

Responsible Antibiotic Prescribing Practices with Current, New, and Emerging Agents to Reduce Antibiotic Resistant Infections

Statement of Need

Antibiotic resistant infections represent a global health threat. In the United States alone, over 2 million people are infected with antibiotic resistant bacteria every year, ultimately resulting in at least 23,000 deaths.¹ In fact, some studies suggest that more people will die from antibiotic resistant infections than cancer by 2050.² Unnecessary or inappropriate antibiotic prescriptions directly contribute to antibiotic resistance. Studies indicate that up to 50% of prescribed antibiotics are inappropriate or unnecessary.³⁻⁴ This is especially troubling since inappropriate and unnecessary prescriptions can put patients at risk. For example, antibiotics are responsible for approximately 20% of emergency department visits caused by adverse reactions to drugs. Of these visits, about 80% are due to allergic reactions, but some common antibiotics can also cause neurologic, gastrointestinal, or even psychiatric complications.⁵⁻⁶

There are an increasing number of pathogens that are resistant to first-line and even second-line antibiotic treatments, including strains of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* and *oxytoca*.⁷ In fact, the U.S. Centers for Disease Control and Prevention (CDC) have classified these and other pathogenic microorganisms as urgent health threats due to their increasingly limited number of effective treatment options.⁸ These cumulative antibiotic resistant infections are also a major burden on the healthcare system due to prolonged hospitalizations and the high cost of many antibiotics.⁹ In fact, studies estimate that the toll of controlling and treating antibiotic resistant infections falls between \$100 million and \$30 billion each year.¹⁰⁻¹² These antibiotic resistant infections can also be particularly harmful to certain at-risk populations, including immunocompromised patients or those undergoing dialysis.⁷

Clinicians may underestimate the burden of infectious diseases and their own contribution to the problem.¹³⁻¹⁴ Education about basic principals of antibiotic resistance and how to responsibly prescribe new and emerging treatment options for infectious diseases is incredibly important to improving overall patient care. Similarly, many clinicians may underestimate the danger of antibiotic resistant infections to certain populations. They may require training about the importance of the rapid and effective diagnosis of infections in these populations and how to select of an appropriate therapy.^{7, 15-16} Unfortunately, many clinicians have negative attitudes about antibiotic stewardship programs that are available to help despite their demonstrated effectiveness at promoting responsible prescribing practices and improving patient outcomes.^{13, 17} Similarly, clinicians often fail to follow guidelines that detail appropriate diagnosis and management of common infectious diseases caused by Gram-positive and Gram-negative bacteria.¹⁸⁻²¹ Educational activities that promote responsible treatment of infectious diseases can improve patient treatment and reduce the occurrence of antibiotic resistant infections.

Practice Gaps

Gap 1: Many clinicians underestimate their own contribution to the burden of resistant infectious diseases and may not be up-to-date with new and emerging treatment options for infections caused by Gram-positive and Gram-negative bacteria.

Underestimation of Individual Contribution to Antibiotic Resistance

Some studies suggest that clinicians may not be aware that they are overprescribing antibiotics. A recent survey of about 130 physicians at the Brooklyn Hospital Center revealed that only 49% of respondents thought that providers tended to overprescribe antibiotics.¹³ Other studies suggest that clinicians are aware of the problem, but continue to ignore it anyway. Detailed interviews with 36 primary care providers throughout the United States found that many clinicians knowingly ignored guideline recommendations and selected inappropriate antibiotic treatments, citing reasons like the desire to keep patients happy or not wanting to worry about whether or not a treatment will be strong enough to combat the infection.¹⁸

Clinicians may also disregard or underestimate their own contribution to the development of antibiotic resistant bacteria. Although 95% of respondents in a survey of 139 junior doctors throughout France and Scotland thought that antibiotic resistance was a problem, only 63% of the same respondents viewed it as important to their own daily practice.¹⁴

Similar findings were reported in studies throughout the United States. A survey of 129 physicians involved in ASPs at the Brooklyn Hospital Center found respondents were 20% more likely to believe antibiotics were abused nationally instead of locally. Similarly, only 26% of respondents thought their own practices contributed to the development of antibiotic resistant bacteria.¹³ This indicates a clear need for a better understanding of the principals for how antibiotic resistance spreads and the role that hospitals and individual clinicians can play in reducing the rate of resistant infections. Understanding the gravity of antibiotic resistance could motivate clinicians to practice more responsible prescribing practices.

