Preventing the Spread of Antimicrobial Resistance Among Bacterial Respiratory Pathogens in Industrialized Countries: The Case for Judicious Antimicrobial Use

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The spread of antimicrobial resistance is an important emerging health threat in developed countries. Widespread outpatient antimicrobial use leads to the spread of resistance among community-acquired pathogens such as *Streptococcus pneumoniae*. The Centers for Disease Control and Prevention and partner organizations have initiated a national campaign promoting more judicious antimicrobial use to decrease the spread of resistance. The initial focus is to improve management of respiratory tract infections, which account for most outpatient antimicrobial use. Survey and focus group results indicate that patient pressure and suboptimal diagnosis and treatment contribute to antibiotic overuse. To educate physicians, a series of “principles of judicious antibiotic use” have been developed that identify optimal approaches to management of common respiratory infections. Patient education materials and strategies to improve doctor-patient communication also have been developed. Several studies currently under way will evaluate the impact of intervention on antibiotic use practices and resistant carriage or infection.

The Emergence of Antimicrobial Resistance

The spread of antimicrobial resistance is one of the most important emerging infectious disease threats in the United States [1, 2]. This problem, however, is a complex one with multiple causes. Outpatient antimicrobial use has led to the spread of resistance among bacterial respiratory tract pathogens, such as the pneumococcus. For some enteric pathogens, antimicrobial use in animals is a key contributor to the development and spread of resistant infections [3]. Among nosocomial pathogens, important factors in the spread of resistance include extensive use of broad-spectrum agents in hospitals and person-to-person transmission of resistant strains due to inadequate infection control practices [4]. Finally, other mechanisms, such as noncompliance with therapy, may contribute to the spread of resistance among some pathogens such as *Mycobacterium tuberculosis* [5].

Because multiple factors contribute to the global spread of resistance, any strategy to address this problem will need to be as varied as its causes. Decreasing unnecessary antibiotic use, treating with narrow-spectrum agents whenever possible, improving compliance with therapy, decreasing use of antibiotics in animals and agriculture, and improving infection control all have a role in confronting this problem. In addition, immunization may diminish the impact of resistance by preventing infection or even decreasing carriage and transmission, as has occurred with *Haemophilus influenzae* type b conjugate vaccine.

Although resistant pathogens developed soon after the introduction of antimicrobial therapy [6], the spread of resistance among *Streptococcus pneumoniae* (pneumococci) has made this problem one that virtually no clinician can ignore. Pneumococcal infections, which are the leading cause of community-acquired bacterial meningitis, pneumonia, bacteremia, and otitis media, impact physicians who care for children and adults in a range of settings. While all pneumococci remain susceptible to vancomycin and “untreatable infections” have not occurred, strains have been identified that are no longer susceptible to any oral antimicrobial agent. This raises the specter that some patients with common infections, including otitis media and sinusitis, may need to be treated parenterally at much greater human discomfort and financial cost.

Antimicrobial Use and Resistance

The widespread use of antimicrobials has led to the spread of resistance among pneumococci and other community-acquired pathogens. The association between antimicrobial use and resistance has been documented in a variety of ways. Ecological studies have shown an association between the overall amount of penicillin use in an area and the proportion of penicillin-resistant pneumococci [7, 8]. Cross-sectional studies have shown a significant association between carriage of resistant pneumococci and recent antimicrobial use, while case-control studies have shown a similar association when comparing persons with invasive disease caused by resistant vs. susceptible pneumococci (reviewed in [9]). A longitudinal study of children receiving amoxicillin prophylaxis for recurrent otitis me-
dia showed that the proportion of children carrying resistant pneumococci increased from zero to 25% during prophylaxis and returned to baseline within 3–5 months after prophylaxis was discontinued [10]. Temporal trends in antimicrobial use and resistance also support an association between the two. Since the 1970s, marked increases have occurred in the proportion of children attending out-of-home child care, the number of diagnosed episodes of acute otitis media [11], the rate of pediatric antimicrobial use [12], and the proportion of pneumococcal strains that are resistant.

Promoting Judicious Antimicrobial Use

Responses to the emerging threat of resistance must include (1) improved surveillance, with timely feedback to physicians concerning local resistance patterns; (2) development of diagnostic tests that improve the ability to identify pneumococci and other bacterial pathogens; and (3) development of new antimicrobial agents and vaccines that will be effective in treating or preventing resistant infections. Decreasing or even reversing the spread of resistance, however, requires that selective pressure of antimicrobial use be reduced. The importance of judicious antimicrobial use as a response to the spread of resistance has recently been endorsed by several expert advisory panels [13–15].

The Centers for Disease Control and Prevention (CDC), in collaboration with partner organizations such as the American Academy of Pediatrics (AAP), the American Academy of Family Physicians, and the American Society for Microbiology, has initiated a national campaign in the United States to promote more judicious antimicrobial use in outpatient settings. To achieve a substantial decline in outpatient antimicrobial use will require understanding influences that promote antimicrobial overuse, identifying clinical situations where use could be substantially curtailed without compromising patient care, and convincing medical care providers to change their practices. In part, the ability to change providers’ practices will depend on decreasing the consumer demand for antimicrobials.

