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Antibiotic stewardship: Why we must, how we can

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Abstract

Improving our antibiotic use is critical to the safety of our patients and the future of medicine. This can improve patient outcomes, save money, reduce resistance, and help prevent negative consequences such as *Clostridium difficile* infection. The US Centers for Disease Control and Prevention (CDC) is undertaking a nationwide effort to appropriately improve antibiotic use in inpatient and outpatient settings.

Antibiotic stewardship has always been a good idea. Now it is also required by the Joint Commission and the Center for Medicare and Medicaid Services (CMS). This article reviews the state of antibiotic use in the United States and efforts to improve antibiotic stewardship in practice.

ANTIBIOTICS ARE DIFFERENT FROM OTHER DRUGS

Their efficacy wanes over time

Antibiotics are the only medications that become less useful over time even if used correctly. Although other types of drugs are continuously being improved, the old ones work as well today as they did when they first came out. But antibiotics that were in use 50 years ago are no longer as effective.

They are a shared resource

Antibiotics are regularly used by many specialties to deliver routine and advanced medical care. Surgeries, transplantation, and immunosuppressive therapy would be unsafe without antibiotics to treat infections. Some patients awaiting lung transplant are not considered good candidates if they have evidence of colonization by antibiotic-resistant organisms.

Individual use may harm others

Even people who are not exposed to an antibiotic can suffer the consequences of how others use them.

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In a retrospective cohort study, Freedberg et al[1] analyzed the risk of hospitalized patients developing *Clostridium difficile* infection and found that the risk was higher if the previous occupant of the bed had received antibiotics. The putative mechanism is that a patient receiving antibiotics develops altered gut flora, leading to *C difficile* spores released into the environment and not eradicated by normal cleaning. The next patient using the bed is then exposed and infected.

ANTIBIOTIC USE IS HIGH

The US Centers for Disease Control (CDC) monitors antibiotic prescriptions throughout the United States. In the outpatient setting, enough antibiotics are prescribed nationwide for 5 out of every 6 people to get 1 course of antibiotics annually (835 prescriptions per 1,000 people). Rates vary widely among states, with the lowest rate in Alaska (501 prescriptions per 1,000 people) and the highest in West Virginia (1,285 prescriptions per 1,000 people).[2] In comparison, Scandinavian countries prescribe about 400 courses per 1,000 people, about 20% less than our lowest-prescribing state.[3]

Antibiotics are probably the most frequently prescribed drugs in US hospitals. Data from 2006 to 2012 showed that 55% of hospitalized patients received at least 1 dose of an antibiotic and that overall about 75% of all hospital days involved an antibiotic.[4] Rates did not vary by hospital size, but nonteaching hospitals tended to use antibiotics more than teaching hospitals. Antibiotic use is much more common in intensive care units than in hospital wards (1,092 and 720 days of antibiotic treatment per 1,000 patient-days, respectively).

Although overall antibiotic use did not change significantly over the years of the survey, use patterns did: fluoroquinolone use dropped by 20%, possibly reflecting rising resistance or increased attention to associated side effects (although fluoroquinolones remain the most widely prescribed inpatient antibiotic class), and use of first-generation cephalosporins fell by 7%. A cause for concern is that the use of broad-spectrum and “last-resort” antibiotics increased: carbapenem use by 37%, vancomycin use by 32%, beta-lactam/beta-lactamase inhibitor use by 26%, and third- and fourth-generation cephalosporin use by 12%.[4]

About one-third of use is unnecessary

Many studies have tried to measure the extent of inappropriate or unnecessary antibiotic use. The results have been remarkably consistent at 20% to 40% for both inpatient and outpatient studies. One study of hospitalized patients not in the intensive care unit found that 30% of 1,941 days of prescribed antimicrobial therapy were unnecessary, mostly because patients received antibiotics for longer than needed or because antibiotics were used to treat noninfectious syndromes or colonizing microorganisms.[5]

ANTIBIOTIC EXPOSURE HAS NEGATIVE CONSEQUENCES

Any exposure to a medication involves the potential for side effects; this is true for antibiotics whether or not their use is appropriate. An estimated 140,000 visits to emergency departments occur annually for adverse reactions to antibiotics.[6] In hospitalized patients, these reactions can be severe, including renal and bone marrow toxicity. As with any medications, the risks and benefits of antibiotic therapy must be weighed patient by patient.

