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Antibiotic Resistance in Outpatient Populations

The discovery and development of antibiotics, which were first employed in medical practice in the 1940's, stands as one of the major accomplishments of medicine. Antibiotics, combined with vaccination programs and improvements in sanitation, contributed to the remarkable decline in deaths from infectious diseases during the past century (1). However, increasing antimicrobial drug resistance is now threatening these medical advances. The problem of antimicrobial resistance has been identified as the most pressing infectious disease threat to public health by a number of leading organizations (2). Often, nosocomial resistance problems garner more attention than community-based problems, since some of the most resistant organisms, such as vancomycin-resistant enterococci, have been centered in hospitals. Yet, resistance in community-acquired pathogens such as *Streptococcus pneumoniae*, *Escherichia coli*, and *Salmonella spp*, is rising at substantial rates, which are comparable to that of organisms that are typically hospital-based (3-5). In reality, antimicrobial resistance is an evolving problem that spans all health care settings, including everyday ambulatory practice.

In this review, we first present an overview of the problem of antibiotic resistance in bacterial pathogens in the outpatient setting as it relates to antibiotic usage in humans and animals, and then discuss selected pathogens in more detail.

Antimicrobial usage in humans

Antimicrobial agents are the second most commonly prescribed group of medications, and they account for a significant proportion of total health care costs (6). Their use, not surprisingly, has been shown to be increasing over the years, although in the period between 1980 and 1992, they represented a fairly constant percentage of all medications prescribed in the United States (7). During that period, the estimated number of antimicrobial prescriptions rose from 86 million in 1980 to 110 million in 1992, with the highest rates of antibiotic use seen in children less than 15 years of age (7). Of particular importance, the aminopenicillins, amoxicillin and ampicillin, were the most commonly used agents in all years studied and their use increased overall during the study period. In contrast, the use of narrower-spectrum penicillins decreased by two-thirds during the same period. Several other studies have been published in recent years showing similar trends in antimicrobial use in other countries (8-10). Overall, the data substantiate the rising use of newer or broader-spectrum agents and the declining use of older or narrower-spectrum agents.

The indications for these outpatient antibiotic prescriptions are difficult to assess, but in 1992 a study using physician surveys revealed that, in the United States, five diagnoses accounted for 76% of all antibiotic prescriptions in community practice:

otitis media, upper respiratory infections, bronchitis, pharyngitis, and sinusitis (7). Most outpatient antimicrobial prescriptions, therefore, are for the treatment of respiratory tract infections. Many of these conditions are considered to be of viral etiology and typically do not benefit from antibiotic therapy, and therefore a substantial proportion of outpatient antibiotic prescriptions can be considered inappropriate or unnecessary.

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Assessing the appropriateness of antibiotic prescribing, however, is a difficult task given that the criteria for what constitutes inappropriate or unnecessary use are open to debate. Nevertheless, some studies in the United States have attempted to evaluate antibiotic use in what are generally considered to be inappropriate conditions. A study of antibiotic prescribing practices for adults with colds, upper respiratory infections, and bronchitis during the year 1992 revealed antibiotic prescribing rates of 51, 52, and 66%, respectively (11). Similarly, an analysis of pediatric office visits during the same year revealed prescribing rates of 44, 46, and 75%, respectively, for children younger than 18 years with the same conditions (12). By extrapolating to the entire United States, the authors estimated that 6.5 million prescriptions—12% of all prescriptions for children—were written for children diagnosed with a URI or the common cold.

The situation is more controversial for acute otitis media (AOM), for which 20.6 million antibiotic prescriptions were written in 1990 (6). In one study utilizing physician surveys, patients diagnosed with AOM in Australia and the United States received antibiotic prescriptions at rates of 98.2 and 97.9%, respectively (13). The diagnosis of AOM in clinical practice, however, is often based on a combination of symptoms and physical findings, most of which are either not specific for AOM, or of variable reliability (14). Furthermore, there is good evidence that antibiotics may be safely withheld from patients during the first few days of illness, as one study demonstrated that 90% of children with AOM had symptomatic resolution within 4 days through the use of nose drops and oral analgesics alone (15). Thus, AOM appears to be an illness that is both overdiagnosed and overtreated.

