Chapter 1

The Need for Antibiotic Stewardship Programs

An Introduction

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Access to effective antibiotic therapy is essential to modern medicine. Not only are antibiotics lifesaving for the treatment of many infections, but they also provide the means for preventing and treating life-threatening complications among the growing numbers of patients receiving chemotherapy and stem cell and solid organ transplantation, thus making those therapeutic advances possible. However, antibiotic resistance has developed with each new drug introduced to the market. Although we know the development of resistance is almost certain with exposure to any antibiotic, inappropriate and/or unnecessary antibiotic use is accelerating the process. Realizing antibiotic resistance threatens the achievements of modern medicine, infectious diseases (ID) physicians, pharmacists, and public health officials have warned of the consequences of inappropriate antibiotic use for decades and advocated for preservation of these lifesaving drugs. Halting unnecessary antibiotic use has undoubtedly become one of the leading public health concerns of our time.

An estimated 50% of antibiotic use is inappropriate and/or unnecessary.[1–3] These estimates span inpatient and outpatient settings, various types of providers, and various indications or diagnoses, highlighting the breadth of the problem. Rates of antibiotic resistance have risen dramatically over the last 30 years. In 2013, the Centers for Disease Control and Prevention (CDC) estimated that 2 million people are infected annually in the United States with antibiotic-resistant bacteria, with at least 23,000 resultant deaths.[4] Additionally, roughly 453,000 people contract *Clostridium difficile* infections (CDIs) annually in the United States with nearly 30,000 deaths attributable to this single bacterium. CDI is frequently directly related to antibiotic use.[5]

Antibiotic stewardship programs (ASPs) date back to the 1970s and encompass multidisciplinary efforts to optimize antibiotic use.[6–8] Evidence has shown that effective ASPs not only reduce inappropriate antibiotic use but also improve patient safety and clinical outcomes.[9] Thus, ASPs have expanded across various healthcare settings in an effort to optimize antibiotic use and minimize adverse events and emergence of antibiotic resistance. This chapter focuses mostly on antibiotic stewardship efforts in the United States, although a brief discussion of global strategies is also addressed.

Numerous societies and public health officials have advocated for the expansion of antibiotic stewardship efforts across healthcare. In response to antibiotic overuse, evidence supporting the role of ASPs, and the critical threat antibiotic resistance poses to public health, they have called for mandatory implementation of stewardship through legislative and regulatory mechanisms.[10] These efforts culminated with the release of President Obama's *National Strategy for Combating Antibiotic-Resistant Bacteria* in September 2014, which outlines a framework for implementation of stewardship across the healthcare continuum, improved surveillance of antibiotic use, and national goals for reductions in inappropriate prescribing.[11] These

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national goals lend new urgency to efforts to implement antibiotic stewardship strategies across healthcare settings and to develop standardized measures for appropriate antibiotic use.

Our goal in this chapter is to highlight the issues surrounding misuse of antibiotics that underscore the importance and need for ASPs, review evidence supporting the role of ASPs in improving patient care and safety, discuss policy initiatives and the evolution of antibiotic stewardship efforts to date, and underline next steps in preserving the precious shared resource of antibiotics.

Rationale for Antibiotic Stewardship Programs

The Scope of the Problem

Hospitals

Antibiotics are among the most frequently prescribed medications. Systematic surveys of inpatients at Boston City Hospital as far back as the 1960s found nearly 30% of patients received antibiotics during their hospitalization, with almost 10% receiving more than one antibiotic.[12, 13] Similar rates of antibiotic use have been reported in a variety of inpatient settings including acute care hospitals based in the community and tertiary care settings,[12, 14] as well as long-term care facilities (LTCFs).[15] Using data from a national administrative database of billing records for patients from a large sample of US hospitals, investigators from the CDC estimated 56% of patients discharged from 323 hospitals in 2010 received an antibiotic during their hospitalization.[3] These rates of antibiotic use have been reported among various patient populations, with the highest prescribing rates often among pediatric and surgical services.[14, 15]

More recent estimates of inpatient antibiotic consumption in the United States come from single or multicenter point-prevalence surveys. Although limited by lack of nationally representative samples and varying sources of data (e.g., pharmacy purchasing data, pharmacy order data, or antibiotic administration data), estimates have repeatedly found that nearly half of hospitalized adults and children receive an antibiotic during their hospitalization.[1, 16] Recognizing limitations of using indirect measurements such as administrative data to delineate the epidemiology of inpatient antibiotic use, CDCs' Emerging Infections Program (EIP) conducted an antibiotic use point-prevalence survey in 183 acute care hospitals across multiple states in one day in 2011.[1] The EIP is a network of ten state health departments and local collaborators representative of the US population. It conducts surveillance and evaluates methods for prevention and control of emerging IDs. Investigators determined not only the prevalence of inpatient antibiotic use across EIP sites, but also the most commonly used drugs and indications. Magill and colleagues found 50% of 11,282 inpatients evaluated received an antibiotic at some point during their hospitalization.[1] The most commonly prescribed drugs included vancomycin (14%), ceftriaxone (11%), piperacillin/tazobactam (10%), and levofloxacin (9%), in total accounting for approximately 45% of all antibiotic therapy.[1] This survey is one of the largest evaluations of inpatient antibiotic use in the United States to date. It confirms previous estimates of inpatient antibiotic use and additionally highlights the common use of broad-spectrum agents even for community-onset infections. The National Healthcare Safety Network (NHSN) recently launched the Antimicrobial Use and Resistance (AUR) Module, facilitating electronic reporting of antibiotic use data that will allow for prospective antibiotic use surveillance and assist with local and national stewardship efforts.[17]

Numerous evaluations of inpatient antibiotic prescribing quality have been conducted to estimate rates of inappropriate and therefore, modifiable antibiotic use. From these evaluations, 25% to 50% of inpatient antibiotic use is deemed inappropriate and/or unnecessary.[1–3] Common reasons for unnecessary or inappropriate antibiotic use include treatment of noninfectious or nonbacterial syndromes, treatment of colonization or contamination, use of overly broad-spectrum antibiotic therapy, and longer than necessary durations of therapy.[18] Most published assessments come from single center evaluations and focus on empiric and definitive drug selection.[14, 19–25] More recent evaluations involve in-depth evaluations of antibiotic prescribing including diagnostic evaluation, drug dosing, and duration of therapy.[26–31] No standard definition of inappropriate antibiotic use exists or is applied across studies, limiting interpretation of results and application to other settings. Most studies rely on expert opinion based on chart review to define appropriate therapy.[22, 23, 26, 28, 30, 32, 33] While more detailed in scope, these evaluations are often labor intensive and difficult to reproduce. Recently, large-scale national and multi-national antibiotic prescribing surveys have been conducted with the use of audit tools developed based on national guidelines and consensus expert opinion.[34–36] These tools are designed for use across various healthcare settings and by professionals of varying clinical expertise. For example, the Australian National Antibiotic Prescribing Survey (NAPS) is conducted annually using a published audit tool. The 2014 results showed a 38% prevalence of antibiotic use among inpatients, with nearly a quarter (23%) considered inappropriate.[37] In the United States, CDC in collaboration with external experts developed audit tools aimed at assessing the appropriateness of inpatient antibiotic use. These tools served as a foundation for the 2011 EIP Antibiotic Use Point Prevalence Survey, which on review of 296 inpatient antibiotic courses found prescribing could be improved in 37% of cases (40% of 111 urinary tract infection [UTI] cases and 36% of 185 vancomycin courses).[3] Standard audit tools are facilitating larger scale qualitative evaluations of antibiotic prescribing. With expanded use of electronic medical records, electronic audits may be possible in the future, making broader evaluations of antibiotic prescribing quality and real-time alerting of patients' charts for ASP review feasible.

Outpatient Settings

While we are gaining a better understanding of the epidemiology of inpatient antibiotic prescribing, the prevalence and various factors affecting antibiotic prescribing patterns have been better characterized for outpatient settings. Data from nearly 50 years ago shows antibiotics are the most commonly prescribed medication in outpatient settings, accounting for 15% of all prescriptions.[38] In 2009, antibiotic expenditures in outpatient settings in the United States totaled $10.7 billion, accounting for over 60% of all antibiotic expenditures across all healthcare settings.[39] Data highlighting the large role outpatient settings play in overall antibiotic use stresses the importance of effective outpatient antibiotic stewardship efforts.