The initial focus for the campaign is to reduce antimicrobial use for several common pediatric respiratory infections. In 1992, an estimated 110 million prescriptions for oral antimicrobial drugs were written by office-based physicians in the United States. The highest rate of antimicrobial use was among children <15 years old (928 prescriptions per 1,000 children), and the leading indications for antimicrobial use were otitis media (almost 24 million prescriptions) and nonspecific upper respiratory tract infection (URI) (almost 18 million prescriptions). Overall, five respiratory diagnoses—otitis media, nonspecific URI, bronchitis, pharyngitis, and sinusitis—accounted for ~84 million prescriptions, or 76% of all outpatient antimicrobial use [12].

To identify the factors that result in antimicrobial overuse, we conducted surveys of physicians, parents, and pharmacists and held focus group discussions with physicians and parents. Of 370 pediatricians and family physicians in Georgia who responded to the survey, >90% agreed with the statements that overuse of antimicrobials contributes to the spread of resistance and that selective pressure for resistance should be considered in choosing an antimicrobial. In addition, 89% indicated that they would be willing to change their diagnostic and therapeutic practices to decrease the spread of resistance (CDC, unpublished data).

In the focus group discussions, when physicians were asked by what proportion they could decrease antibiotic use in their practice without compromising patient care, answers generally ranged between 10% and 50% [16]. Although expectations of parents or patients were identified in the focus groups as the leading contributor to antimicrobial overuse, survey results suggested that improving physicians’ diagnostic practices and their understanding of the natural history of URIs also are important factors.

To address these factors, the CDC, in collaboration with members of the AAP and the American Academy of Family Physicians, has published evidence-based recommendations that will identify these and other situations in which antimicrobial use can safely be avoided [17]. Examples include otitis media with effusion [18], most nonstreptococcal pharyngitis, nonspecific URI including purulent rhinitis [19], and most episodes of cough illness that currently may be diagnosed as bronchiolitis. These recommendations will be promoted as the basis for locally developed practice guidelines, which have been shown to be an effective means of changing clinical practices [20].

A second key element in the strategy to reduce unnecessary antimicrobial use is to decrease patient demand for therapy and to improve the ability of clinicians to respond to patient expectations without an antimicrobial prescription. To educate patients and parents, the CDC is developing pamphlets, posters, and a video to relay the message that antibiotics are not needed for many respiratory infections and that unnecessary antimicrobial therapy can harm patients by increasing their risk of resistant infection. (CDC patient education materials are available free; call (404) 639-4702.) The emphasis of this message is different from previous “rational antibiotic use” campaigns, which focused on taking prescribed medications correctly or curtailing overall use for the good of society. Recommendations that pediatricians educate parents about antimicrobial therapy and respiratory infections also are being incorporated into the AAP guidelines for well-child-care visits—a setting where a clinician may have more time and where parents may be more receptive to the message.

Educating the public will be complemented by programs to actively promote judicious antimicrobial use among clinicians. Face-to-face communication between physicians and their peers or drug educators has been effective in changing antimicrobial-prescribing practices [21, 22]. The formation of state-based coalitions that include the health department, state medical society, and professional medical-care-provider organizations is being promoted to implement this intervention.
Providing feedback to physicians on how their antimicrobial-prescribing practices compare with those of their peers or with standards established by guidelines also has been effective in changing behavior [23]. This intervention is particularly feasible in managed care settings where databases that include outpatient diagnoses and prescriptions may be available. In order to promote intervention in managed care, an indicator has been accepted for inclusion in the HEDIS 3.0 system on treatment of uncomplicated otitis media with a first-line antimicrobial agent [24]. The need for managed care organizations to report on performance for this indicator will be an incentive to improve performance through the use of interventions such as education and feedback. State health departments also can provide feedback to physicians by analyzing antimicrobial use practices from Medicaid databases [21, 22].

As interventions are implemented, continued research is important to document the impact of intervention on the knowledge and behaviors of physicians and patients or parents, as well as on patient satisfaction and health outcomes. The CDC has initiated several controlled trials of interventions. Outcomes will include changes in antimicrobial-prescribing practices, carriage of and infection with resistant pathogens, and health care costs. Data from ongoing population-based surveillance for invasive infections caused by resistant \(S.\ pneumoniae\), which is being conducted in 10 areas of the United States, and from national databases on outpatient antimicrobial prescriptions will be analyzed to more broadly assess trends in antimicrobial use and resistance.

The emergence and spread of resistance presents a challenge that can be met only through an effective response of a broad coalition that includes the public health community, health care providers, professional societies, pharmaceutical manufacturers, the mass media, and the public. A new paradigm is needed in which providers and patients act as partners to ensure that antimicrobial therapy is prescribed only when truly necessary. Through such a change, patients can be protected now from the increased risk of resistant infection incurred by unnecessary antibiotic use, and the effectiveness of antimicrobial therapy can be preserved for the future.

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