Both physicians and patients seem to share in the responsibility for the continued use of antibiotics for conditions for which antibiotics provide little benefit. Some studies suggest that patient expectations might be an important factor. For example, in one 1997 study, 79% of adults surveyed in Kentucky and Louisiana believed antibiotics were indicated and effective in the setting of a URI with discolored nasal discharge (16). In contrast, a later study suggested that physician prescribing practices may in turn influence their patients' attitudes about the need for antibiotics. In one emergency department-based survey, over 20% of patients believed that their physicians routinely prescribed antimicrobials for cold symptoms (17). Not surprisingly, almost one-fifth of their subjects had used antibiotics in the previous year without the advice of a physician, confirming suspicions that patients misuse oral antibiotics left over from previous illnesses (17). Although it is difficult to estimate the degree to which these behaviors contribute to antimicrobial resistance in the community, it seems clear that both physicians and patients exhibit patterns of behavior that may need to be altered if we are to successfully stem the rising tide of bacterial antibiotic resistance.

Antimicrobial usage in animals

Antibiotics, both similar to and different from those used in humans, are employed extensively in the field of animal husbandry. Bacterial diseases in animals can be potentially fatal, spread rapidly among those kept in close proximity, and dramatically reduce the efficiency of animal food production. Antibiotics are therefore utilized in animals for both disease treatment and prophylaxis, the latter of which is more common in veterinary medicine than in human medicine. In addition, antibiotics are often used in low, generally subtherapeutic concentrations as antimicrobial growth promoters, resulting in enhanced animal derived food production through improved feed conversion efficiency (18). Overall, it is estimated that more than 40 percent of the 23 million kilograms of antibiotics produced in the United States are administered to animals, mostly in feed, and predominantly in subtherapeutic doses (19).

Whether for therapy, prophylaxis, or performance enhancement, this widespread exposure of animals to antibiotics is a risk for the development of antibiotic resistant bacteria. Clearly, the administration of subtherapeutic doses of antimicrobials over a long period of time for growth promotion is a strong selection mechanism for resistant organisms. Antibiotic-resistant bacteria in animals from any cause, however, can potentially present a hazard to human health. Resistant organisms could be transmitted to humans via contaminated food, which may subsequently cause disease. Alternatively, a nonpathogenic species may transfer its resistance genes to other species that are pathogenic to humans. The risk to humans is increased when the agent used in animals is also used to treat human disease, or if there is cross-resistance with similar antibiotics used in humans. For example, one agent used in the poultry industry, virginiamycin, is a streptogramin similar to quinupristin-dalfopristin. In the United States, the use of this agent has been associated with carriage of quinupristin-dalfopristin-resistant enterococci in poultry, presenting a potential health risk to humans (20).

Epidemiologic studies of animal husbandry in the United States have traced the emergence of resistant strains of some bacteria to the use of antimicrobial agents in livestock, as has been the case with *Salmonella* (21). Furthermore, one recent report has documented a case of *Salmonella* enteritis caused by a ceftriaxone-resistant organism, which was demonstrated via molecular methods to be related to isolates from cattle from the patient's local region (22). In addition, with the introduction of fluoroquinolones to veterinary practice, fluoroquinolone-resistant isolates of *Salmonella* and *Campylobacter* have emerged among animals and poultry (23-25). Although this topic remains under significant debate, it appears that data are accumulating which implicate the use of antimicrobials in animals in the growing threat of antimicrobial resistance in human pathogens.