Indeed, several studies further highlight this educational need. In one survey of 317 medical students at various institutions throughout the United States, only one-third of respondents were confident in their understanding of some fundamental concepts of antibiotic use. Relatedly, 90% of the same respondents expressed an interest in additional education about appropriate antibiotic use.²²

New and Emerging Antibiotics for Gram-positive Bacteria

A multitude of studies are finding that many prescribed antibiotics are inappropriate or unnecessary. For example, one recent study examining thousands of medical records found that over 30% of prescribed antibiotics were inappropriate or even harmful to patients.²³ Similarly, several studies indicate that up to 50% of antibiotics are unnecessary and may even hurt patient outcome.³⁻⁴ Keeping clinicians abreast of new and emerging antibiotic treatment options how to responsibly prescribe these treatments may help improve patient outcome and reduce the occurrence of antibiotic resistance. There are many new and emerging treatments for common Gram-positive and Gram-negative infections that can be difficult to treat.

Skin and soft tissue infections are one of the most common causes of emergency department visits and hospital admissions. The emergence of antibiotic resistant strains like MRSA have only complicated the treatment of these infections and caused an increased burden on health systems.²⁴ The infections can be caused by a variety of both Gram-negative and Gram-positive bacteria and can be associated with wounds, cutaneous abscesses, burns, or other skin conditions.²⁵

Acute bacterial skin and soft structure infections (ABSSSI) are skin and soft tissue infections that have variable clinical presentations and a lesion size of at least 75 cm².²⁴ Several antibiotics are available for the treatment of skin and soft tissue infections and ABSSSI, but many of the most commonly prescribed are suboptimal and inactive against MRSA. However, several fairly new long-acting agents (eg, dalbavancin and oritavancin) can provide single-dose treatments that permit earlier patient discharge, and some emerging oxazolidinone antibiotics also show promising activity against antibiotic resistant infections.²⁶

Dalbavancin is an effective lipoglycopeptide antibiotic approved against ABSSI.²⁵ Several *in vitro* and animal studies also demonstrate the drug has good efficacy against MRSA, one of the most problematic causes of ABSSSI. More recently, there is emerging data that the treatment is safe for pediatric patients. A recent phase 1 study demonstrated good tolerance in pediatric patients while a second *in vitro* study showed good efficacy against Gram-positive isolates causing ABSSSI in children.²⁷⁻²⁹ In addition to skin infections, recent studies also suggest the antibiotic has good *in vitro* activity against Gram-positive isolates responsible for many bone-joint infections and osteomyelitis.³⁰

Similarly, oritavancin is approved against ABSSI and can also be very effective against Gram-positive pathogens. The antibiotic has a single-dose regimen and a more encouraging safety profile compared to linezolid or vancomycin.²⁶ A recent study also demonstrated better efficacy and an enhanced mechanical force of antibiotic action against antibiotic resistant bacteria compared to vancomycin.³¹

The oxazolidinones are a class of synthetic antibiotic agents that also have promise against skin and soft tissue infections caused by Gram-positive bacteria. Some also display modest activity against Gram-negative bacteria. Linezolid, a newer antibiotic from the class, shows promise against most Gram-positive pathogens, but its use may be limited by hematological toxicity.³² Alternatively, tedizolid is efficacious against many ABSSSI-associated Gram-positive pathogens and has a better hematological safety profile.³³

Recently, the FDA also approved the use of ceftaroline fosamil, a cephalosporin antibiotic, for pediatric patients with ABSSSI.²⁷ The antibiotic was already approved for use in adults with ABSSSI and Community-acquired bacterial pneumonia (CABP) in 2010 and studies since have demonstrated similar efficacy and safety profiles in children.²⁷ Importantly, the antibiotic ceftaroline fosamil is also effective against community-acquired pneumonia (discussed more in-depth below).²⁷ The treatment has been most thoroughly studied in Gram-positive bacteria like MRSA and *Streptococcus pneumoniae*, but also has activity against Gram-negative bacteria.

