Antimicrobial Resistance

By

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Antimicrobial Resistance

ABSTRACT

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Antimicrobial resistance is not a new concept. For over half a century, health care providers have been faced with this problem. The overuse and misuse of antimicrobial therapy by health care providers has contributed largely to the problem, but several other factors have also been associated with antimicrobial resistance. This article reviews current literature regarding antimicrobial resistance in an effort to educate health care providers to make judicious decisions in the treatment of bacterial infections and stem the rise of antibiotic resistance by carefully scrutinizing prescribing practices. Contributing factors to antimicrobial resistance and recommendations for the control of antimicrobial resistance will be reviewed. Treatment recommendations for common health ailments (i.e. acute otitis media, rhinitis, sinusitis, and pharyngitis) will be provided. The threat of a post-antibiotic era looms. The fight against antimicrobial resistance must start now.
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Historical Perspective

For more than half a century, medical literature has been filled with articles concerning the increasing problem of antimicrobial resistance. The cause of this health problem has been linked to the widespread use of antimicrobials promoting the spread of antimicrobial resistance (APUA, 1999; Bax, 1997; CDC, 1999; Jones, 1999; McCaig & Hughes, 1995; Pulcini, 1999; Rossen, 1999). Antimicrobial agents are the second leading therapeutic category of drugs prescribed by office-based physicians in the United States (Billstein, 1994; McCaig & Hughes, 1995). Expenditures incurred from antimicrobial resistance have been estimated to range from $75 million to $7.5 billion annually (McCaig & Hughes, 1995; Tenover & McGowan, 1996). In 1954, two million pounds of antibiotics were produced in the United States. Today the figure exceeds 50 million pounds (CDC, 1999; Joshi & Milfred, 1995).

Antimicrobial resistance has become more prevalent but not more resistant over the years (Cunha, 1998). In 1928, Alexander Fleming, a Scottish scientist, discovered the first antibiotic, penicillin, when he noticed that bacteria could not survive on a plate that contained a mold commonly found on bread. Ten years after his discovery, group A streptococci and pneumococci had developed modes of resistance (Macleod & Daddi, 1939). By the 1950s and 1960s, the widespread acquisition of penicillin resistance by staphylococcus aureus was seen (Liu, 1999). The 1960s endured outbreaks of resistant gram-negative enteric bacilli, and by the 1970s; widespread use of antibiotics led to more antibiotic-resistant bacteria, notably methicillin-resistant staphylococci and multiply resistant gram-negative rod bacteria (Levy, 1998). The 1970s also saw the emergence of beta-lactamase-producing bacteria, such as Haemophilus influenzae and Moraxella
catarrhalis (Jones, 1999). The 1980s brought multidrug-resistant pneumococci. Vancomycin-resistant enterococci has made its way into the 1990s (Kujdych, 1999).

Currently, as we enter the 21st century, several resistant pathogens are on the rise. These problem pathogens include gram-positive bacteria: penicillin-resistant Streptococcus pneumoniae (PRSP), Group A streptococci of enhanced virulence, vancomycin-resistant enterococci (VRE), and methicillin-resistant staphylococci (MRSA) (Pulcini, 1999).

The purpose of this paper is to review current literature and to present guidelines in an effort to assist the practitioner in making judicious decisions in the treatment of bacterial infections and stem the rise of antibiotic resistance by carefully scrutinizing prescribing practices.

Definition of Antimicrobial Resistance

Antimicrobial resistance occurs when the antibiotics taken to stop the infection do not kill bacteria that cause infection. The bacteria survive and continue to multiply causing more harm. “Resistance reflects the ability of a microorganism to avoid the inhibitory or lethal activity of an antimicrobial agent” (Fraimow & Abrutyn, 1995).