Disturbance of gut microbiome

Antibiotics' disruptive effects on normal gut flora are becoming better understood and are even believed to increase the risk of obesity and asthma.[7,8]

Animal models provide evidence that altered flora is associated with sepsis, which is attributed to the gut microbiome's role in containing dissemination of bacteria in the body.[9] An ecological study provides further evidence. Baggs et al[10] retrospectively studied more than 9 million patients discharged without sepsis from 473 US hospitals, of whom 0.6% were readmitted for sepsis within 90 days. Exposure to a broad-spectrum antibiotic was associated with a 50% increased risk of readmission within 90 days of discharge because of sepsis (odds ratio 1.50, 95% confidence interval 1.47–1.53).

Increase of *C difficile* infections

Antibiotics exert selective pressure, killing susceptible bacteria and allowing resistant bacteria to thrive.

The risk of *C difficile* infection is 7 to 10 times higher than at baseline for 1 month after antibiotic use and 3 times higher than baseline in the 2 months after that.[11] Multiple studies have found that stewardship efforts to reduce antibiotic use have resulted in fewer *C difficile* infections.

A nationwide effort in England over the past decade to reduce *C difficile* infections has resulted in 50% less use of fluoroquinolones and third-generation cephalosporins in patients over age 65. During that time, the incidence of *C difficile* infection in that age group fell by about 70%, with concomitant reductions in mortality and colectomy associated with infection. No increase in rates of hospital admissions, infection complications, or death were observed.[12–14]

GOAL: BETTER CARE (NOT CHEAPER CARE OR LESS ANTIBIOTIC USE)

The primary goal of antibiotic stewardship is better patient care. The goal is not reduced antibiotic use or cost savings, although these could be viewed as favorable side effects. Sometimes, better patient care involves using more antibiotics: eg, a patient with presumed sepsis should be started quickly on broad-spectrum antibiotics, an action that also falls under antibiotic stewardship. The focus for stewardship efforts should be on optimizing appropriate use, ie, promoting the use of the right agent at the correct dosage and for the proper duration.

Stewardship improves clinical outcomes

Antibiotic stewardship is important not only to society but to individual patients.

Singh et al[15] randomized patients suspected of having ventilator-associated pneumonia (but with a low likelihood of pneumonia) to either a 3-day course of ciprofloxacin or standard care (antibiotics for 10 to 21 days, with the drug and duration chosen by the treating physician). After 3 days, the patients in the experimental group were reevaluated, and antibiotics were stopped if the likelihood of pneumonia was still deemed low. In patients who received only the short course of antibiotics, mean length of stay in the intensive care unit was 9 days and the risk of acquiring an antibiotic-resistant superinfection during hospitalization was 14%, compared with a 15-day length of stay and 38% risk of antibiotic-resistant superinfection in patients in the standard treatment group.

Fishman[16] reported a study at a single hospital that randomized patients to either receive standard care according to physician choice or be treated according to an antibiotic stewardship program. Patients in the antibiotic stewardship group were almost 3 times more likely than controls to receive appropriate therapy according to guidelines. More important, the antibiotic stewardship patients were almost twice as likely to be cured of their infection and were more than 80% less likely to have treatment failure.

DEVELOPING EFFECTIVE ANTIBIOTIC STEWARDSHIP PROGRAMS

A good model for improving antibiotic use is a recent nationwide program designed to reduce central line-associated bloodstream infections.[17] Rates of these infections have dropped by about 50% over the past 5 years. The program included:

- Research to better understand the problem and how to fight it
- Well-defined programs and interventions
- Education to implement interventions, eg, deploying teams to teach better techniques of inserting and maintaining central lines
- A strong national measurement system (the CDC's National Healthcare Safety Network) to track infections.

What constitutes an antibiotic stewardship program?

The CDC examined successful stewardship programs in a variety of hospital types, including large academic hospitals and smaller hospitals, and identified 7 common core elements that could serve as general principles that were common to successful antibiotic stewardship programs[18]:

- Leadership commitment from administration
- A single leader responsible for outcomes
- A single pharmacy leader
- Tracking of antibiotic use
- Regular reporting of antibiotic use and resistance
- Educating providers on use and resistance
- Specific improvement interventions.

Stewardship is harder in some settings

In reply to a CDC survey in 2014, 41% of more than 4,000 hospitals reported that they had antibiotic stewardship programs with all 7 core elements. The single element that predicted whether a complete program was in place was leadership support.[19] The following year, 48% of respondents reported that they had a complete program in place. Percentages varied among states, with highs in Utah (77%) and California (70%) and lows in North Dakota (12%) and Vermont (7%). Large hospitals and major teaching hospitals were more likely to have a program with all 7 elements: 31% of hospitals with 50 or fewer beds had a complete program vs 66% of hospitals with at least 200 beds.[20]

Short-stay, critical-access hospitals pose a special challenge, as only 26% reported having all core elements.[19,20] These facilities have fewer than 25 beds, and many patient stays are less than 3 days. Some do not employ full-time pharmacists or full-time clinicians. The CDC is collaborating with the American Hospital Association and the Pew Charitable Trusts to focus efforts on helping these hospitals, which requires a more flexible approach. About 100 critical-access hospitals nationwide have reported implementing all of the core elements and can serve as models for the others.