The antibiotic omadacycline has similar dual action against both skin and soft tissue infections and community-acquired pneumonia, including MRSA and *Streptococcus pneumoniae*. The drug is still in development but has received Qualified Infectious Disease Product designation and Fast Track status by the FDA to accelerate its approval.³⁴

New and Emerging Antibiotics for Gram-negative Bacteria

There are also several notable new and emerging antibiotics against Gram-negative bacteria. "Gram-negative pathogens are among the most urgent antibiotic resistance

threats and cause more than 40,000 resistant infections in the U.S. alone each year," said David Nicholson, PhD in a recent press release.⁸ It is important to educate clinicians about new and emerging treatments that target these dangerous pathogens and how to responsibly prescribe the treatments.

Gram-negative bacteria are responsible for a variety of infections. A few areas of high interest include intra-abdominal infections, urinary tract infections, and pneumonia. These conditions are each widespread across the United States and other countries and represent a huge burden to public health.³⁵⁻³⁶ These infections are usually easily treated by first-line antibiotics, but emerging antibiotic resistant strains are making more complicated infections very difficult to treat. There are several new and emerging treatments for these conditions.³⁵⁻³⁶

The cephalosporin ceftazidime combined with the non- β -lactam β -lactamase inhibitor avibactam is an effective and newer treatment against intra-abdominal infections and complicated urinary tract infections, including pyelonephritis.²⁵ More recently, the FDA approved a supplemental New Drug Application to update the ceftazidime/avibactam treatment label with clinical data from two phase 3 trials that support its use against complicated urinary tract infections caused by Gram-negative microorganisms.⁸ The combination treatment also has *in vitro* efficacy against a range of antibiotic resistant bacteria, including *K. pneumonia* carbapenemase-producing bacteria and *Pseudomonas aeruginosa* in the presence of some AmpC beta-lactamases.^{8, 37}

Similarly, treatment with ceftolozane/tazobactam presents a novel broad-spectrum cephalosporin/ β -lactamase inhibitor combination. The treatment is approved for intra-abdominal infections and complicated urinary tract infections, including pyelonephritis.³⁸ Recent studies with the medication also demonstrate *in vitro* efficacy against antibiotic resistant *Pseudomonas aeruginosa* isolates from pediatric patients.³⁹ Additionally, a small study of three patients showed success against pneumonia at higher doses.⁴⁰ A larger phase 3 trial is currently examining the effectiveness of the combination against hospital acquired and ventilator-associated pneumonia.⁴¹

Alternatively, treatments that inhibit the assembly or function of adhesive type 1 pili are beginning to gain attention for the treatment of urinary tract infections. One upcoming class of treatments in this category are FimH antagonists. Early studies show that oral mannoside derivatives can work prophylactically in mouse models to prevent bacterial invasion of bladder tissue.³⁵

Eravacycline is an additional upcoming antibiotic for the treatment of intra-abdominal infection and complicated urinary tract infections, including pyelonephritis. Phase 3 trials indicated good efficacy and safety in comparison with levofloxacin.⁴² *In vivo* studies also indicate excellent efficacy against a variety of difficult-to-treat pathogens.⁴²

Learning Objective 1. Explain basic principals of antibiotic resistance and how to responsibly prescribe antibiotics, including new and emerging treatment options for infectious diseases.

Gap 2: Clinicians may underestimate the danger of antibiotic resistant infections to special, at-risk populations and not understand the importance of rapid and responsible diagnosis and management of infections in these patients.

