. Every healthcare facility is able to perform stewardship, and institution of an ASP is attainable and of great importance to public health.

Notes

Acknowledgments. The expert panel expresses its gratitude to Drs Elizabeth Dodds Ashley, Annie Wong-Beringer, and Stan Deresinski for their thoughtful reviews of earlier drafts of the guideline. The panel greatly appreciates the work of Charles B. Wessels and Michele Klein Fedyshin of the Health Sciences Library System of the University of Pittsburgh for the development and execution of the systematic literature searches for this guideline, and Jennifer J. Padberg, MPH, for her administrative assistance throughout the guideline development process.

Financial support. Support for these guidelines was provided by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America.

Potential conflicts of interest. The following list is a reflection of what has been reported to IDSA. To provide thorough transparency, IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process that includes assessment by the Standards and Practice Guidelines Committee (SPGC) chair, the SPGC liaison to the

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