Outpatient antibiotic prescribing rates are highest for children and for adults over the age of 65 years; 50–60% of all antibiotic prescriptions written are for acute respiratory infections (ARIs), which are largely viral in etiology.[40–43] While prescriptions for ARIs in children are declining,[40] data from the Veterans Affairs population and others suggests antibiotic prescriptions for ARIs in adults have remained relatively stable; 69% of Veterans received antibiotics for ARI diagnoses in 2012 as compared to 68% in 2005.[43, 44] Additionally, broad-spectrum agents such as macrolides and fluoroquinolones are commonly used when either an antibiotic is not indicated or a narrower spectrum drug would suffice.[41, 43]

Further characterizations of outpatient antibiotic prescribing patterns have highlighted geographic and provider factors associated with high prescribing rates, potential targets for outpatient stewardship efforts. Higher outpatient antibiotic prescription rates are seen in southern states with family practice physicians prescribing the largest proportion of antibiotic courses.[42, 45] Interestingly, counties with higher proportions of obese patients, children under the age of two years, females, and prescribers per capita have higher antibiotic prescribing rates.[45] Substantial variation in providers' prescribing practices exists, and understanding factors associated with high prescribing is paramount to reducing unnecessary antibiotic use.[43] Interviews of primary care providers indicate providers are knowledgeable about guideline recommendations; however, they often stray from guideline recommendations due to the fear the infection is bacterial, belief that broad-spectrum antibiotics are more likely to cure the infection, and concern for poor patient and parent satisfaction if an antibiotic is not prescribed.[46] Additionally, knowledge of definitions of broad and narrow-spectrum antibiotic agents is poor;[46] therefore, providers may not understand the implications of the antibiotic choice. This information highlights variations in knowledge and attitudes around antibiotic use that may explain variation in practice (see Chapter 3) and should be tackled in order to limit unnecessary antibiotic use.

The Rise of Antibiotic Resistance and Other Adverse Events

Antibiotic resistance has been regarded as a modern phenomenon; however, resistance predates human use of antibiotics and evolving evidence implicates environmental organisms as reservoirs of antibiotic resistance genes. Resistance genes have been detected in 30,000-year-old permafrost sediment and culturable microbiome from a cave isolated from human contact.[47, 48] When populations of bacteria are exposed to antibiotics, susceptible organisms are killed and subpopulations harboring resistance genes may survive resulting in a population of antibiotic-resistant bacteria capable of causing subsequent infection in the host, or spread to others.[49] Additionally, new resistance mutations can develop upon exposure to antibiotics. The more antibiotics are used, the faster these processes happen.

We have seen this repeatedly since the first antibiotics were introduced into clinical practice over 70 years ago. As new antibiotics are released for clinical use, resistance to most is detected within five to ten years.[50] Case-control studies confirm the relationship between antibiotic exposure and subsequent antibiotic-resistant infections. For example, strong associations have been noted with antecedent carbapenem exposure and carbapenem-resistant *Klebsiella pneumoniae* infections. Similarly, receipt of cephalosporins has been identified as a risk factor for subsequent extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* and *Klebsiella* species infections.[51, 52] In 2013, CDC released a report providing the first overview of antibiotic-resistant organisms and other infections directly related to antibiotic use such as *Clostridium difficile*, and their threat to human health.[4] Carbapenem-resistant *Enterobacteriaceae*, drug-resistant *Neisseria gonorrhoeae* and *C. difficile* are among the most urgent threats. While antibiotic resistance is on the rise, development of new antibiotics has slowed,[53] highlighting the urgent need to curb unnecessary antibiotic prescribing and begin an era of responsible antibiotic use.

Antibiotic use is the single most significant risk factor for CDI.[54] Individual drug risks may vary, but nearly every antibiotic carries a threat of CDI with risk accumulating with

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increasing numbers of drugs, dose and duration.[55] The epidemiology of *C. difficile* changed in the early 2000s with emergence of the North American pulsed-field gel electrophoresis type 1 (NAP1) strain. The NAP1 strain is associated with higher rates of infection, more severe disease, increased risk of relapse, and increased mortality.[56, 57] Not only has *C. difficile* become the most common cause of healthcare-associated infections in US hospitals, but it is increasingly reported in community settings as well.[58] Based on active population surveillance through CDC's EIP network that encompasses both inpatient and outpatient locations, it is estimated that nearly 500,000 incident CDIs occur annually in the United States, with nearly 30,000 deaths.[5] Although possibly influenced by use of more sensitive testing methods, increasing rates of this largely preventable infection are alarming. CDI has arguably become one of the most difficult infections of our time; antibiotic stewardship is and will continue to be a key component of its prevention.

CDI is one of the most severe adverse side effects resulting from antibiotic use; however, adverse drug events (ADEs) such as allergic reactions, drug toxicities, organ dysfunction, and unintended drug interactions may occur. Data suggest ADEs related to antibiotic use are not uncommon. An estimated 142,505 annual visits are made to emergency departments in the United States for antibiotic-related ADEs.[59] Antibiotics are implicated in 20% of all emergency department visits for ADEs, with the majority related to allergic reactions (78.7%).[59] Antibiotics are the most common drugs implicated in emergency department visits for ADEs in children.[4] Additionally, antibiotic ADEs in inpatients are associated with longer lengths of stay and higher hospital costs.[60] Providers do not always seem to appreciate the harms associated with antibiotic use; perhaps greater awareness of the harms of antibiotic use will bring about more judicious prescribing.

In summary, despite growing awareness of the harms of indiscriminate use, rates of antibiotic use have remained stable, and by some estimates have increased.[1, 43] Inappropriate and/or unnecessary antibiotic use is contributing to alarming rates of antibiotic-resistant infections and potentially life-threatening ADEs.

Evidence to Support Antibiotic Stewardship

Antibiotic stewardship is a multidisciplinary program of activities aimed at optimizing antibiotic use to achieve best clinical outcomes, while minimizing unintended adverse events and limiting selective pressures that drive the emergence of antibiotic-resistant organisms.[10, 61] Stewardship programs promote six principles of appropriate antibiotic use including prescribing: 1) for the right patients (e.g., only in patients with infections for which an antibiotic is indicated); 2) at the right time (e.g., as soon as possible in serious infections like sepsis); 3) with the right drug choice; 4) right route; 5) right dose; and 6) right duration of therapy. Antibiotic stewardship interventions have been shown to decrease antibiotic use, lead to more appropriate antibiotic use, reduce healthcare costs and antibiotic resistance, and most importantly, improve patient outcomes and safety.[62–64]

Impact on Antibiotic Use and Costs

Inpatient stewardship programs have shown significant improvements in antibiotic use in the form of both overall reductions in antibiotic consumption as well as more appropriate therapy, typically defined as improvements in drug selection, adherence to guidelines, and optimization of durations of therapy.[64] As an example, restrictions requiring prior authorization from ID for dispensing of third-generation cephalosporins led to an 86%

decrease in use of target drugs over a ten-year period at a large academic medical center.[65] Similarly, a comprehensive ASP including prior authorization for use of certain antibiotics, a comprehensive educational program, creation of local guidelines, and biannual feedback to providers on prescribing practices led to an overall 35% reduction in antibiotic use.[66] Prospective audit and feedback to hospitalists about prescribing habits for broad-spectrum antibiotics led to higher rates of appropriate antibiotic prescriptions from 43% at baseline to 74% post-intervention.[67] Camins and colleagues conducted a prospective cluster randomized trial assigning medicine teams at a large urban teaching hospital to either prospective audit and feedback focused on use of vancomycin, levofloxacin and piperacillin/tazobactam, or to use of indication-based guidelines for antibiotic use without any feedback.[68] Assessing nearly 800 prescriptions for vancomycin, levofloxacin, and piperacillin/tazobactam, intervention teams were more likely to prescribe antibiotics appropriately, compared with teams that did not receive the intervention, whether for empiric (82% vs. 73%) or definitive therapy (82% vs. 43%).[68]

These improvements in antibiotic use are achieved with the added benefit of reduced hospital costs, without negative impacts on mortality, length of stay, or readmission rates. [64] Reported annual cost savings from ASPs range from $150,000 to $900,000, with varying savings based on facility type and number of stewardship strategies implemented. [69–74] Conversely, Standiford et al. reported that discontinuation of an ASP at their hospital resulted in a 32% increase in antibiotic costs within two years of program discontinuation.[75] Antibiotic-related cost savings often plateau after initial reductions; however, this report underscores the ongoing role ASPs play in controlling antibiotic use and costs.

Antibiotic stewardship interventions aimed at improving outpatient antibiotic prescribing have been shown to reduce antibiotic prescriptions for conditions in which antibiotics are not indicated (e.g., ARIs) and improve choice when antibiotics are indicated.[76–78] Passive educational strategies such as use of printed educational materials alone have little to no impact as compared to active educational interventions including interactive meetings (vs. didactic lectures), individual provider level feedback and in-person education.[76, 77] Although impacts have been modest, clinical decision support (CDS) and care pathways provided either in paper form or integrated into the electronic medical record at the time of prescribing have been shown to reduce antibiotic prescriptions for ARIs and lead to more guideline-concordant management.[79–81] Patient-focused interventions, such as delayed antibiotic prescribing in which a patient is asked to wait a few days before starting an antibiotic to determine if the antibiotic is needed, can lead to reductions in unnecessary antibiotic use without negative impacts on symptom resolution, clinical outcome, or patient satisfaction.[82–84] Posters placed in examination rooms with the clinician's picture, signature, and commitment to use antibiotics appropriately led to a 20% reduction in inappropriate prescribing for respiratory conditions.[85] While several interventions have been shown to improve outpatient antibiotic prescribing, more effort is needed to better understand how to maximize their effect, which combinations of interventions provide the most benefit with available resources and how best to scale up outpatient stewardship interventions in a sustainable manner.