Irresponsible prescribing practices can be especially harmful to certain patient populations who are at greater risk of antibiotic resistant infections. Such patient populations include patients undergoing renal failure and dialysis, immunocompromised patients, or elderly and diabetic patients. For example, one recent study found that special patient populations were at greater risk of contracting carbapenem-resistant Enterobacteriaceae (CRE) infections. Patients on dialysis, those that had previously had infections, those that were taking antibiotics, and those treated at hospitals with a higher prevalence of CRE were at greater risk of infection.⁷

There are also similar risks and challenges associated with responsibly treating immunocompromised patients. These patients often present differently and may not immediately show obvious signs of an infection. However, once they do develop symptoms, their condition can deteriorate rapidly. Immunocompromised patients therefore require a timely diagnosis and rapid access to an appropriate antibiotic treatment.¹⁵ For populations like this, it is especially important that clinicians adhere to responsible prescribing practices. "It's making sure that you give the patient the right antibiotic, in the right time, for the appropriate duration when they really need it," said Dr. Lilian Abbo, the Chief of Infection Prevention and Antimicrobial Stewardship at Jackson Health System in Miami, Florida in a recent interview. "It's a little different than doing stewardship in other populations, but it's doable. It just takes a little more time."¹⁵

Similarly, there are distinct challenges with treating other at-risk populations, including older patients and those with diabetes. An on-going study is examining the medical records of around 250,000 outpatients that were treated with pneumonia between 2011 and 2015. Investigators of the study noted in a recent interview that older patients were almost twice as likely to be hospitalized due to their infections.¹⁶ "Elderly patients are more vulnerable and should be treated more carefully, potentially with more aggressive antibiotic therapy," said Dr. James A. McKinnell, an infectious disease specialist involved in the study at the Los Angeles Biomedical Research Institute. Investigators involved in the study are also noticing that clinicians may not be sticking to guidelines and recommendations for treating these special and at-risk populations. Elderly patients and patients with diabetes were not always given a stronger course of treatment.¹⁶

Clinician education about the importance of a rapid diagnosis of infections and the selection of appropriate treatment for these special populations could help improve patient care and outcome.

Learning Objective 2: Describe populations that are at a higher risk for infectious diseases and how to effectively diagnosis and manage these populations.

Gap 3: Many clinicians have negative attitudes about antibiotic stewardship programs despite their effectiveness at reducing antibiotic resistant infections and improving patient outcomes.

Hospital and medical center utilization of antibiotic stewardship programs can be more effective in regulating antibiotic use than relying on national guidelines alone. One recent study analyzed the effectiveness of the 2011 national guidelines published by the Pediatric Infectious Diseases Society (PIDS) and Infectious Diseases Society of America (IDSA) for the treatment of pediatric community-acquired pneumonia. Findings showed a clear difference between hospitals that made an active effort to implement the recommendations and those that did not. "Changes in antibiotic prescribing occurred

quickly among hospitals that implemented a local [recommendation] or order set targeting guideline-concordant antibiotic use," write Williams et. al. in their recent study.⁴³ The research suggested that local programs and implementation efforts can greatly enhance the adoption of responsible prescribing practices.

Dedicated antibiotic stewardship programs at hospitals and medical centers can help improve antibiotic use and fight the development of antibiotic resistance. The programs help ensure that patients receive appropriate antibiotic treatments at the right dosage, thereby improving patient care while minimizing the negative consequences associated with antibiotic use.^{4,44} The programs can utilize several types of interventions to accomplish these goals, including monitoring patterns of antibiotic resistance and associated prescribing patterns, keeping clinicians and relevant staff aware of antibiotic use and resistance, or educating clinicians about resistance and effective prescribing practices.⁴

These programs can be incredibly effective in the ongoing fight against antibiotic resistance. A recent literature review of over 30 studies examining the effectiveness of different programs found that those that make use of infectious disease specialists in particular were almost always associated with significantly improved antibiotic use.⁴⁵ Several recent studies also demonstrated that these programs can help reduce the rate of hospital-related infections, including *Clostridium difficile* infections.^{4,46-47} Therefore, a 2014 report by the Center of Disease Control and Prevention called for all hospitals to have stewardship programs by 2020.^{4,48}