There are two types of resistance, intrinsic (relative) resistance is the gradual increase in the minimal inhibitory concentration (MIC) that occurs in susceptible organisms over time. This is an inherent attribute of a particular species (i.e. lacks the drug susceptible target or possesses natural barriers that prevent the agent from reaching the target). For example, in the treatment of acute otitis media due to an infection caused by Streptococcus pneumoniae, the dosage of amoxicillin has increased from 40-45/mg/kg/day to 80-90/mg/kg/day to achieve effective middle ear fluid concentrations to
treat the organism (Dowell et al., 1999). The mechanism of antimicrobial resistance in Streptococcal pneumoniae is an altering of protein binding sites within the bacterial cells (Fitzgerald, 1998). This results in resistance to lower levels of beta lactams, rendering lower doses of amoxicillin ineffective.

Acquired (absolute) resistance is when a previously sensitive organism suddenly is no longer sensitive to an antibiotic, independent of dose. This occurs by a change in the genetic composition of a bacterium or the organism becomes tolerant to an agent. For example, in the treatment of acute otitis media caused by an infection with Haemophilus influenzae, amoxicillin would be an ineffective drug therapy. The mechanism of antimicrobial resistance in Haemophilus influenzae is the production of beta lactamase, which renders amoxicillin ineffective (Fitzgerald, 1998). Antimicrobials effective against Haemophilus influenzae must inhibit or be stable in the presence of beta lactamase. Amoxicillin with clavulanate (Augmentin), a beta lactamase inhibitor, is highly effective against the Haemophilus influenzae that produces beta lactamase (Gilbert, Moellering, & Sande, 1998).

Mechanisms of Resistance-Absolute or Acquired Resistance

The health care community is returning to a pre-antimicrobial agent era because of the development of multi-resistant organisms (Cohen, 1992; Danziger & Pendland, 1995). Some organisms are so multiresistant that no antimicrobial of established efficacy is available to combat them (Murray, 1992). Bacteria are remarkably adaptable and will continue to evolve and acquire new mechanisms of resistance to antimicrobial agents. To date resistance has developed to all antimicrobial drugs (Gold & Moellering, 1996). The
development of appropriate strategies for eradicating infectious pathogens requires an understanding of their mechanisms of resistance.

There are five general mechanisms by which resistance occurs (see Table 1). The first involves decreased cell permeability. The bacteria have the ability to prevent antibiotic cell entry, which prevents the antimicrobial from reaching its target (Fraimow & Abrutyn, 1995). The second mechanism allows the drug into the cell, but then pumps it back out (Bodey, 1997). This is known as drug efflux. The third mechanism of resistance involves neutralization of the antimicrobial agent by enzymes that reversibly or irreversibly inactivate the drug (Kujdych, 1999; Volk, Benjamin, Kadner, & Parsons, 1986). For example, the production of beta-lactamase, an enzyme, penicillinase, that breaks down the four-membered beta-lactam ring, rendering the beta-lactam antibiotics ineffective (Liu, 1999; Moellering, 1998).

The fourth mechanism of resistance is alteration of the target so that the agent no longer will interfere with it (Danziger & Pendland, 1995). Some of these alterations may require, as little as a single mutational event in the primary target to create a new functional target with reduced affinity for the antimicrobial agent. Other alterations of the target site include incorporation of foreign DNA, modification of penicillin-binding proteins, and modification of the gene encoding DNA gyrase (Volk et al., 1986).

A fifth mechanism of resistance is the elimination of the target altogether by the creation of new metabolic pathways. Resistant genes can be moved from their original hosts into new organisms, causing them to become resistant to additional antimicrobial agents (Murray, 1992; Moellering, 1998). The geographic spread of resistant clones is also a mechanism of antimicrobial resistance.
Contributing Factors to Antimicrobial Resistance

The causes of antimicrobial resistance are multifactorial (see Table 2). Antibiotic prescribing practices play a primary role in the emergence of resistant microorganism strains (Acar, Kaplan, & O’Brien, 1997). Inappropriate or imprudent use of antimicrobial agents has exacerbated the resistance problem (Fitzgerald, 1998; Joshi & Milfred, 1995; Kujdych, 1999; Kunin, 1993; Levy, 1998; Reece, 1999). The Centers for Disease Control and Prevention reports that humans consume 235 million doses of antibiotics, annually. It is estimated that 20-50% of that use is unnecessary; being prescribed for colds, coughs, and other viral infections (CDC, 1999).