Impact on Antibiotic Resistance

The impact of antibiotic stewardship interventions on antibiotic resistance is difficult to assess given available data is often in the form of antibiograms that aggregate susceptibility data for only initial isolates. This precludes an evaluation of antibiotic resistance that developed over time in hospitalized patients. Additionally, antibiograms- in their traditional form- do not allow for evaluation of multidrug resistance. These limitations combined with the additional factors influencing the development and spread of antibiotic resistance, such as lapses in infection control practices, make measuring the impact of stewardship interventions on antibiotic resistance difficult and results to date have been mixed.[86–88] However, studies have shown associations between antibiotic stewardship interventions and reductions in individual- and population-level antibiotic resistance. In a randomized controlled trial evaluating use of a clinical pulmonary infection score as criteria for antibiotic decision-making, investigators found randomization of patients with low risk of infection to short course empiric therapy as compared to standard of care, not only led to reductions in antibiotic use, but also reduced rates of antibiotic resistance and superinfections among patients receiving short course therapy (15% vs. 35%).[89] Implementation of a requirement for prior authorization of selected broad-spectrum parenteral antibiotics at one institution led to a 32% reduction in antibiotic expenditures coupled with increased activity against Gram-negative organisms for all targeted agents.[69] Interestingly, susceptibilities to both restricted and unrestricted antibiotic agents increased after the intervention, highlighting the selective pressure one class of antibiotics can exert on others.

Impact on CDI and Clinical Outcomes

Arguably one of the most important impacts of ASPs has been their contribution to reducing hospital rates of CDI. Antibiotics are the single most important risk factor for CDI; therefore, stewardship interventions promoting judicious antibiotic use are imperative for prevention. Guidelines recommend implementing an ASP as part of multidisciplinary efforts paired with infection control to prevent CDI in hospital settings.[90, 91] Multiple studies demonstrate the significant impact of ASPs on minimizing CDIs. A comprehensive antibiotic stewardship intervention at a community hospital involving antibiotic detailing with individual provider education as well as automatic stop orders resulted in a 22% decrease in broad-spectrum antibiotic use and a drop in CDI incidence from 2.2 to 1.4 per 1,000 patient days.[74] Decreasing rates of healthcare-associated infections (HAIs) due to resistant *Enterobacteriaceae* were also noted.[74] A combined strategy of restricted use of cephalosporins, a complete ban on fluoroquinolones and infection control measures resulted in termination of a toxigenic NAP1 CDI outbreak in the Netherlands in 2005.[92] After infection control measures were unable to control a hospital outbreak of NAP1 CDI in Quebec, implementation of a nonrestrictive stewardship intervention including dissemination of local guidelines combined with prospective audit and feedback resulted in reductions in antibiotic consumption followed by a marked 60% decrease in CDIs.[93] These studies highlight the significant impact ASPs can have on reducing CDIs. Nearly 30,000 people die annually from CDI in the United States;[5] minimizing unnecessary antibiotic use is critical to preventing this devastating infection and saving lives.

Optimizing antibiotic therapy improves patient outcomes including increased infection cure rates and possible reductions in mortality. Implementation of a guideline to promote effective prescribing for community-acquired pneumonia was associated with decreased 30-day mortality across a large health system.[94] Additionally, growing evidence suggests involvement of ID specialists in the management of patients with *Staphylococcus aureus* bacteremia leads to more appropriate and guideline-concordant management as well as reductions in hospital mortality.[95, 96]

Antibiotic stewardship is a patient safety initiative aimed at preventing antibiotic-associated harms. In addition to CDI, ASPs play an integral role in promoting patient safety through reductions in ADEs,[97] and by working with multidisciplinary teams to improve perioperative surgical prophylaxis in hopes of preventing surgical site infections. Hospitals with pharmacists performing therapeutic drug monitoring of vancomycin and aminoglycosides have lower rates of renal impairment, hearing loss, and overall mortality.[98] In many institutions, therapeutic drug monitoring is performed or supervised by an ASP pharmacist in addition to antibiotic medication reconciliation, evaluation of discharge antibiotics and monitoring drug-drug interactions to avoid adverse reactions. ASPs also play a role in determining the nature of antibiotic allergies, minimizing false labeling of drug allergies that promote use of broad-spectrum therapy, recommending appropriate alternative therapy when necessary and preventing use of drugs to which patient are allergic.[99, 100] Optimizing perioperative antibiotic prophylaxis is associated with reductions in surgical site infections; [101, 102] measures evaluating perioperative prophylaxis are incorporated into The Centers for Medicare and Medicaid Services (CMS) value-based purchasing program. Pharmacist-directed management of perioperative prophylaxis has been associated with improved survival and decreased costs and length of stay.[103] Finally, an evolving body of literature underscores further opportunity to avoid harm by involving ASPs in evaluation of patients for outpatient parenteral antibiotic therapy (OPAT).[104, 105] Use of OPAT is on the rise, adverse events related to antibiotics are frequent, and an estimated 15–30% of use is avoidable or unnecessary.[104–106] ASPs play a pivotal and effective role in not only minimizing unnecessary antibiotic use, but importantly, avoiding unnecessary harm and costs.

Making Antibiotic Stewardship a Reality

Evolution of Antibiotic Stewardship Goals

Despite numerous concerns about misuse of antibiotics and calls for improved prescribing,[7, 8] coordinated efforts to raise awareness, improve prescribing and impact policy did not take hold until the mid-1990s. In response to increased recognition of unnecessary antibiotic prescribing in outpatient settings, the US CDC launched the National Campaign for Appropriate Antibiotic Use in the Community in 1995, which was subsequently renamed Be Antibiotics Aware in 2017.[107] This program focuses on common illnesses that account for the majority of antibiotic prescriptions written in outpatient settings, and works with a wide range of partners to not only raise awareness about the threat of antibiotic-resistant infections and adverse effects of antibiotics, but also provide various clinical and informational resources for providers and patients to improve antibiotic use. The program has expanded to measure and characterize outpatient antibiotic prescribing,[42] evaluate interventions to improve prescribing,[108] and develop policies and guidelines to promote appropriate outpatient antibiotic prescribing.[109, 110] The program also includes Antibiotics Awareness Week, a yearly observance in November to raise awareness about antibiotic resistance and the importance of judicious antibiotic use.[107] During this week, CDC partners with a variety of organizations and over 40 countries to educate clinicians, the public, policymakers, hospital administrators, and the media about the critical issue of antibiotic resistance.

National ID professional societies worked for years to address the rising tide of antibiotic-resistant infections through development of prevention and treatment guidelines, promoting and funding research, and advocating for effective policies to address antibiotic resistance. Recognizing the implications of rising rates of antibiotic-resistant pathogens coupled with dramatic declines in development of new antibiotic agents, the Infectious Diseases Society of America (IDSA) originally published guidelines for improving antibiotic use in hospitals in 1988.[111] This was followed by a joint publication on the topic by IDSA and the Society for Healthcare Epidemiology of America (SHEA) in 1997.[112] These societies more specifically promoted the concept of antibiotic stewardship when they released new guidelines in 2007.[61] This document outlines ideal ASP team members and needed resources as well as core and supplemental strategies for ASPs to improve antibiotic use; yet, it lacked practical details of how to implement an ASP. The 2007 guidelines were followed by an IDSA policy paper titled Combating Antibiotic Resistance: Policy Recommendations to Save Lives that recommended requiring ASPs in all US healthcare facilities.[113] This document recommended new incentives and requirements be established for implementation and maintenance of ASPs across all health care settings as just one part of a multi-faceted approach to address antibiotic resistance.[113] IDSA recommended ASPs be required as a condition of participation in federal CMS programs.[113] A companion policy statement on antibiotic stewardship published the following year by SHEA, IDSA, and the Pediatric Infectious Diseases Society (PIDS) echoed these calls for mandatory implementation of ASPs across health care and additionally outlined minimum program requirements that should be enforced, process and outcome measures to be monitored, and deficiencies in national antibiotic surveillance and research that need to be addressed.[10] SHEA in partnership with other organizations promoting antibiotic stewardship published a guidance document outlining the knowledge and skills necessary for physicians, pharmacists or other healthcare providers to develop and lead an antibiotic stewardship program.[114] Finally, IDSA and SHEA released recommendations for implementation and measurement in antibiotic stewardship in 2016, specifically outlining best approaches and interventions to optimize antibiotic use.[115]

Initial experience with regulation mandating processes to improve antibiotic use in the United States comes from the state of California. California Senate Bill 739, signed into law in 2006, directed the California Department of Public Health to require general acute care hospitals to develop a process for evaluating the judicious use of antibiotics with results jointly monitored by representatives and committees involved in quality improvement.[116] While Senate Bill 739 did not explicitly state ASPs be established, nor outline or require methods for intervening to improve antibiotic use, a preliminary assessment of its impact identified 22% of California hospitals instituting ASPs.[117] While antibiotic stewardship initiatives expanded under this regulation, barriers persisted including staffing constraints and lack of funding. In September 2014, California Senate Bill 1311 [118] expanded previous regulations and required that hospitals adopt and implement an antibiotic stewardship policy adherent with guidelines established by the federal government and professional societies with leadership required by either a physician or pharmacist with training in antibiotic stewardship. California not only learned that legislation is effective in expanding antibiotic stewardship initiatives, but also that the language of such mandates is integral to developing appropriately constructed and funded programs.

