Appropriate Use of Antimicrobial Drugs
A Better Prescription Is Needed

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The problem of antimicrobial resistance has been evident almost from the time antimicrobial drugs entered the pharmacopoeia. However, the clinical impact of resistance has been difficult to measure for a variety of reasons, including separating out the effect of underlying illness and the availability of at least 1 effective drug for most infections. Antimicrobial resistance also has economic consequences, but even those have been difficult to quantify. Nevertheless, the decrease in new drug development and increasing resistance to multiple drug classes among various infections require effective interventions now to mitigate the inevitable increase in morbidity and mortality.

Recognizing the potential for serious consequences of resistance to antimicrobial drugs, medical societies, health plans, and insurers, as well as local, state, and federal government agencies, have conducted education and media campaigns to improve use of antimicrobials, with the intent of reducing the evolutionary pressure toward proliferation of resistant pathogens and transfer of resistance mechanisms. Many of these activities have focused on reducing the prescribing of outpatient antimicrobial drugs for viral infections in pediatrics, an area of antimicrobial use that has had the potential for dramatic decreases, given the evidence for vast overuse and the viral etiology of the common diagnoses for which prescriptions are being written. Prescribing of antimicrobial drugs has declined in the face of these educational efforts, but there is still room for improvement.

In this issue of JAMA, 2 articles address the prescribing of antimicrobial drugs. Linder et al present the results of an analysis of data from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) on prescription of antimicrobials for the diagnosis of sore throat and the impact on prescribing of testing for group A β-hemolytic streptococci (GABHS). Samore et al describe a randomized trial to test the effectiveness of a clinical decision support system (CDSS) to reduce inappropriate prescribing of antimicrobials for acute respiratory infections in rural settings, measuring prescriptions through retail pharmacy data and chart review.

Linder et al measured rates of prescribing antimicrobial drugs and the effect on prescribing of the use of a GABHS test among children presenting with a sore throat. The findings are at once encouraging and discouraging. Because there has been demonstrated overuse of antimicrobials in this situation, the decline in prescribing observed, from 66% of visits in 1995 to 54% of visits in 2003, is welcome news. Unfortunately, this decline was limited to antimicrobials that are recommended for GABHS (penicillin, amoxicillin, and erythromycin; first-generation cephalosporins as acceptable alternatives). The use of nonrecommended antimicrobials (eg, amoxicillin/clavulanate, clarithromycin, and azithromycin) remained stable over the 9-year study period but at an unacceptably high level of 27% among those who received antimicrobials. A beneficial effect may be inferred from the data regarding GABHS testing. When a GABHS test was performed, antimicrobials were prescribed in 57% of visits with the diagnosis of pharyngitis, tonsillitis, and streptococcal sore throat, compared with 73% of visits when a test was not documented (either because the test was not performed or the survey form was left incomplete). Since the results of GABHS testing are not available in the data sets analyzed, further interpretation is speculative. Although not highlighted in the article, antimicrobials were prescribed in 94% of visits for the diagnosis of acute bronchitis, a condition caused by viral infection in this age group.

In the second report on the prescribing of antimicrobial drugs in this issue, Samore et al designed a cluster randomized trial involving communities divided into 2 groups. One group received a community intervention that included meetings, news releases, distribution of educational materials, a mailing to parents of young children, and news articles about antimicrobial use. The other group received the same community-level intervention as well as a clinical decision support tool given to primary care clinicians, either on paper or

See also pp 2305 and 2315.

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in an electronic version accessible through a personal digital assistant, whichever they preferred. These tools were accompanied by lectures, meetings, one-on-one interactions with physicians from the study team, and a voluntary continuing medical education session.

Over 2 years, prescription of antimicrobial drugs declined by 10% in CDSS communities, in contrast with a 1% decline in community intervention communities. The prescribing of macrolides (mostly azithromycin) decreased most markedly, with CDSS communities having a 28% reduction. There were reductions in prescribing for acute bronchitis and colds, for which antimicrobials are never indicated, with a greater decline in the CDSS communities than in the community intervention communities. However, antimicrobials were still prescribed for more than 24% of these diagnoses.

The combined findings of Linder et al and Samore et al are revealing. Linder et al describe signs that appropriate use of antimicrobial drugs continues to improve but with the particular exception of macrolides. Using as a foundation an appropriate-use education campaign directed toward primary care clinicians and the public, Samore et al have added the effective, although modestly so, intervention of a clinical decision support system that is focused on the primary care encounter, not on the global or even community-wide specter of resistant infection. The repetition of the intervention was designed to break habits of inappropriate prescribing that may have formed over many years. The reduction in prescribing included the macrolides, largely azithromycin, an important achievement given the spread of resistance to these agents. This success, for a narrow range of diagnoses within small communities (<100,000 population), required a significant investment of time, expertise, and practice-specific tools. In addition, measuring the effect of the intervention by collecting prescribing data required further resources.