Prescribing Practices

Prescription practices are among the largest contributors to the resistance problem. Medical practitioners tend to prescribe antibiotics for prophylactic use, in the treatment of viral URI due to pressures from patients (Bauchner & Phillip, 1998; Joshi & Milfred, 1995; Murray, 1992). Physicians frequently prescribe antibiotics for upper respiratory infections, when they believe patients expect it. One study conducted to look at patients’ and physicians’ expectations for antibiotics and the effects of the patient-physician interaction on patient satisfaction found that 65% of 113 adult patients with respiratory infection expected antibiotics. Antibiotics were prescribed to over 75% of patients with sinusitis or bronchitis and to 18% of those diagnosed with only viral infections. There was no association found between a prescription for antibiotics and patient satisfaction; however, patient satisfaction did correlate with patients’ report that they understood the illness and that the physician spent enough time with them (Hamm, Hicks, & Bemben, 1996).
Health care providers have admitted to responding to parental requests for antibiotics. Prescribing patterns of 610 U.S. pediatricians were analyzed in a study (Bauchner, Pelton, & Klein, 1999). This study found that 95% of the pediatricians described some parents who requested unnecessary antibiotics and 10% of the physicians acknowledged complying with the request. The researchers listed issues that the physicians noted as contributory to inappropriate or imprudent antibiotic use: parent pressure (54%), need to be efficient in practice (19%), legal liability concerns (12%), and other (15%) (Bauchner et al., 1999).

**Time Limitations**

Time limitations in practice contribute to the problem of antibiotic resistance. Educating the parent was felt to be imperative for decreasing antibiotic use in 78% of the physicians, but “not enough time” was cited as a major reason for simply complying with parental requests (Bauchner et al., 1999). Medical providers report that they don’t have enough time during clinical visits to educate patients about their illnesses and about antibiotic use (Schwartz, Freij, Ziai, & Sheridan, 1997).

**Inconsistent Infection Control Techniques**

Inconsistent infection control techniques by medical care personnel cause the dissemination of resistant strains via person-to-person transmission (Goldmann & Huskins, 1997). Despite extensive efforts at behavior modification, caregivers often neglect to wash their hands before and after patient contact. Gloves are not used when contact precautions are indicated, and hands are not washed when gloves are removed. The risk of person-to-person transmission of antimicrobial-resistant pathogens via the
contaminated hands of caregivers tends to be greatest in overcrowded, understaffed ICUs (Goldmann & Huskins, 1997).

**Increased Empiric Use of Broad-Spectrum Antibiotics**

Economics is yet another contributing factor to antimicrobial resistance. Inadequate insurance coverage for patients and pharmaceutical companies’ marketing techniques have lead to the use of more broad-spectrum antibiotics. To promote new antimicrobials, pharmaceutical companies supply medical clinics with complimentary drug samples that are rarely first-line, narrow-spectrum drugs needed for common infections. Patients without insurance coverage for drugs are often treated with these free samples (Reece, 1999).

Medical practitioners fear treatment failures or legal liability due to antibiotic-resistant pathogens, which has lead to increased empiric use of broad-spectrum antibiotics which exacerbates the resistance problem (Goldmann & Huskins, 1997; Jones, 1999; Liu, 1999; Murray, 1992). These broad-spectrum antibiotics kill many different types of bacteria, including beneficial (normal) strains. Antibiotics pose several problems that include excessive cost and the emergence of multiple drug-resistant organisms as a result of “selection pressure” (Joshi & Milfred, 1995). A study performed from 1980 to 1992, assessed changes in the oral antimicrobial drug prescribing by office-based physicians to treat otitis media, sinusitis, and other common infections. The study found that 51% of patients diagnosed with “colds” were treated with antibiotics. The study found an increasing prescribing rate for the more expensive, broader-spectrum antimicrobial drugs, such as the cephalosporins. The study also noted decreasing rates
for the use of less expensive antimicrobial drugs with a narrower spectrum, such as the penicillins (McCaig & Hughes, 1995).