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Problem pathogens

Respiratory tract

S. pneumoniae is the leading cause of serious community-acquired bacterial infections including pneumonia and meningitis, and is the primary bacterial pathogen responsible for otitis media and sinusitis. It is also responsible for up to 50,000 deaths annually (26). The emergence of antimicrobial resistance in this pathogen is therefore a serious threat to public health. Prior to 1987, resistance to penicillin was uncommon, but during the 15-year period from 1979 to 1994, resistance rates in the United States rose from 5% to over 23% (27). Furthermore, an analysis of *S. pneumoniae* isolates from around the United States collected during 1999 and 2000 revealed an even higher rate of penicillin resistance of about 35%, two-thirds of which were highly resistant with MICs≥2 µg/ml (28). In addition, the prevalence of reduced susceptibility to penicillin exceeds 40%-50% in several Asian and European countries, with rates over 60% recently seen in Hong Kong and Madrid (29-31).

Of additional concern is that penicillin-resistant organisms are also frequently resistant to other agents, particularly cephalosporins, erythromycin, tetracycline, and trimethoprim-sulfamethoxazole. In one U.S. study, the prevalence of resistance to erythromycin, tetracycline, and trimethoprim-sulfamethoxazole among isolates with intermediate susceptibility to penicillin was 37%, 27%, and 42%, respectively (5). In addition, the percentage of isolates from the U.S. from 1997-98 found to be multidrug resistant almost doubled when compared with a similar study by the same group just three years earlier (5).

The two other typical bacterial pathogens associated with community-acquired respiratory infections, *Haemophilus influenzae* and *Moraxella catarrhalis*, have also shown increasing rates of antimicrobial resistance. These organisms exhibit strong resistance to beta-lactams, primarily via plasmid-mediated beta-lactamase production, although *H. influenzae* can also produce altered penicillin-binding proteins. In a recent review of isolates from the United States and Canada from 1997, 33.5% of *H. influenzae* isolates were found to produce beta-lactamase, a number which has been relatively stable during the 1990s but which has increased from about 15% during the mid-1980s (32). The level of antibiotic resistance among *H. influenzae* has reached sufficient levels such that one source recommends against using penicillin, ampicillin, amoxicillin, erythromycin, tetracycline, and first-generation cephalosporins for the treatment of infections caused by *H. influenzae* (4). Resistance to trimethoprim-sulfamethoxazole also appears to be rising, with resistance rates in the United States and Canada of over 16% in 1997 (32).

Beta-lactamase-producing strains of *M. catarrhalis* have also been increasing over the past few decades. In the same review of isolates from the United States and Canada from 1997, over 92% of *M. catarrhalis* isolates were found to be beta-lactamase producers (32). Despite the high prevalence of resistance to beta-lactams, however, resistance to other antimicrobials has not become a significant problem to date.

Community-acquired infections due to *Streptococcus pyogenes* are numerous and varied, and despite the use of penicillin for more than 40 years, there are little data to suggest any change in the susceptibility of these organisms to penicillin. Numerous reports have been surfacing in recent years attempting to link treatment failures with the emergence of penicillin resistance, but to date there are no well-documented reports of a strain of *S. pyogenes* that is resistant to penicillin.

In contrast, although *S. pyogenes* has remained quite susceptible to penicillin, reports have shown high rates of resistance to erythromycin in a number of countries, including Japan, Finland, and other European countries. As the use of macrolides in Japan increased dramatically during the 1970s, resistance to erythromycin climbed to 22% by 1981 (33). By 1990, however, the rate had dropped to only 1%, coinciding with a marked fall-off in the production of macrolides in that country. In Finland, erythromycin resistance rose as high as 31% in the late 1980s (34), but through nationwide reductions in the use of oral outpatient macrolide therapy, a significant decline in the rate of erythromycin resistance among these organisms was seen during the 1990s (35). In the United States, however, resistance to erythromycin has not been a major problem, and it is still recommended as second line therapy in patients who cannot be treated with beta-lactam antibiotics.