Antibiotic resistance is a public health issue and in many ways addressing it falls within the scope of public health services. At a federal level, US CDC has been involved with

Table 1 Core Elements of Hospital Antibiotic Stewardship Programs

1)	**Leadership Commitment:** Dedicating necessary human, financial and information technology resources.
2)	**Accountability:** Appointing a single leader responsible for program outcomes. Experience with successful programs show that a physician leader is effective.
3)	**Drug Expertise:** Appointing a single pharmacist leader responsible for working to improve antibiotic use.
4)	**Action:** Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e., "antibiotic time out" after 48 hours).
5)	**Tracking:** Monitoring antibiotic prescribing and resistance patterns.
6)	**Reporting:** Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff.
7)	**Education:** Educating clinicians about resistance and optimal prescribing.

promoting antibiotic stewardship activities for nearly two decades and has worked to make improving antibiotic use a national priority. CDC has worked to not only provide education about antibiotic stewardship, but also tools and resources to implement effective programs.[107] CDC has worked to describe the human impact of antibiotic resistance in the United States as well as the extent and patterns of our antibiotic use and opportunities for improvement.[1, 3, 4] In 2014, CDC published a report calling for implementation of ASPs in all hospitals and soon after released a document outlining core elements of successful hospital-based ASPs (See Table 1).[3, 119] While acknowledging some flexibility is needed to tailor ASPs to local resources and culture, CDC emphasized success is dependent on leadership and defined multidisciplinary approaches. For the first time, the CDC provided a framework for components of a successful ASP in the Core Elements of Hospital Antibiotic Stewardship Programs [119] and has since outlined core elements of antibiotic stewardship in nursing homes and core elements of outpatient antibiotic stewardship."[120, 121]

In September 2014, President Obama signed Executive Order 13676: *Combating Antibiotic-Resistant Bacteria* which addresses the policy recommendations of the President's Council of Advisors on Science and Technology (PCAST) and identified priorities for combating antibiotic-resistant bacteria further detailed in the *National Strategy on Combating Antibiotic-Resistant Bacteria*.[122, 123] The Executive Order instructed CMS to review regulations and ensure acute care hospitals and LTCFs have ASPs that implement best practices by 2020.[122] Additionally, the national strategy called for reductions in inappropriate prescribing by 20% in inpatient settings and 50% in outpatient settings by 2020 as a key strategy in reducing antibiotic resistance. The subsequent *National Action Plan for Combating Antibiotic-resistant Bacteria* further outlined steps for implementing these goals and the national strategy over the next five years (www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf).[11] In response to these national efforts, the Joint Commission published a new standard for the implementation of ASPs for hospitals, critical access hospitals, and nursing centers for accreditation, which became effective in January 2017.[124]

Similar warnings about the threat of antibiotic resistance and calls for improved antibiotic use have echoed around the world. The World Health Organization (WHO) published a report on global antibiotic resistance in 2014, which describes not only global levels of antibiotic-resistant bacteria, but also highlights the lack of coordinated surveillance efforts.[125] The report declares antibiotic resistance a threat to the achievements of modern medicine that may lead to a post-antibiotic era where common infections cannot be cured. The WHO subsequently published a Global Action Plan on Antimicrobial Resistance in 2015, which was adopted by the World Health Assembly.[126] The action plan outlines five objectives: 1) improve awareness around antibiotic resistance, 2) strengthen knowledge and evidence base through surveillance and research, 3) reduce the incidence of infection, 4) optimize use of antibiotics in humans and animals, and 5) develop the economic case for sustainable investment in new medicines, diagnostic tools, vaccines and other interventions. The action plan calls for coordinated efforts around the globe and the development of multi-sector (i.e., human and veterinary medicine, agriculture, finance, environment and consumer) national action plans by the 2017 World Health Assembly. Finally, in September 2016 Heads of State convened at the United Nations General Assembly signed a commitment to broad, coordinated approaches to addressing antibiotic resistance across human health, veterinary medicine and agriculture, and reaffirmed the blueprint for tackling antibiotic resistance in the WHO global action plan.[127]

The overuse of antibiotics in food animal production and its relationship to antibiotic-resistant bacteria in humans has gained increasing recognition. The first ban on antibiotic use in food animals for growth promotion was enacted in Sweden in 1986, followed by numerous European countries and a European Union ban on all antibiotics in food animals for growth promotion in 2006.[128] The United States has not been so quick to act; however, appreciation of the relationship with antibiotic use in animals and human health motivated reviews of agricultural practices around the world and led the US Food and Drug Administration (FDA) to implement strategies in 2015 to minimize antibiotic overuse by identifying certain antibiotics that require veterinary oversight via the Veterinary Feed Directive.[129] The FDA also worked with drug companies to re-label antibiotics and remove feed efficiency and growth promotion claims. Global initiatives and the push for regulatory requirements have advanced antibiotic stewardship across healthcare, veterinary medicine and agriculture. Work must continue but these efforts have lent new urgency toward efforts to systematically measure antibiotic use and develop standardized measures of appropriate use.

Progress on Measurement and Quality Measures

Quantifying where, when and how antibiotics are used in various healthcare settings is imperative to identifying areas for improvement and implementing change. In conjunction, antibiotic surveillance data is imperative to set and monitor national goals for improvement. In the 1990s, CDC encouraged national reporting of inpatient antibiotic use through the AUR Module of the National Nosocomial Surveillance System, which was transitioned to the NHSN in 2006. Due to difficulties with manual aggregation of data, nearly all reporting to the AUR stopped by 2006.[130] Eliminating the need for manual data entry, CDC released the Antimicrobial Use (AU) option of the AUR Module in 2011 based on electronic medication administration record (eMAR) or bar coding medication administration (BCMA) systems and began receiving antibiotic use data in 2012. Antibiotic use in the AUR Module is measured in days of therapy per 1,000 days present (DOT/1,000 days present) with the short-term goal to provide facilities with local data for quality improvement activities and a means for measuring the effectiveness of stewardship interventions. A forthcoming benefit will be a national database of inpatient antibiotic use with the ability to report risk adjusted facility benchmarks, enabling comparison between facilities. Currently, submission of antibiotic use data is voluntary; however, the national action plan strongly encourages healthcare facilities to submit usage data, and the PCAST report recommends requiring this reporting as part of the Inpatient Quality Reporting Program of CMS.[123]

CDC developed the Standardized Antibiotic Administration Ratio (SAAR) as a risk adjusted quality measure for antibiotic use and a first step toward national antibiotic benchmarking for US hospitals. The SAAR compares observed antibiotic use with expected or predicted use (observed/expected). There are multiple SAARs calculated including those based on adult and pediatric patient location groupings (e.g., ward vs. intensive care unit) and antibiotic groupings [e.g., anti-methicillin resistant *S. aureus* (anti-MRSA) agents, broad-spectrum agents predominantly used for community-acquired infection]. Although questions remain regarding the relationship between the SAAR and appropriate antibiotic prescribing and patient outcomes, it is an initial effort that will inform future benchmarking efforts. While there is no established reference standard with which to measure appropriate antibiotic use, recent efforts by CDC and others have focused on defining quality indicators and developing standardized audit tools for measuring antibiotic prescribing quality based on objective criteria that can be assessed by trained personnel.[34] Future work is needed to validate the SAAR as an inpatient quality measure against these measures of appropriate antibiotic prescribing.

Antibiotic Stewardship Across the Healthcare Continuum

Reported estimates of the prevalence of antibiotic stewardship programs in US hospitals vary, and little is known about the structure and robustness of these programs, number and type of interventions used, and process and outcome measures followed.[117] With increasing recognition of the benefits of antibiotic stewardship as well as recent calls for establishment of ASPs in all acute care hospitals, understanding the national landscape of antibiotic stewardship and current barriers to implementation efforts are imperative.