Marketing of Antimicrobials

Pharmaceutical companies have also contributed to the resistance problem. Clearly, it is in the best interests of pharmaceutical companies to promote wide use of antibacterials in order to justify their research and development costs. Currently, it costs $100-$500 million to bring a new drug from discovery to the marketplace in the U.S. (Billstein, 1994; Hancock, 1997; Moellering, 1998). The average cost for antibiotics is much lower than for cardiovascular, central nervous system, and gastrointestinal agents. Therefore, pharmaceutical companies are stopping or cutting back on their antibiotic research programs because of lack of financial incentives (Billstein, 1994).

Unfortunately, the number of new antimicrobial agents being developed is at an all time low. The market for antibiotics was growing at 25% per year in the 1970’s-1980’s, but this growth has slowed in the 1990’s to 6% per year (Bax, 1997). It is of concern that there are no new major antibiotics in phase III development that could result in marketing applications in the next 3-4 years (Hancock, 1997).

Inadequate Consumer Knowledge

The public has also contributed to the emergence of antimicrobial resistance through their lack of knowledge about antibiotic use in bacterial versus viral illnesses and the importance of following an appropriate treatment regimen. Parents misunderstand appropriate indications for antibiotics. In a survey of 400 parents, the researchers found that parents believed that antibiotics were always or sometimes required for throat infections (83%), colds (32%), cough (58%), and fever (58%) (Palmer & Bauchner,
Patients tend to insist on antibiotic prescriptions, share their prescriptions with family members, fail to take all of their prescription, “shop” around for providers that will prescribe antibiotics, and follow poor sanitation and infection control (e.g., failure to wash hands) (Fitzgerald, 1998; Reece, 1999).

Lack of Global Regulation

In many parts of the world antibiotics are available without prescriptions (Levy, Burke, & Wallace, 1987). This is thought to account for the increased resistance seen in developing countries. Three quarters of the world’s population live in Africa, the Middle East, Latin America, and Asia. They purchase only 20% of the worldwide supply yet are burdened by the highest rates of resistance to the older antimicrobial drugs (O’Brien, 1992). This increased rate of resistance has been linked to a combination of factors: the heavy burden of infectious diseases; huge populations without appropriate primary health care; inappropriate use of the available antimicrobial drugs; and rapid spread through crowding, poor sanitation, and sexual contact (Kunin, 1993).

Antimicrobial Use in Agriculture

Antimicrobial agents are used on agriculture crops to ward off blights, added to livestock feed to stimulate growth, and used in aquaculture, and a variety of veterinary settings (Moellering, 1998). There is widespread use of subtherapeutic concentrations of antimicrobial agents as growth promoters for a variety of farm animals, and this practice undoubtedly leads to the emergence of resistant organisms in this setting (Murray, 1992). Over 40% of the 50 million pounds of antibiotics produced in this country are used in animals. Of this 40% more than 80% by weight is used subtherapeutically for growth promotion; the rest is for therapy (Levy, 1998).
Recommendations for the Control of Antimicrobial Resistance

Judicious Use of Antimicrobials

Strategies to prevent the spread of resistant strains are the responsibility of the health care provider and the public. Numerous recommendations have been suggested (see Table 3) and are encouraged to be followed to control and prevent the emergence of resistant organisms. The judicious use of antibiotics to prevent the promotion of antimicrobial resistance is an important control strategy. The percentage of resistant bacteria strains has decreased significantly in countries where changes in antibiotic practices have been implemented. A study done in Iceland found that by following strategies to control resistance (public campaign, physician education, and increased antibiotic cost), the incidence of penicillin resistant streptococcal pneumoniae declined by 5% from 1993 to 1996 (Stephenson, 1996).