Genitourinary Tract

Acute uncomplicated cystitis accounts for a large number of outpatient visits by young women each year, and *E. coli* is responsible for between 80 and 90% of all cases. Antibiotic selection for this disorder is largely empirically guided rather than culture-driven, which has raised concern over the possible rise in *E. coli* of resistance to the recommended empiric agents. A recent study assessing the antimicrobial resistance patterns of *E. coli* isolates from the mid-1990s revealed that the prevalence of resistance to ampicillin ranged from 26 to 34% between 1992 and 1996 (36). Although resistance to trimethoprim-sulfamethoxazole—currently considered the standard therapy for acute uncomplicated cystitis—was relatively low in 1992 (9%), it doubled by 1996 (18%). During the same time period, however, resistance to ciprofloxacin and nitrofurantoin remained less than 1 and 2%, respectively. Fluoroquinolones are now well-accepted alternatives to trimethoprim-sulfamethoxazole in this disorder, but reports are already surfacing describing *E. coli* urinary tract isolates that are resistant to fluoroquinolones. Recently published recommendations (37,38) suggest to refrain from using fluoroquinolones universally as first-line agents for acute uncomplicated cystitis, and to consider their use only when the local prevalence of trimethoprim-sulfamethoxazole resistance has reached 20%.

Neisseria gonorrhoeae, a major cause of pelvic inflammatory disease and a facilitator of HIV transmission, accounted for over 360,000 cases of urethritis in the United States in 1999 (39). Despite an overall decline in the incidence of gonorrhea in most industrialized countries, antibiotic resistance in these organisms is increasing. Penicillin remained the therapeutic drug of choice for gonorrhea infections until the 1980s, when penicillinase-producing strains became widespread. From 1988 to 1994, resistance to penicillin in the United States rose from 8.4 to 15.6% (40), and much higher rates are found in other parts of the world, particularly in Southeast Asia. Alternatives to penicillin, including fluoroquinolones, have been recommended since the early 1990s, but now it appears that resistance to these agents is on the rise as well. Infections with fluoroquinolone-resistant gonorrhea are now endemic in many Asian countries (41), and although such pathogens have been documented only sporadically in the continental United States, data now suggests that resistant *N. gonorrhoeae* are being spread endemically in Hawaii. In fact, in 1999, the percentage of gonococcal isolates resistant to ciprofloxacin had risen to an alarming 9.5% (42). This finding prompted the CDC to recommend that clinicians in Hawaii no longer use fluoroquinolones to treat gonococcal infections, and to use a cephalosporin instead (42).

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Central Nervous System

Neisseria meningitidis is one of the leading causes of meningitis in the United States and an important cause of community-acquired septicemia, with an associated mortality that is significant. Penicillin has traditionally been the antimicrobial agent of choice for this organism, although strains with decreased susceptibility to penicillin have been described in a number of countries for many years. Interestingly, the rates of resistance vary widely among different parts of the world. In Spain, for instance, overall penicillin-resistance rates rose from about 9% in 1986 to over 71% in 1997 (43). In contrast, the prevalence of intermediate penicillin resistance in meningococci isolated during 1993 and 1994 in the Netherlands was only 3.3% (44). Penicillin-resistant *N. meningitidis* has rarely been reported in the United States, and penicillin remains the first-line therapy in this country. There have been reports in the past of meningococcal strains with high-level penicillin resistance due to beta-lactamase production, however, and although none have been identified in the United States, concern exists over the potential for these strains to spread.

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Gastrointestinal System

Campylobacter and *Salmonella* are the two most frequent causes of infectious gastroenteritis in many countries. Antimicrobial treatment has not definitively been shown to be of benefit for these infections in otherwise healthy people, and the routine use of antibiotics for the treatment of gastroenteritis from these organisms is not recommended. Nevertheless, antibiotics are still often prescribed, and they are recommended for those with severe or extraintestinal infection, or in patients with risk factors for such.