In order to identify gaps and improve stewardship efforts throughout the State of Michigan, Collins and colleagues in conjunction with the Michigan Society of Health-System Pharmacists (MSHP) conducted a survey of health systems in 2014 to characterize current antibiotic stewardship practices and perceived stewardship-related needs.[131] Of the 47 respondents, 45% were from facilities with less than 150 beds, and the majority of respondents (76%) represented nonteaching facilities. Although response rates were low (26%), 83% of respondents reported having antibiotic stewardship strategies in place.[131] Most stewardship programs were less than two years old (66%), and the majority (63%) reported multidisciplinary ASP teams.[131] Formulary restriction, intravenous to oral conversion, and pharmacist led prospective audit and feedback were the most common interventions used; however, pharmacists in hospitals with fewer than 150 beds were less likely to make interventions related to de-escalation or discontinuation of antibiotics (52% vs. 85%).[131] The most commonly reported barriers to antibiotic stewardship were lack of ASP funding (47%) and other resources (49%, e.g., information technology resources, lack of ID expertise), as well as opposition from physicians and lack of hospital administration support.[131] Interestingly, a low%age of programs (44%) reported following antibiotic utilization patterns, one of the seven core elements for hospital ASPs identified by CDC. Reasons for not monitoring antibiotic use trends were not explored, but highlight the need for further support for program evaluation. This survey underlines significant differences in stewardship practices and resources between large and small hospitals. Most studies evaluating inpatient ASPs come from large academic centers, and there is a limited evidence base with which to guide successful implementation of ASPs in smaller community hospitals.[132] Although resources are often limited in nonacademic settings, successful examples of ASPs in these settings exist,[133] and future efforts are needed to understand how best to implement stewardship in small community hospitals.

The National Veterans Affairs Antimicrobial Stewardship Task Force (ASTF) is a resource for stewardship education and for the development and dissemination of stewardship resources across the VA, the largest integrated healthcare system in the United States. The VA ASTF, in collaboration with the VA Healthcare Analysis and Information Group (HAIG), performed a cross-sectional survey across all VA facilities in 2012 to characterize existing antibiotic stewardship structure and practices.[134] At the time of the survey, 38% of 130 VA facilities reported having an antibiotic stewardship team, defined as an ID physician and a clinical pharmacist who routinely meet to discuss antibiotic stewardship-related issues.[134] Twenty-two% of facilities had a policy establishing an ASP; another 42% reported having a policy under development.[134] The most commonly utilized stewardship activities and processes were formulary restrictions (92%) use of automatic stop orders for antibiotics (75%) and clinical care pathways (74%). Activities that seemed underutilized included systematic review of positive blood cultures, prospective audit and feedback, and group or provider-specific feedback on antibiotic usage.[134] Interestingly, of the 49 facilities with antibiotic stewardship teams, 51% reported working in the outpatient setting and 67% in community living centers, which are VA LTCFs.[134] In January 2014, the VA released a directive establishing a policy for the implementation of ASPs across all VA medical facilities. This policy was significant and affirms the VA's commitment to antibiotic stewardship.

To better characterize inpatient antibiotic stewardship practices across the United States, CDC incorporated antibiotic stewardship questions into the 2015 NHSN facility survey. Questions were aimed at assessing how many hospitals had ASPs meeting the seven core elements of hospital ASPs as outlined by the CDC.[119] In 2014, 39% of US hospitals reported having ASPs meeting all seven core elements.[135] Ninety-four% of hospitals reported compliance with the action core element, meaning they had implemented at least one recommended stewardship intervention, while only 60% of hospitals reported leadership commitment dedicating resources for stewardship. Larger bed size, teaching hospital status and hospital leadership commitment for the ASP were all associated with fulfilling all seven core elements. For example, 56% of hospitals with greater than 200 beds had ASPs meeting all core elements as compared to 22% of hospitals with less than 50 beds. Similarly, 76% of hospitals with dedicated salary support for stewardship resources met all seven core elements, versus only 27% of those without dedicated salary support. While these data suggest a substantial proportion of US hospitals of varying sizes have taken on the antibiotic stewardship charge, more than half of programs do not meet all core elements. Leadership commitment and dedicated resources are clearly associated with more robust ASPs. If we intend to improve antibiotic use in any significant way, garnering hospital leadership support is imperative.

There are over 15,000 nursing homes in the United States with an estimated 1.4 million residents, and these numbers are expected to rise as the US population ages.[136] Between 50% and 80% of LTCF patients receive antibiotics, often coupled with high rates of antibiotic-resistant infections.[137, 138] LTCFs are in great need of antibiotic stewardship given their medically complex patients and care process models, combined with high rates of antibiotic utilization and resistance among their vulnerable patients. Resources and access to ID expertise are often limited in LTCFs and data are limited regarding most effective stewardship practices in this setting. The lack of resources and evidence to guide best practices necessitate creative stewardship approaches to optimize antibiotic use in LTCF settings.[139] Given limited data regarding existing antibiotic stewardship practices coupled with forthcoming regulation requiring ASPs in all LTCFs, the Michigan Department of Health and Human Services conducted a survey of Michigan LTCFs in 2014 to define current stewardship practices and needs.[138] Seventy-five% (60/80) of responding LTCFs reported having ASP policies and procedures, yet only 23% reported having a formal ASP with dedicated staff. Perceived obstacles to ASP implementation included lack of knowledge (54%), absence of an ASP proposal (50%), and staffing constraints (8%). Most commonly involved ASP team members in LTCFs include infection preventionists, medical directors and nurses.[138, 140] Lack of access to ID expertise has been identified as a limitation in other surveys[140]; however, respondents report a strong belief that antibiotics are overused (54%), that an ASP would be beneficial (89%) and a keen interest in pursuing antibiotic stewardship education.[138] These findings are encouraging, but underscore the need for more education of local champions paired with availability of ID and stewardship expertise.

To bolster antibiotic stewardship efforts in long-term care settings, the US CDC released "Core Elements of Antibiotic Stewardship Programs in Nursing Homes" in 2015.[120]. This document outlines the key components and functions of ASPs in nursing homes and will provide a useful foundation as nursing homes work toward implementing stewardship programs (see Chapter 12).

New models for delivering ambulatory care with improved access have grown over the last decade in the form of retail and urgent care clinics and telemedicine. Retail clinics are often located in pharmacies or grocery stores and provide walk-in care for a limited set of low acuity conditions with upper respiratory illnesses, unspecified viral illnesses and UTIs accounting for 88% of visits.[141] Use of retail clinics grew ten-fold between 2007 and 2009; [141] an estimated 3 million patients visited retail clinics in 2008.[142] Use of telemedicine and e-visits where interactions occur virtually over the internet have grown dramatically and these services are now reimbursed by numerous health plans.[143] An evaluation comparing e-visits to office visits at primary care practices within the University of Pittsburgh Health System, found 99% of e-visits for UTIs resulted in an antibiotic prescription as compared to 49% of in-person office visits.[143] Providers were also less likely to order relevant diagnostic tests at e-visits as compared to in-person visits (8% vs. 51%).[143]

Administration of antibiotic infusion therapy in the ambulatory setting, or OPAT, is also increasingly common. It can be safe, efficacious and cost saving with appropriate patient selection.[144] However, there is mounting evidence that as use of OPAT is on the rise so is unnecessary antibiotic use and inadequate follow-up to monitor for antibiotic and central venous catheter-related toxicities.[145] Stewardship interventions to monitor and determine the need for OPAT have been shown to reduce unnecessary use and costs, and improve patient safety and outcomes.[105, 146, 147] While these growing healthcare delivery models have potential advantages including convenience, efficiency and lower costs, evidence suggests they contribute to over-prescribing. They represent the next frontier where we must not only characterize antibiotic prescribing, but also begin to design, implement and evaluate innovative stewardship interventions to reduce overuse.

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Where Do We Go from Here?

Next Steps for Antibiotic Stewardship

We are at a pivotal moment for antibiotic stewardship. Previous, smaller efforts to improve antibiotic use have now been galvanized into a formal action plans. Antibiotic stewardship is recognized as a key to combating antibiotic resistance. An unprecedented number of stakeholders have now joined this effort, as evidenced by the White House Forum on Antibiotic Stewardship in 2015, which brought together more than 100 stakeholder groups to discuss ways to expand antibiotic stewardship, and the commitment made by global leaders to coordinate efforts to fight antibiotic resistance at the United Nations General Assembly in September 2016. Regulatory, accreditation and payer organizations are also beginning to explore and implement policies and incentives to promote stewardship. The critical steps lie ahead. The task of harnessing this momentum increasingly rests with the thousands of individual facilities and providers who must now implement stewardship programs in all healthcare settings. Fortunately, there are a large number of groups that stand ready to support providers in their efforts. There is also a great need for more research in antibiotic stewardship to build an evidence base to support even greater change. Stewardship programs must investigate optimal ways to implement interventions known to be effective as well as develop and test new interventions. Federal agencies are helping address the knowledge gap in antibiotic stewardship through increased funding opportunities. There is no doubt ASPs will continue to improve patient care while optimizing healthcare resources.