The rate of stewardship programs has grown significantly in recent years. One survey of over 500 members of the Infectious Diseases Society of America Emerging Infectious Network (IDSA EIN) found that the percentage of respondents that belonged to institutions with antimicrobial stewardship programs had increased by 23% over the last 10 years.⁴⁹ However, the programs are still not widely used despite their effectiveness. Only 39% of hospitals in the United States had programs in a national survey conducted in 2016. The rate of programs also varied widely between states, with 58% of hospitals in California having programs but only 7% in Vermont.^{44,48} Additionally, small community hospitals are less likely to have stewardship programs.⁴⁹

"Despite its rational theoretical foundation, stewardship programs are known to persistently encounter prescriber resistance," write Sikkens et al in a recent groundbreaking study discussing stewardship programs grounded in behavioral theory. "This resistance is generated by the tension between the governance of the stewardship team and the autonomy of individual prescribers."¹⁷ A study of physicians at the Brooklyn Hospital Center further supported this when it found that 33% of medical resident respondents felt that the programs forced clinicians to select inappropriate antibiotics for their patients.¹³

There are implementation methods that can counteract these negative attitudes and improve physician compliance with guideline recommendations and hospital policies. For example, the same aforementioned study that developed a stewardship program based in behavioral theory found that programs that preserved prescriber autonomy helped improve optimal prescription practices over the course of year by 21%.⁵⁰ Similarly, an additional of over 2,500 physicians suggested that the hospital training environment and peer viewpoints may shape physician attitudes and clinical practice behaviors.^{48,51-52} Making stewardship programs a cultural norm could help improve clinician participation,

thereby promoting more responsible antibiotic use and cutting healthcare costs.⁴⁸

Providing general education about stewardship programs and inspiring clinicians to become actively involved in their development is one way to help make the programs more accepted throughout the medical community. For example, several studies show that how hospitals educate and implement their diagnosis and management guidelines can have a huge impact on clinician adherence and prescribing practices.^{10, 53-54}

Although national guidelines are useful, local guidelines can be even more valuable in effective antibiotic stewardship programs.⁵⁴ One study found that active involvement in the development of local guidelines helped improve diagnosis and management practices over the utilization of recommendations that had already been developed, like the aforementioned national guidelines.^{10, 53-54} This can increase clinician participation in programs and adherence to appropriate prescribing practices by giving clinicians more autonomy and taking into account local epidemiological data. Consequently, the 2016 guidelines published by the IDSA on the implementation of antibiotic stewardship programs recommends that stewardship programs work to develop practice guidelines specific to the individual facility.⁵⁴

Education about the effectiveness of antibiotic stewardship programs and the basic principals involved in their implementation could improve physician reception, participation, and compliance with the programs. It may also encourage physician to play more active roles in program development, implementation, and maintenance.

Learning Objective 3: Describe the role of antibiotic stewardship programs and the importance of local diagnosis and management guidelines for infectious diseases.

Gap 4: Clinicians often fail to follow national diagnosis and management guidelines for common infectious diseases for Gram-positive and Gram-negative infections.

Various organizations have published national guidelines detailing the best practices for antibiotic selection for a variety of common conditions over the last several years.^{26, 55-58} However, a multitude of studies indicate that a large percentage of clinicians do not adhere to these and other diagnosis and management guidelines.¹⁸⁻²¹ For example, a recent study examined clinician adherence to national guidelines for antibiotic selection for different conditions during over 184,000 ambulatory visits from 2010-2011. Over 30% of prescribed antibiotics were thought to have been inappropriate or unnecessary.²³ Similarly, a study examining clinician adherence to guidelines for the management of nontuberculosis mycobacterial lung disease found that a mere 13% of prescribed antibiotic treatments were appropriate while the remainder were suboptimal or even harmful.⁵⁹ Other similar studies indicate that up to 50% of currently prescribed antibiotics are inappropriate or unnecessary.³⁻⁴