All interventions for improving appropriate use of antimicrobial drugs must be introduced and promoted in the context of efforts to improve awareness among the public and to further educate prescribers. Additional interventions can include formulary restrictions, practice measures such as those currently used and planned for the Health Plan Employer Data and Information Set, clinical decision support systems, and other measures indirectly related to prescribing. These interventions, as well as algorithms and guidelines to improve antimicrobial use, must be transparently evidence-based. Such interventions that improve quality of care for individual patients save time, reduce prescribing errors, and reduce costs and are those most likely to be acceptable, effective, and sustainable. Increased use of an electronic health record may serve as the framework for some of these practice changes. The electronic health record also may help answer the need for better, more universal, readily available data for designing and evaluating interventions that include patient-linked microbiological testing and results, diagnoses, and prescriptions. Surveillance systems under development, such as the National Healthcare Safety Network, may also provide the data required for better study of antimicrobial use and resistance.

The efforts to improve prescribing and administration of antimicrobial drugs must reach beyond respiratory infections, including antimicrobial prophylaxis to prevent surgical wound infections, adherence to antiretroviral therapy for human immunodeficiency virus, malaria treatment, and use of antimicrobial agents in agriculture. To optimize the use of existing drugs, clinical trials should be conducted for new indications and to demonstrate whether the drugs are needed for conditions for which they are commonly prescribed but for which there is no evidence from controlled trials.

The need for these interventions and trials has become urgent with the recent decline in the development and approval of new antimicrobial drugs—particularly for agents effective against the most resistant bacterial infections. The lack of new drug classes has resulted from difficulties in discovery of new compounds, as well as market forces. Pharmaceutical companies are finding better markets for other disease treatments in industrialized nations and lower profits in nonindustrialized countries. No novel class of antibacterial drug was approved for use in the United States between 1968 and 2000; most of the new drugs approved since 1968 have been chemical modifications of existing drugs. Because several major pharmaceutical companies have withdrawn from antimicrobial research and development, near-term reversal of this trend appears unlikely, although 2 new drug classes have been approved by the US Food and Drug Administration since 2000.

The time between introduction of new antimicrobial agents and the consequences related to resistance can be short. For example, between 1995 and 2002, fluoroquinolone prescribing increased from 10% to 24% of all antimicrobial prescribing, making fluoroquinolones the class of antimicrobials that are most commonly prescribed among adults in the United States. This increase was driven by the introduction and increasing use of newer, broader-spectrum fluoroquinolones, principally levofloxacin, and occurred while there was no overall change in the proportion of adults receiving a prescription for antimicrobials at outpatient visits. In addition, much prescribing of fluoroquinolones was for unapproved indications. Unsurprisingly, resistance has appeared in the pathogens for which these agents are targeted (eg, Streptococcus pneumoniae, Escherichia coli, and Klebsiella pneumoniae). Multiple outbreaks of Clostridium difficile—associated disease with greater than expected mortality have been detected since 2000 with a novel strain that has unique putative virulence factors and increased resistance to fluoroquinolones. Clostridium difficile disease has been associated with fluoroquinolone use in the past and recently has been associated with use of one of the newer-generation fluoroquinolones.
broad-spectrum fluoroquinolones, moxifloxacin, has excellent activity against *Mycobacterium tuberculosis*, rivaling that of isoniazid and rifampin. \(^{27,28}\) Inappropriate use of this agent may unnecessarily hasten the emergence of fluoroquinolone resistance to *M. tuberculosis* in countries with a high burden of tuberculosis and other respiratory diseases, where new agents are urgently needed for treatment and shorter-course therapy would aid control. The usefulness of fluoroquinolones in the treatment and control of *Neisseria gonorrhoeae* is being lost worldwide because of increasing resistance.\(^{29}\) In 2005, the US Food and Drug Administration withdrew approval for use of fluoroquinolones in poultry because of the increasing incidence and human health consequences of fluoroquinolone-resistant *Campylobacter* infections.\(^{30}\)

To ensure appropriate use of antimicrobial drugs, the issue must be addressed across all diseases and all sectors of society. Failure to do so will result in wasting the valuable resource of effective antimicrobial agents—a resource that still could be preserved for some time to come.

**Financial Disclosures:** None reported.

**REFERENCES**