References

1. Magill SS, Edwards JR, Beldavs ZG, et al. Prevalence of antimicrobial use in US acute care hospitals, May–September 2011. *JAMA* 2014; 312:1438–1446.
2. van de Sande-Bruinsma N, Grundmann H, Verloo D, et al. Antimicrobial drug use and resistance in Europe. *Emerging Infect Dis* 2008; 14:1722–1730.
3. Fridkin S, Baggs J, Fagan R, et al. Vital signs: improving antibiotic use among hospitalized patients. *MMWR Morb Mortal Wkly Rep* 2014; 63:194–200.
4. Centers for Disease Control and Prevention. Antibiotic Resistance Threats. 2013; 1–114. (Accessed Nov 20, 2016, at www.cdc.gov/drugresistance/threat-report-2013/.)
5. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med* 2015; 372:825–834.
6. Kunin CM, Dierks JW. A physician-pharmacist voluntary program to improve prescription practices. *N Engl J Med* 1969; 280:1442–1446.
7. Kunin CM, Tupasi T, Craig WA. Use of antibiotics: a brief exposition of the problem and some tentative solutions. *Ann Intern Med* 1973; 79:555–560.
8. McGowan JE. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Rev Infect Dis* 1983; 5:1033–1048.
9. Tamma PD, Holmes A, Ashley ED. Antimicrobial stewardship: another focus for patient safety? *Curr Opin Infect Dis* 2014; 27:348–355.
10. Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America

(IDSA), and the Pediatric Infectious Diseases Society (PIDS). *Infect Control Hosp Epidemiol* 2012; 33:322–327.

11. National Strategy for Combating Antibiotic-Resistant Bacteria. (Accessed Nov 20, 2016, at www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf.)
12. Barrett FF, Casey JI, Finland M. Infections and antibiotic use among patients at Boston City Hospital, February, 1967. *N Engl J Med* 1968; 278:5–9.
13. Kislak JW, Eickhoff TC, Finland M. Hospital-acquired infections and antibiotic usage in the Boston City Hospital–January, 1964. *N Engl J Med* 1964; 271:834–835.
14. Scheckler WE, Bennett JV. Antibiotic usage in seven community hospitals. *JAMA* 1970; 213:264–267.
15. Borda I, Jick H, Slone D, Dinan B, Gilman B, Chalmers TC. Studies of drug usage in five Boston hospitals. *JAMA* 1967; 202:506–510.
16. Kelesidis T, Braykov N, Uslan DZ, et al. Indications and types of antibiotic agents used in 6 acute care hospitals, 2009–2010: A pragmatic retrospective observational study. *Infect Control Hosp Epidemiol* 2016; 37:70–79.
17. Centers for Disease Control and Prevention. National Healthcare Safety Network. (Accessed April 26, 2016, at www.cdc.gov/nhsn/acute-care-hospital/aur/.)
18. Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. *Arch Intern Med* 2003; 163:972–978.
19. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999; 115:462–474.
20. Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH. Pseudomonas aeruginosa bloodstream infection: importance of appropriate initial antimicrobial treatment. *Antimicrob Agents Chemother* 2005; 49:1306–1311.
21. Fraser A, Paul M, Almanasreh N, et al. Benefit of appropriate empirical antibiotic treatment: thirty-day mortality and duration of hospital stay. *Am J Med* 2006; 119:970–976.
22. Seaton RA, Nathwani D, Burton P, et al. Point prevalence survey of antibiotic use in Scottish hospitals utilising the Glasgow Antimicrobial Audit Tool (GAAT). *Int J Antimicrob Agents* 2007; 29:693–699.
23. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest* 2009; 136:1237–1248.
24. Ciccolini M, Spoorenberg V, Geerlings SE, Prins JM, Grundmann H. Using an index-based approach to assess the population-level appropriateness of empirical antibiotic therapy. *Journal of Antimicrobial Chemotherapy* 2015; 70:286–293.
25. Parta M, Goebel M, Thomas J, Matloobi M, Stager C, Musher DM. Impact of an assay that enables rapid determination of staphylococcus species and their drug susceptibility on the treatment of patients with positive blood culture results. *Infect Control Hosp Epidemiol* 2010; 31:1043–1048.
26. Casaroto E, Marra AR, Camargo TZS, et al. Agreement on the prescription of antimicrobial drugs. *BMC Infect Dis* 2015; 15:248.
27. Vlahovic-Palcevski V, Francetic I, Palcevski G, Novak S, Abram M, Bergman U. Antimicrobial use at a university hospital: appropriate or misused? A qualitative study. *Int J Clin Pharmacol Ther* 2007; 45:169–174.
28. Osowicki J, Gwee A, Noronha J, et al. Australia-wide point prevalence survey of antimicrobial prescribing in neonatal units: How much and how good? *Pediatr Infect Dis J* 2015; 34:e185–90.
29. Osowicki J, Gwee A, Noronha J, et al. Australia-wide point prevalence survey of the use and appropriateness of antimicrobial prescribing for children in hospital. *Med J Aust* 2014; 201:657–662.

30. Peron EP, Hirsch AA, Jury LA, Jump RLP, Donskey CJ. Another setting for stewardship: high rate of unnecessary antimicrobial use in a veterans affairs long-term care facility. *J Am Geriatr Soc* 2013; 61:289–290.

31. van Buul LW, Veenhuizen RB, Achterberg WP, et al. Antibiotic prescribing in Dutch nursing homes: How appropriate is it? *J Am Med Dir Assoc* 2015; 16:229–237.

32. Cooke DM, Salter AJ, Phillips I. The impact of antibiotic policy on prescribing in a London teaching hospital: a one-day prevalence survey as an indicator of antibiotic use. *J Antimicrob Chemother* 1983; 11:447–453.

33. Raveh D, Levy Y, Schlesinger Y, Greenberg A, Rudensky B, Yinnon AM. Longitudinal surveillance of antibiotic use in the hospital. *QJM* 2001; 94:141–152.

34. James RS, McIntosh KA, Luu SB, et al. Antimicrobial stewardship in Victorian hospitals: a statewide survey to identify current gaps. *Med J Aust* 2013; 199:692–695.

35. James R, Upjohn L, Cotta M, et al. Measuring antimicrobial prescribing quality in Australian hospitals: development and evaluation of a national antimicrobial prescribing survey tool. *Journal of Antimicrobial Chemotherapy* 2015; 70:1912–1918.

36. Zarb P, Goossens H. European Surveillance of Antimicrobial Consumption (ESAC): Value of a point-prevalence survey of antimicrobial use across Europe. *Drugs* 2011; 71:745–755.

37. Antimicrobial prescribing practice in Australian hospitals. Sydney: 2015. (Accessed Nov 20, 2016, at www.safetyandquality.gov.au/wp-content/uploads/2015/07/Antimicrobial-prescribing-practice-in-Aust-hospitals-NAPS-2014-Results.pdf.)

38. Stolley PD, Becker MH, McEvilla JD, Lasagna L, Gainor M, Sloane LM. Drug prescribing and use in an American community. *Ann Intern Med* 1972; 76:537–540.

39. Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Danziger LH. A national evaluation of antibiotic expenditures by healthcare setting in the United States. *J Antimicrob Chemother* 2013; 68(3):715–718.

40. Centers for Disease Control and Prevention (CDC). Office-related antibiotic prescribing for persons aged ≤ 14 years–United States, 1993–1994 to 2007–2008. *MMWR Morb Mortal Wkly Rep* 2011; 60:1153–1156.

41. Shapiro DJ, Hicks LA, Pavia AT, Hersh AL. Antibiotic prescribing for adults in ambulatory care in the USA, 2007–09. *Journal of Antimicrobial Chemotherapy* 2014; 69:234–240.

42. Hicks LA, Taylor TH, Hunkler RJ. U.S. outpatient antibiotic prescribing, 2010. *N Engl J Med* 2013; 368:1461–1462.

43. Jones BE, Sauer B, Jones MM, et al. Variation in outpatient antibiotic prescribing for acute respiratory infections in the veteran population: a cross-sectional study. *Ann Intern Med* 2015; 163:73–80.

44. Barnett ML, Linder JA. Antibiotic prescribing for adults with acute bronchitis in the United States, 1996–2010. *JAMA* 2014; 311:2020–2022.

45. Hicks LA, Bartoces MG, Roberts RM, et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. *Clin Infect Dis* 2015; 60(9):1308-1316.

46. Sanchez GV, Roberts RM, Albert AP, Johnson DD, Hicks LA. Effects of knowledge, attitudes, and practices of primary care providers on antibiotic selection, United States. *Emerging Infect Dis* 2014; 20:2041–2047.

47. D'Costa VM, King CE, Kalan L, et al. Antibiotic resistance is ancient. *Nature* 2011; 477:457–461.

48. Bhullar K, Waglechner N, Pawlowski A, et al. Antibiotic resistance is prevalent in an isolated cave microbiome. *PLoS ONE* 2012; 7:e34953.

49. Mulvey MR, Simor AE. Antimicrobial resistance in hospitals: how concerned should we be? *CMAJ* 2009; 180:408–415.

50. Clatworthy AE, Pierson E, Hung DT. Targeting virulence: a new paradigm for

antimicrobial therapy. *Nat Chem Biol* 2007; 3:541–548.