Tuberculosis resurged with a vengeance in the 1990’s due to laxity in public health measures that had controlled the disease for more than half a century. Strong public health measures such as directly observed therapy (DOT) were re-instituted, and great strides were made in reconquering the disease. Tuberculosis cases dropped 26% from 1992 to 1997 (CDC, 1999; Pulcini, 1999). It is the health care practitioner’s responsibility to be familiar with local data on antibiotic resistance, to observe and report suspected resistance, keep in contact with microbiology laboratories, and to consult with experts on infectious disease (Reece, 1999). The Centers for Disease Control and Prevention (CDC) (www.cdc.gov.) and the Alliance for the Prudent Use of Antibiotics (APUA) (www.apua.org.) have web sites that provide further up-to-date information concerning antimicrobial resistance.
Antimicrobials should not be used for prophylactic purposes in settings where the likelihood of infection is low such as for upper respiratory tract infections (Dowell, Mary, Phillips, Gerber, & Schwartz, 1998; Liu, 1999; Moellering, 1998; O'Brien et al., 1998). Whenever possible cultures should be obtained to treat the appropriate organism before “empiric” antibiotic therapy is initiated (Liu, 1999; Schwartz & Bell et al., 1998). Care must be taken to select the most appropriate narrow-spectrum antibiotic to treat the organism (Dowell et al., 1998; Reece, 1999; Schwartz et al., 1997). For example, the use of amoxicillin for the treatment of acute otitis media caused by Streptococcal pneumoniae instead of using a broad spectrum antibiotic such as azithromycin. Utilizing the full dose of an antibiotic with the shortest course eradicates the greatest number of organisms without selecting out resistant strains (Kujdych, 1999). Low doses result in subinhibitory concentrations predisposing the development of antibiotic resistance and long-term use causes changes in the patients microbial flora favoring the proliferation of fungi, as well as bacteria (Liu, 1999; Reece, 1999).

The use of antibiotics with little or no resistance potential can prevent the emergence of resistant organisms (Cunha, 1998). The use of restricted or rotating formularies and computer directed antibiotic selection programs that contain antibiotics that have not been associated with resistance can also decrease selective pressure for a specific compound before resistance becomes prevalent (Cunha, 1998; Danziger & Pendland, 1995; Murray, 1992).

The World Health Organization (WHO) Model List of Essential Drugs provides a common core of basic drugs needed for the majority of the population. A selected number of well-established antiinfective agents are included in the ninth list, and since
1989 there has also been a section devoted to reserve antiinfective agents (WHO, 1995). Information must be available and prescribing guidelines need to be developed for the rational use of these drugs to prevent the development of resistance to them (Couper, 1997).

Infection Control and Prevention

Infection control and prevention is extremely important in the control of antibiotic resistance. Recent data shows that lack of basic hygiene (i.e., not washing hands or changing gloves between patients) is still a principle cause for the spread of infection (Neu, 1993). Good hand washing techniques before and after each patient contact should be reinforced, and gloves must be changed between patient visits. Control and prevention of the dissemination of antibiotic resistant organisms in hospitals and nursing homes is also a solution to the problem of antimicrobial resistance. Infection control measures have failed to control the emergence of antibiotic-resistant organisms in hospitals and nursing homes. Universal precautions should be taken and aseptic technique should be scrupulously followed. Patients should be instructed on good hand washing techniques. They should be encouraged to rinse off fruits and vegetables before eating, and meats should be cooked thoroughly (APUA, 1999; CDC, 1999).

Susceptibility Surveillance

The use of local and global surveillance studies to index susceptibility patterns in order to help identify species and resistances to guide the selection of appropriate antimicrobial agents will also help control antimicrobial resistance. Antimicrobial resistance needs monitoring and management at the global level because resistant genes
and strains travel between countries and many countries may differ greatly in their practices, policies, and problems (Jones, 1999; O’Brien, 1997; Stelling & O’Brien, 1997).

Data recovered from several national surveillance studies should help guide decisions about empiric therapeutic treatment. To avoid antimicrobial resistance, the choice of empiric therapy for managing bacterial infections should be based, whenever possible, on epidemiological information collected from local and regional clinics or hospitals. The World Health Organization’s Network (WHONET) program is currently tracking bacterial resistance through contact with tens of thousands of laboratories around the world that identify and test the susceptibility of strains of bacteria from patients every day (Stelling & O’Brien, 1997).