MEASURING IMPROVEMENT

The CDC has adopted a 3-pronged approach to measuring improvements in hospital antibiotic use:

- Estimate national aggregate antibiotic use described above
- Acquire information on antibiotic use at facility, practice, and provider levels
- Assess appropriate antibiotic use.

In hospitals, the CDC has concentrated on facility-level measurement. Hospitals need a system to track their own use and compare it with that of similar facilities. The CDC's monitoring program, the Antibiotic Use Option of the National Healthcare Safety Network, captures electronic data on antibiotic use in a facility, enabling monitoring of use in each unit. Data can also be aggregated at regional, state, and national levels. This information can be used to develop benchmarks for antibiotic use, so that similar hospitals can be compared.

What is the 'right' amount of antibiotic use? Enter SAAR

Creating benchmarks for antibiotic use poses a number of challenges compared with most other areas in healthcare. Most public health measures are binary—eg, people either get an infection, a vaccination, or a smoking cessation intervention or not—and the direction of progress is clear. Antibiotics are different: not everybody needs them, but some people do. Usage should be reduced, but by exactly how much is unclear and varies between hospitals. In addition, being an outlier does not necessarily indicate a problem: a hospital unit for organ transplants will have high rates of antibiotic use, which is likely appropriate.

The CDC has taken initial steps to develop a risk-adjusted benchmark measure for hospital antibiotic use, the Standardized Antimicrobial Administration Ratio (SAAR). It compares a hospital's observed antibiotic use with a calculation of predicted use based on its facility characteristics. Although still at an early stage, SAAR has been released and has been endorsed by the National Quality Forum. About 200 hospitals are submitting data to the CDC and collaborating with the CDC to evaluate the SAAR's utility in driving improved antibiotic use.

Problems in measuring appropriate use

Measuring appropriate antibiotic use is easier in the outpatient setting, where detailed data have been collected for many years.

Fleming-Dutra et al[21] compared medications prescribed during outpatient visits and the diagnoses coded for the visits. They found that about 13% of all outpatient visits resulted in an antibiotic prescription, 30% of which had no listed diagnosis that would justify an antibiotic (eg, viral upper respiratory infection). This kind of information provides a target for stewardship programs.

It is more difficult to conduct such a study in a hospital setting. Simply comparing discharge diagnoses to antibiotics prescribed is not useful: often antibiotics are started presumptively on admission for a patient with signs and symptoms of an infection, then stopped if the diagnosis does not warrant antibiotics, which is a reasonable strategy.

Also, many times, a patient with asymptomatic bacteriuria, which does not warrant antibiotics, is misdiagnosed as having a urinary tract infection, which does. So simply looking at the discharge code may not reveal whether therapy was appropriate.

Some studies have provided useful information. Fridkin et al[22] studied 36 hospitals for the use of vancomycin, which is an especially good candidate drug for study because guidelines exist for appropriate use. Data were collected only from patients given vancomycin for more than 3 days, which should have eliminated empiric use of the drug and included only pathogen-driven therapy. Cases where therapy was for skin and soft-tissue infections were excluded because cultures are not usually obtained for these cases. Of patients given vancomycin, 9% had no diagnostic culture obtained at antibiotic initiation, 22% had diagnostic culture but results showed no gram-positive bacterial growth, and 5% had culture results revealing only oxacillin-susceptible *Staphylococcus aureus*. In 36% of cases, opportunities existed for improved prescribing.

Such data could be collected from the electronic medical record, and the CDC is focusing efforts in this direction.

NATIONAL ACTIVITIES IN ANTIBIOTIC STEWARDSHIP

In 2014, the White House launched a national strategy to combat antibiotic resistance,[23] followed by an action plan in 2015.[24] As a result, new investments have been made to improve antibiotic use, including funding for state health departments to begin stewardship efforts and to expand public awareness of the problems of antibiotic overuse. Research efforts are also being funded to improve implementation of existing stewardship practices and to develop new ones.

CMS is also exploring how to drive improved antibiotic use. In October 2016, it started requiring all US nursing homes to have antibiotic stewardship programs, and a similar requirement for hospitals has been proposed.

The Joint Commission issued a standard requiring that all their accredited facilities, starting with hospitals, have an antibiotic stewardship program by January 2017. This standard requires implementation of all the CDC's core elements.