51. Zaoutis TE, Goyal M, Chu JH, et al. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and Klebsiella species in children. *Pediatrics* 2005; 115:942–949.
52. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infect Control Hosp Epidemiol* 2008; 29:1099–1106.
53. Spellberg B, Guidos R, Gilbert D, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2008; 46:155–164.
54. Thomas C, Stevenson M, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile*-associated diarrhoea: a systematic review. *J Antimicrob Chemother* 2003; 51:1339–1350.
55. Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of *Clostridium difficile* infection. *Clinical Infectious Diseases* 2011; 53:42–48.
56. Bartlett JG. Narrative review: the new epidemic of *Clostridium difficile*-associated enteric disease. *Ann Intern Med* 2006; 145:758–764.
57. Redelings MD, Sorvillo F, Mascola L. Increase in *Clostridium difficile*-related mortality rates, United States, 1999–2004. *Emerging Infect Dis* 2007; 13:1417–1419.
58. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. *Amer J Gastroenterology* 2012; 107:89–95.
59. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clinical Infectious Diseases* 2008; 47:735–743.
60. Lin RY, Nuruzzaman F, Shah SN. Incidence and impact of adverse effects to antibiotics in hospitalized adults with pneumonia. *J Hosp Med* 2009; 4:E7–15.
61. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clinical Infectious Diseases* 2007; 44:159–177.
62. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. *Journal of Antimicrobial Chemotherapy* 2011; 66:1223–1230.
63. Davey P, Brown E, Charani E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2013; 4:CD003543.
64. Wagner B, Filice GA, Drekonja D, et al. Antimicrobial stewardship programs in inpatient hospital settings: a systematic review. *Infect Control Hosp Epidemiol* 2014; 35:1209–1228.
65. Lautenbach E, LaRosa LA, Marr AM, Nachamkin I, Bilker WB, Fishman NO. Changes in the prevalence of vancomycin-resistant enterococci in response to antimicrobial formulary interventions: impact of progressive restrictions on use of vancomycin and third-generation cephalosporins. *Clinical Infectious Diseases* 2003; 36:440–446.
66. Rüttimann S, Keck B, Hartmeier C, Maetzel A, Bucher HC. Long-term antibiotic cost savings from a comprehensive intervention program in a medical department of a university-affiliated teaching hospital. *Clinical Infectious Diseases* 2004; 38:348–356.
67. Kisuule F, Wright S, Barreto J, Zenilman J. Improving antibiotic utilization among hospitalists: a pilot academic detailing project with a public health approach. *J Hosp Med* 2008; 3:64–70.
68. Camins BC, King MD, Wells JB, et al. Impact of an antimicrobial utilization program on antimicrobial use at a large teaching hospital: a randomized controlled

trial. *Infect Control Hosp Epidemiol* 2009; 30:931–938.

69. White AC, Atmar RL, Wilson J, Cate TR, Stager CE, Greenberg SB. Effects of requiring prior authorization for selected antimicrobials: expenditures, susceptibilities, and clinical outcomes. *Clinical Infectious Diseases* 1997; 25:230–239.
70. Fishman N. Antimicrobial stewardship. *Am J Med* 2006; 119:S53–61– discussion S62–70.
71. Gentry CA, Greenfield RA, Slater LN, Wack M, Huycke MM. Outcomes of an antimicrobial control program in a teaching hospital. *American Journal of Health-System Pharmacy (AJHP)* 2000; 57:268–274.
72. LaRocco A. Concurrent antibiotic review programs–a role for infectious diseases specialists at small community hospitals. *Clinical Infectious Diseases* 2003; 37:742–743.
73. Bantar C, Sartori B, Vesco E, et al. A hospital wide intervention program to optimize the quality of antibiotic use: impact on prescribing practice, antibiotic consumption, cost savings, and bacterial resistance. *Clinical Infectious Diseases* 2003; 37:180–186.
74. Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol* 2003; 24:699–706.
75. Standiford HC, Chan S, Tripoli M, Weekes E, Forrest GN. Antimicrobial stewardship at a large tertiary care academic medical center: cost analysis before, during, and after a 7-year program. *Infect Control Hosp Epidemiol* 2012; 33:338–345.
76. Arnold SR, Straus SE. *Interventions to improve antibiotic prescribing practices in ambulatory care*. Chichester, UK: John Wiley & Sons, 1996.
77. Ranji SR, Steinman MA, Shojania KG, Gonzales R. Interventions to reduce unnecessary antibiotic prescribing: a systematic review and quantitative analysis. *Med Care* 2008; 46:847–862.
78. Drekonja DM, Filice GA, Greer N, et al. antimicrobial stewardship in outpatient settings: a systematic review. *Infect Control Hosp Epidemiol* 2014; 36:142–152.
79. Gonzales R. A cluster randomized trial of decision support strategies for reducing antibiotic use in acute bronchitis. *JAMA Intern Med* 2013; 173:267.
80. Rattinger GB, Mullins CD, Zuckerman IH, et al. A sustainable strategy to prevent misuse of antibiotics for acute respiratory infections. *PLoS ONE* 2012; 7:e51147.
81. Jenkins TC, Irwin A, Coombs L, et al. Effects of clinical pathways for common outpatient infections on antibiotic prescribing. *Am J Med* 2013; 126:327–335.e12.
82. Chao JH, Kunkov S, Reyes LB, Lichten S, Crain EF. Comparison of two approaches to observation therapy for acute otitis media in the emergency department. *Pediatrics* 2008; 121:e1352–6.
83. Little P, Moore MV, Turner S, et al. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. *BMJ* 2010; 340: c199.
84. Little P, Moore M, Kelly J, et al. Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: Pragmatic, factorial, randomised controlled trial. *BMJ* 2014; 348:g1606.
85. Meeker D, Knight TK, Friedberg MW, et al. Nudging guideline-concordant antibiotic prescribing: a randomized clinical trial. *JAMA Intern Med* 2014; 174:425–431.
86. McGowan JE. Antimicrobial stewardship–the state of the art in 2011: focus on outcome and methods. *Infect Control Hosp Epidemiol* 2012; 33:331–337.
87. Schulz LT, Fox BC, Polk RE. Can the antibiogram be used to assess microbiologic outcomes after antimicrobial stewardship interventions? A critical review of the literature. *Pharmacotherapy* 2012; 32:668–676.
88. Schechner V, Temkin E, Harbarth S, Carmeli Y, Schwaber MJ. Epidemiological interpretation of studies examining the effect of antibiotic usage on resistance. *Clin Microbiol Rev* 2013; 26:289–307.

89. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000; 162:505–511.

90. Cohen SH, MD, Gerding DN, MD, Johnson S, MD, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol* 2010; 31:431–455.

91. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Amer J Gastroenterology* 2013; 108:478–98–quiz 499.

92. Debast SB, Vaessen N, Choudry A, Wiegers-Ligtvoet EAJ, van den Berg RJ, Kuijper EJ. Successful combat of an outbreak due to *Clostridium difficile* PCR ribotype 027 and recognition of specific risk factors. *Clinical Microbiology and Infection* 2009; 15:427–434.

93. Valiquette L, Cossette B, Garant M-P, Diab H, Pépin J. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. *Clinical Infectious Diseases* 2007; 45 Suppl 2:S112–21.

94. Dean NC, Bateman KA, Donnelly SM, Silver MP, Snow GL, Hale D. Improved clinical outcomes with utilization of a community-acquired pneumonia guideline. *Chest* 2006; 130:794–799.

95. Lahey T, Shah R, Gittzus J, Schwartzman J, Kirkland K. Infectious diseases consultation lowers mortality from *Staphylococcus aureus* Bacteremia. *Medicine* 2009; 88:263–267.

96. Jenkins TC, Price CS, Sabel AL, Mehler PS, Burman WJ. Impact of routine infectious diseases service consultation on the evaluation, management, and outcomes of *Staphylococcus aureus* Bacteremia. *Clinical Infectious Diseases* 2008; 46:1000–1008.

97. Evans RS, Pestotnik SL, Classen DC, et al. A computer-assisted management program for antibiotics and other antiinfective agents. *N Engl J Med* 1998; 338:232–238.

98. Bond CAC, Raehl CL. Clinical and economic outcomes of pharmacist-managed aminoglycoside or vancomycin therapy. *AJHP* 2005; 62:1596–1605.

99. Unger NR, Gauthier TP, Cheung LW. Penicillin skin testing: potential implications for antimicrobial stewardship. *Pharmacotherapy* 2013; 33:856–867.

100. Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. *Pharmacotherapy* 2011; 31:742–747.

101. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med* 1992; 326:281–286.

102. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm* 2013; 70:195–283.

103. Bond CAC, Raehl CL. Clinical and economic outcomes of pharmacist-managed antimicrobial prophylaxis in surgical patients. *Am J Health Syst Pharm* 2007; 64:1935–1942.