Clinicians also have a tendency to overprescribe broad-spectrum antibiotics which should be reserved for second-line treatment to prevent the needless development and spread of antibiotic resistant infections.¹⁸ This seems especially common in the treatment of pediatric pneumonia. One recent study examining the medical records of 10,000 cases at a network of outpatient pediatric practices found that 16.8% of patients were incorrectly prescribed a broad-spectrum antibiotic.⁶⁰

New studies are also beginning to show that national guidelines and education about these guidelines can improve responsible prescribing practices. A recent study

demonstrated the effectiveness of the 2011 national guidelines for the management of community-acquired pneumonia in children published by the PIDS/IDSA. Narrow-spectrum penicillins are considered the first-line treatment for most pediatric patients for both inpatient and outpatient settings. Prescription of the penicillins was previously rare but increased significantly after publication of the guidelines, especially in practices that actively encouraged guideline use.⁴³

In addition to management guidelines, guidelines detailing the diagnosis of different conditions are also critical to selecting appropriate treatments and thereby improving patient outcomes and limiting the development of antibiotic resistance. For example, in a case study included in a recent continuing medical education program, 36% of participants incorrectly diagnosed a patient presenting with seasonal allergies and prescribed some course of antibiotics.³ Incorrect diagnosis can lead to the unnecessary use of antibiotics or the use of suboptimal or even treatments that are harmful to both the patients and the development of antibiotic resistance.

Education about the existence of diagnosis and management guidelines for different conditions and the importance of guideline adherence could promote responsible prescribing practices and reduce the occurrence of antibiotic resistance.

Learning Objective 4: Describe responsible diagnosis, management, and prescribing practices for Gram-positive and Gram-negative infections.

Conclusion

Responsible use of current, new, and emerging antibiotics against infections caused by Gram-negative and Gram-positive bacteria is essential to limiting the spread of antibiotic resistance. Clinicians need to be able to describe essential principals of antibiotic resistance and how to responsibly select new and emerging treatments. Clinicians also need to be aware of populations at greater risk of infectious diseases and how to diagnosis and treat these patients. Finally, clinicians need to understand the importance of local guidelines and stewardship programs in addition to the national guidelines that detail how to responsibly diagnosis and treat infections caused by common Gram-negative and Gram-positive bacteria. This educational activity will provide clinicians with this essential knowledge and the best prescribing practices for antibiotics. This will improve the effective use of current, new, and emerging agents in clinical practices and help limit the spread of antibiotic resistance.

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Suggested Agenda

Activity overview

Pre-activity assessment

Introduction

- The prevalence of antibiotic resistant infections and their burden on public health
- Narrow and broad-spectrum antibiotics

- Importance of responsible antibiotic use
 - General health
 - At-risk populations
- The principals of responsible prescribing
 - Diagnosis
 - Appropriate antibiotic selection
 - Dosing
 - Treatment Length

New and emerging treatments for infectious diseases

- New and emerging antibiotics for Gram-positive bacteria
- New and emerging antibiotics for Gram-negative bacteria
- Responsible prescribing practices

Treatment of Special Populations

- Populations including
 - Dialysis patients
 - Immunocompromised patients
 - Elderly
 - Those with diabetes
- Rapid diagnosis and appropriate treatment
- Importance of communication with entire team

National and local guidelines

- National guidelines for diagnosis and management of Gram-
 - Examples for common infections
 - Benefits to responsible prescribing for currently available treatments
- Local guidelines
 - Introduction
 - Benefits to responsible prescribing for currently available treatments
 - Comparison to national guidelines
 - Local epidemiology
 - Can be tailored to local concerns

Stewardship Programs

- Antibiotic stewardship programs
 - Benefits
 - Role in promoting national guidelines
 - Role in developing local guidelines

Conclusions

Post-activity assessment