PROVEN INTERVENTIONS

Focusing on key interventions that are likely to be effective and well received by providers is a useful strategy for antibiotic stewardship efforts. A number of such interventions have been supported by research.

Postprescription antibiotic reviews or antibiotic 'time-outs'

Antibiotics are often started empirically to treat hospitalized patients suspected of having an infection. The need for the antibiotic should be assessed a few days later, when culture results and more clinical information are available.

Elligsen et al[25] evaluated the effects of providing a formal review and suggestions for antimicrobial optimization to critical care teams of 3 intensive care units in a single hospital after 3 and 10 days of antibiotic therapy. Mean monthly antibiotic use decreased from 644 days of therapy per 1,000 patient-days in the preintervention period to 503 days of therapy per 1,000 patient-days ($P < .0001$). *C difficile* infections were reduced from 11 cases to 6. Overall gram-negative susceptibility to meropenem increased in the critical care units.

Targeting specific infections

Some infections are especially important to target with improvement efforts.

In 2011, Magill et al[26] conducted 1-day prevalence surveys in 183 hospitals in 10 states to examine patterns of antibiotic use. They found that lower respiratory tract infections and urinary tract infections accounted for more than half of all antibiotic use (35% and 22%, respectively), making them good candidates for improved use.

Community-acquired pneumonia can be targeted at multiple fronts. One study showed that almost 30% of patients diagnosed with community-acquired pneumonia in the emergency department did not actually have pneumonia.[27] Duration of antibiotic therapy could also be targeted. Guidelines recommend that most patients with uncomplicated community-acquired pneumonia receive 5 to 7 days of antibiotic therapy. Avdic et al[28] performed a simple intervention involving education and feedback to teams in 1 hospital regarding antibiotic choice and duration. This resulted in reducing the duration of therapy for community-acquired pneumonia from a median of 10 to 7 days.

Asymptomatic bacteriuria is often misdiagnosed as a urinary tract infection and treated unnecessarily.[29–31]

Trautner et al[32] addressed this problem by targeting urine cultures rather than antibiotics, using a simple algorithm: if a patient did not have symptoms of urinary tract infection (fever, acute hematuria, delirium, rigors, flank pain, pelvic discomfort, urgency, frequency, dysuria, suprapubic pain), a urine culture was not recommended. If a patient did have symptoms but a problem other than urinary tract infection was deemed likely, evaluation of other sources of infection was recommended. Use of the algorithm resulted in fewer urine cultures and less antibiotic overtreatment of asymptomatic bacteriuria. Reductions persisted after the intervention ended.

Antibiotic time-out at hospital discharge

Another study evaluated an intervention that required a pharmacist consultation for the critical care team when a patient was to be discharged with intravenous antibiotics (most often for pneumonia). In 28% of cases, chart review revealed that the infection had been completely treated at the time of discharge, so further antibiotic treatment was not indicated. No patients who avoided antibiotics at discharge were readmitted or subsequently visited the emergency department.[33]

Targeting outpatient settings

A number of studies have evaluated simple interventions to improve outpatient antibiotic prescribing. Meeker et al[34] had providers place a poster in their examination rooms with a picture of the physician and a signed letter committing to the appropriate use of antibiotics. Inappropriate antibiotic use decreased 20% in the intervention group vs controls ($P = .02$).

In a subsequent study,[35] the same group required providers to include a justification note in the electronic medical record every time an antibiotic was prescribed for an indication when guidelines do not recommend one. Inappropriate prescribing dropped from 23% to 5% ($P < .001$).

Another intervention in this study[35] provided physicians with periodic feedback according to whether their therapy was concordant with guidelines. They received an email with a subject line of either “You are a top performer” or “You are not a top performer.” The contents of the email provided data on how many antibiotic prescriptions they wrote for conditions that did not warrant them and how their prescribing habits compared with those of their top-performing peers. Mean inappropriate antibiotic prescribing fell from 20% to 4%.[35]

This is a critical time for antibiotic stewardship efforts in the United States. The need has never been more urgent and, fortunately, the opportunities have never been more abundant. Requirements for stewardship programs will drive implementation, but hospitals will need support and guidance to help ensure that stewardship programs are as effective as possible. Ultimately, improving antibiotic use will require collaboration among all stakeholders. CDC is eager to partner with providers and others in their efforts to improve antibiotic use.

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KEY POINTS

Antibiotics are fundamentally different from other medications, posing special challenges and needs for improving their use.

Antibiotic usage in the United States varies widely among healthcare settings.

Antibiotic stewardship efforts should focus on optimizing appropriate use rather than simply reducing use.

Effective interventions include timely consultation on appropriate prescribing, targeting specific infections, and providing feedback to physicians.