104. Spivak ES, Kendall B, Orlando P, et al. Evaluation of outpatient parenteral antimicrobial therapy at a veterans affairs hospital. *Infect Control Hosp Epidemiol* 2015; 36:1103–1105.

105. Gordon SM, Shrestha NK, Rehm SJ. Transitioning antimicrobial stewardship beyond the hospital: the Cleveland Clinic's community-based parenteral anti-infective therapy (CoPAT) program. *J Hosp Med* 2011; 6 Suppl 1:S24–S30.

106. Knackstedt ED, Stockmann C, Davis CR, Thorell EA, Pavia AT, Hersh AL. Outpatient parenteral antimicrobial therapy in pediatrics: An opportunity to expand antimicrobial stewardship. *Infect Control Hosp Epidemiol* 2015; 36:222–224.

107. Centers for Disease Control and Prevention. (Accessed April 26, 2016, at www.cdc.gov/getsmart/.)

108. Sanchez GV, Fleming-Dutra KE, Hicks LA. Minimizing antibiotic misuse through evidence-based management of outpatient acute respiratory infections. *Antimicrob Agents Chemother* 2015; 59:6673.

109. Harris AM, Hicks LA, Qaseem A, High value care task force of the american college of physicians and for the centers for disease control and prevention. appropriate antibiotic use for acute respiratory tract infection in adults: advice for high-value care from the American College of Physicians and the Centers for Disease Control and Prevention. *Ann Intern Med* 2016; 164(6):425-434.

110. Hersh AL, Jackson MA, Hicks LA, American Academy of Pediatrics. Committee on Infectious Diseases. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. *Pediatrics* 2013; 132:1146–1154.

111. Marr JJ, Moffet HL, Kunin CM. Guidelines for improving the use of antimicrobial agents in hospitals: a statement by the Infectious Diseases Society of America. *J Infect Dis* 1988; 157:869–876.

112. Shlaes DM, Gerding DN, John JF, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. *Clinical Infectious Diseases* 1997; 25:584–599.

113. Infectious Diseases Society of America (IDSA), Spellberg B, Blaser M, et al. Combating antimicrobial resistance: Policy recommendations to save lives. *Clinical Infectious Diseases* 2011; 52 Suppl 5: S397–428.

114. Cosgrove SE, Hermsen ED, Rybak MJ, et al. Guidance for the knowledge and skills required for antimicrobial stewardship leaders. *Infect Control Hosp Epidemiol.* 2014; 35:1444–1451.

115. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016; 62(10):1197–1202.

116. California Senate Bill No. 739. (Accessed Nov 20, 2016, at www.dhcs.ca.gov/provgovpart/initiatives/nqi/Documents/SB739.pdf.)

117. Trivedi KK, Rosenberg J. The state of antimicrobial stewardship programs in California. *Infect Control Hosp Epidemiol* 2013; 34:379–384.

118. California Senate Bill No. 1311. https://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201320140SB1311.

119. Pollack LA, Srinivasan A. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. *Clinical Infectious Diseases* 2014; 59 Suppl 3:S97–100.

120. Centers for Disease Control and Prevention. (Accessed April 26, 2016, at www.cdc.gov/longtermcare/pdfs/core-elements-antibiotic-stewardship.pdf.)

121. Sanchez GV, Fleming-Dutra KE, Roberts RM, Hicks LA. Core elements of outpatient antibiotic stewardship. *MMWR Recomm Rep* 2016; 65:1–12.

122. Obama BH. Presidential Executive Order. (Accessed Nov 20, 2016, at www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria.)

123. Report to the President on Combating Antibiotic Resistance. (Accessed Nov 20, 2016, at www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf.)

124. The Joint Commission. Prepublication Standards – New Antimicrobial Stewardship Standard. (Accessed Nov 20, 2016, at www.jointcommission.org/prepublication_standards_antimicrobial_stewardship_standard/.)

125. The World Health Organization. Antimicrobial resistance: a global report on

https://doi.org/10.1017/9781316694411.002 Published online by Cambridge University Press

surveillance. 2014. (Accessed Nov 20, 2016, at www.who.int/drugresistance/documents/surveillancereport/en/.)

126. The World Health Organization. Global action plan on antimicrobial resistance. (Accessed Nov 20, 2016, at www.who.int/antimicrobial-resistance/publications/global-action-plan/en/.)

127. The United Nations General Assembly. Draft political declaration of the high-level meeting of the General Assembly on antimicrobial resistance. (Accessed Nov 20, 2016, at www.un.org/pga/71/wp-content/uploads/sites/40/2016/09/DGACM_GAEAD_ESCAB-AMR-Draft-Political-Declaration-1616108E.pdf.)

128. MaronDF, Smith TJ, Nachman KE. Restrictions on antimicrobial use in food animal production: an international regulatory and economic survey. *Global Health* 2013; 9: 48.

129. The Food and Drug Administration. Veterinary Feed Directive. (Accessed Nov 20, 2016, at www.federalregister.gov/documents/2015/06/03/2015–13393/veterinary-feed-directive.)

130. Fridkin SK, Srinivasan A. Implementing a strategy for monitoring inpatient antimicrobial use among hospitals in the United States. *Clinical Infectious Diseases* 2014; 58(3): 401–406.

131. Collins CD, Miller DE, Kenney RM, et al. The state of antimicrobial stewardship in Michigan: Results of a statewide survey on antimicrobial stewardship efforts in acute care hospitals. *Hospital Pharmacy* 2015; 50:180–184.

132. Stenehjem E, Hersh AL, Sheng X, et al. Antibiotic use in small community hospitals. *Clinical Infectious Diseases* 2016; 63:1273–1280.

133. Trivedi KK, Kuper K. Hospital antimicrobial stewardship in the non university setting. *Infect Dis Clin North Am* 2014; 28:281–289.

134. Chou AF, Graber CJ, Jones M, et al. Characteristics of antimicrobial stewardship programs at veterans affairs hospitals: results of a nationwide survey. *Infect Control Hosp Epidemiol* 2016; 37 (6):647–654.

135. Pollack LA, van Santen KL, Weiner LM, Dudeck MA, Edwards JR, Srinivasan A. Antibiotic stewardship programs in U.S. acute care hospitals: findings from the 2014 National Healthcare Safety Network (NHSN) Annual Hospital Survey. *Clinical Infectious Diseases* 2016; 63(4):443–449.

136. Centers for Disease Control and Prevention. (Accessed Apr 26, 2016, at www.cdc.gov/nchs/fastats/nursing-home-care.htm.)

137. Rhee SM, Stone ND. Antimicrobial stewardship in long-term care facilities. *Infect Dis Clin North Am* 2014; 28:237–246.

138. Malani AN, Brennan BM, Collins CD, Finks J, Pogue JM, Kaye KS. Antimicrobial stewardship practices in Michigan long-term care facilities. *Infect Control Hosp Epidemiol* 2016; 37:236–237.

139. Doernberg SB, Dudas V, Trivedi KK. Implementation of an antimicrobial stewardship program targeting residents with urinary tract infections in three community long-term care facilities: a quasi-experimental study using time-series analysis. *Antimicrob Resist Infect Control* 2015; 4:54.

140. Van Schooneveld T, Miller H, Sayles H, Watkins K, Smith PW. Survey of antimicrobial stewardship practices in Nebraska long-term care facilities. *Infect Control Hosp Epidemiol* 2011; 32:732–734.

141. Ashwood JS, Reid RO, Setodji CM, Weber E, Gaynor M, Mehrotra A. Trends in retail clinic use among the commercially insured. *Am J Manag Care* 2011; 17:e443–448.

142. Laws M, Scott MK. The emergence of retail-based clinics in the United States: Early observations. *Health Aff (Millwood)* 2008; 27:1293–1298.

143. Mehrotra A, Paone S, Martich GD, Albert SM, Shevchik GJ. A comparison of care at e-visits and physician office visits for sinusitis and urinary tract infection. *JAMA Intern Med* 2013; 173:72–74.

144. Tice AD, Rehm SJ, Dalovisio JR, et al. Practice guidelines for outpatient

parenteral antimicrobial therapy. IDSA guidelines. Clinical Infectious Diseases 2004; 38:1651–1672.

145. Lane MA, Marschall J, Beekmann SE, et al. Outpatient parenteral antimicrobial therapy practices among adult infectious disease physicians. *Infect Control Hosp Epidemiol* 2014; 35:839–844.

146. Shrestha NK, Bhaskaran A, Scalera NM, Schmitt SK, Rehm SJ, Gordon SM. Contribution of infectious disease consultation toward the care of inpatients being considered for community-based parenteral anti-infective therapy. *J Hosp Med* 2012; 7:365–369.

147. Madigan T, Banerjee R. Characteristics and outcomes of outpatient parenteral antimicrobial therapy at an academic children's hospital. *Pediatr Infect Dis J* 2013; 32:346–349.