Continuing Education

Continuing education of health care personnel, veterinarians, users in the agricultural sector and the public about the importance of the rational use of antimicrobial drugs is a very important control strategy in the prevention of resistance. The use of pamphlets and public health messages regarding antibiotic resistance, when antibiotics are needed, how to take correctly, proper duration and how to avoid spread, and education regarding earlier detection of therapeutic failure will help in the fight against resistance (APUA, 1999; CDC, 1999).

Pharmaceutical Research and Development

The discovery and development of new antimicrobials will aid in the fight against antimicrobial resistance. The development of antibiotics with new chemical entities designed to overcome or circumvent resistance appears to be the best prospect for dealing with resistance (Moellering, 1998). Unfortunately, despite intensive research, no novel
chemical class of antibiotics has been discovered in the past 20 years (Hancock, 1997). We can no longer continue to depend on new products to solve the problem of resistance. Use of any product, especially heavy use, will eventually result in the development of resistant strains of bacteria (Danziger & Pendland, 1995).

The newest medications being developed to treat multiresistant gram-positive bacteria such as vancomycin-resistant enterococci, multiresistant, methicillin-resistant staphylococci, and multiresistant, penicillin-resistant pneumococci are Synercid and Zyvox. Unfortunately, two cases of resistance have already been reported to Zyvox; and Synercid has been reported to work only 66% of the time (Rossen, 1999). New targets for pharmaceutical research and development include chemical modification of currently known agents to overcome resistance mechanisms. The problem is diminishing returns and continued evolution of established resistance mechanisms (Kessler, 1997).

Other developments are focusing on drugs that inhibit bacterial cell wall synthesis, DNA inhibition, and the creation of potentiatators of known antimicrobials. Immunization therapy is becoming more popular with the development of new vaccines each day. For example, studies are currently being done on vaccines to prevent many viral illnesses as well as bacterial infections such as acute otitis media, sinusitis, and pneumonia caused by Streptococcal pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis (Giebink, 1994). Since many of the problems of drug resistance among nosocomial pathogens are greatly exacerbated by neutropenia or human immunodeficiency virus infection, research on immune function enhancement (e.g., macrophage proliferation and activation) in order to bolster defense against bacterial and fungal pathogens will continue to be important (Kessler, 1997). The use of cytokines
such as granulocyte colony-stimulating factor is just the beginning of new avenues to be explored.

Laboratory Research and Development

The development of rapid diagnostic methods that would provide the identity of an infecting organism in minutes or hours instead of days, would make it possible to use antimicrobial agents more intelligently. New diagnostic methods could also significantly cut down on the indiscriminate use of broad-spectrum antibiotics that has seemingly contributed so much to the development of antimicrobial resistance (Hancock, 1997; Kessler, 1997).

Global Regulation

Control of antimicrobial drug use in developing countries is yet another strategy to controlling drug resistance. The World Health Organization has been active in promoting the rational use of drugs in developing countries and in monitoring the problems associated with the emergence of resistant microorganisms. It has developed a useful list of essential drugs and provides educational materials for the development of national drug policies (Couper, 1997; Kunin, 1993). Several organizations have made important contributions to the problems of drug treatment and distribution in developing countries (APUA, 1999; CDC, 1999). The efforts of these groups are limited to demonstration projects, training, and advocacy due to lack of funding.

Treatment Recommendations for Common Health Ailments in an Effort to Control or Prevent Resistance

In January 1998, the American Academy of Pediatrics and the Centers for Disease Control and Prevention issued guidelines for improving the use of antimicrobial drugs in
outpatient settings (Dowell et al., 1998). A summary of recommendations for the
treatment of acute otitis media, rhinitis and sinusitis, and pharyngitis is presented in the
next section.