The current recommendation for the empiric treatment of infectious gastroenteritis in these situations is a fluoroquinolone, because of their effectiveness against these and other enteric pathogens. Since the late 1980s, however, there has been a growing body of literature describing fluoroquinolone resistance in both *Campylobacter* and *Salmonella* species. Reports from Spain have found the rate of ciprofloxacin resistance to be as high as 75-81% among *C. jejuni* isolates recovered between 1995 and 1998 (45,46), while in Thailand ciprofloxacin resistance reached 84% in 1995 (47). In the United States, resistance to fluoroquinolones has not been as dramatic, but it does appear to be on the rise. A recent report from Minnesota found that the rate of fluo-

roquinolone resistance in *C. jejuni* isolates from humans increased from 1.3 to 10.2% from 1992 to 1998 (48). As early as 1992, ciprofloxacin resistance was found to be associated with treatment failure for *Campylobacter* enteritis among U.S. military personnel (49).

The situation is similar for *Salmonella* species, which now show rising levels of resistance in some areas of the world to ampicillin, chloramphenicol, tetracycline, and sulfonamides, much of which is attributed to a multidrug-resistant strain of Salmonella referred to as definitive type 104 (DT104)(50). This strain has become a major cause of disease in humans in Europe, particularly in the United Kingdom, and it is becoming more widespread in the United States as well. With the emergence of this strain, isolates with decreased susceptibility to fluoroquinolones have now been found, and evidence appears to link this event with the approval of quinolones for veterinary use (50). Even more concerning is the recent emergence of strains resistant to extended-spectrum cephalosporins, as mentioned previously, which may be of particular concern given these drugs are the agents of choice for *Salmonella* infections in children.

Summary

Rising levels of resistance are being found among common community-acquired pathogens, and outpatient antibiotic regimens which traditionally have been effective are now failing at increasing rates. We are also beginning to understand the degree to which inappropriate or unnecessary antibiotic use in humans, as well as large-scale antibiotic use for growth promotion in animals, is contributing to the problem. Antimicrobial resistance is thus a critically important outpatient problem that needs to be addressed if we are to have any impact on its evolution.

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Educational Objectives After reading this publication, the reader should be able to:

- Discuss the role of antimicrobial use in humans and in animals and their relationship to antimicrobial resistance.
- Discuss the resistance trends, if any, for the most common bacterial pathogen causing the following community acquired infections:
  - a) Respiratory tract infections
  - b) Uncomplicated cystitis
  - c) Meningitis
  - d) Infectious gastroenteritis

CME Self-Assessment Examination

1. Which of the following is not among the top 4 reasons for antibiotic prescriptions in community practice in the United States?
   a. Otitis media
   b. Diarrhea
   c. Upper respiratory infection
   d. Bronchitis
   e. Pharyngitis

2–5. Circle True (T) or False (F) as appropriate for each of the following statements:

T F 2. *S. pneumoniae* is a leading cause of serious community acquired bacterial pneumonia and meningitis, and of otitis media and sinusitis.

T F 3. In the past decade, *S. pneumoniae* has shown increasing resistance to penicillin but not to other antimicrobials tested.

T F 4. The primary mechanism of beta-lactam (e.g., penicillin group) resistance in *M. catarrhalis* and *H. influenza* is the production of beta-lactamase.

T F 5. A significant increase in penicillin resistance in *S. pyogenes* has been reported in the last decade

6. Which of the following statements about genitourinary tract infections is false?
   a Ampicillin-resistance among *E. coli* causing community acquired urinary tract infections ranged from 26-34% in the period 1992-1996.
   b. While resistance to trimethoprim-sulfamethoxazole (TMS) among *E. coli* causing community acquired urinary tract infection has increased somewhat in the past decade, TMS is still an acceptable empiric standard therapy.
   c. The incidence of *N. gonorrhea* urethritis has been increasing in the United States in the past decade.
   d. Penicillinase producing strains of *N. gonorrhea* are widespread in the United States.

7. Which of the following statements is true?
   a. Penicillin resistance among *N. meningitidis* does not appear to be a problem in the United States, although significant levels of resistance has been reported in other countries.
   b. Increasing fluoroquinolone resistance has not been noted among strains of campylobacter recently isolated in the United States.
   c. Increasing fluoroquinolone resistance has not been noted among strains of *N. gonorrhea* recently isolated in the United States.
   d. All of the above

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