The Judicious Treatment of Acute Otitis Media

In the United States, acute otitis media has been the leading diagnosis for the
dispensing of antibiotics to outpatients, resulting in 30 million physician visits, annually
(APUA, 1999; Bauchner & Phillip, 1998). Unfortunately, it is often over diagnosed and
otitis media with effusion is often inappropriately treated with antibiotics, thus promoting
antimicrobial resistance (Dowell et al., 1998). Differentiation of acute otitis media
(AOM) from otitis media with effusion (OME) is an important issue for promoting
judicious antibiotic use (see Figure 1). Avoiding unnecessary treatment of OME would
save up to 6-8 million courses of antibiotics each year (Otitis Media Guideline Panel,
1994). Causative infectious agents are Streptococcus pneumoniae in 70% of chronic
OM, Pneumococci in 25-50%, H. influenzae in 15-30%, and M. catarrhalis in 3-20% of
infections.

The Centers for Disease Control and Prevention recommend pneumatic otoscopy
or tympanometry to confirm middle ear effusions (CDC, 1999). If no effusion is present,
or an effusion is present without signs or symptoms of acute infection, antibiotics are not
necessary. Treatment may be indicated for bilateral effusions persisting for three months
or more. Residual effusions after AOM normally persist for up to 6 weeks. There is no
evidence of benefit from treatment in these cases (Williams, Chalmers, Stange, Chalmers,
& Bowlin, 1993).
A patient who presents with AOM (effusion, ear pain, fever, or bulging yellow or red TM) should be treated with a narrow-spectrum drug. Oral amoxicillin remains the first-line antimicrobial agent for treating AOM (Gilbert et al., 1998). Due to the increasing prevalence of Drug-Resistant Streptococcus pneumoniae (DRSP) and evidence that higher dosages of amoxicillin can achieve effective middle ear fluid concentrations, an increase in the dosage used for empiric treatment from 40-45/mg/kg/day to 80-90/mg/kg/day in children and 1.5/g/day to 3/g/day (a minimum of 500mg t.i.d.) in adults is recommended by most experts (Barnett & Klein, 1995; Dowell et al., 1999; Gilbert et al., 1998; McCracken, 1994).

The other 13 FDA-approved otitis media drugs lack good evidence for efficacy against DRSP (Dowell et al., 1999). For patients with clinically defined treatment failure after three days of therapy, useful alternative agents include oral amoxicillin-clavulanate (Augmentin), cefuroxime axetil (Ceftin), and intramuscular ceftriaxone (Rocephin) (Gilbert et al., 1998).

Antibiotic prophylaxis should only be considered for recurrent AOM as defined by >3 distinct, well-documented episodes in 6 months (or >4 in 12 months), children under age 2, Native American children, and children in day care (Reece, 1999). Tympanocentesis for culture and sensitivity is indicated before prophylactic therapy is started to rule out a resistant bacteria and guide treatment (Bluestone, 1994). The antibiotics of choice for prophylaxis are sulfisoxazole and amoxicillin (20/mg/kg/day); these should not be used longer than 6 months (Dowell et al., 1999; Gilbert et al., 1998), due to the increase in bacterial resistance to commonly prescribed agents. It is important to consider surgical intervention (eg., tympanocentesis, myringotomy, tympanostomy
tube insertion, adenoidectomy, and/or tonsillectomy) as a reasonable alternative to antimicrobial prophylaxis in selected children who have recurrent episodes in the communities that have determined that resistance is a problem, children who have bilateral hearing loss of at least 20 dBs, prophylactic drug failures, and children who attend large day-care centers (Bluestone, 1994; Teele, 1994).

The Judicious Treatment of Rhinitis and Sinusitis

Children have 2-9 viral illnesses per year (Monto & Ullman, 1974).

Mucopurulent rhinitis (thick, opaque, or discolored nasal discharge) frequently accompanies viral rhinosinusitis. This is not an indication for antibiotic treatment unless it persists without improvement for more than 10-14 days (see Figure 2) (Bauchner & Phillip, 1998). A 50% reduction in antimicrobial use would result if treatment was initiated on >10-14 days of symptoms with a savings of 6.5 million unnecessary antibiotic prescriptions (CDC, 1999).

In a case-scenario questionnaire, Schwartz & Freij et al., reported that 71% of family practitioners and 53% of pediatricians would immediately prescribe antibiotics for infants with mucopurulent nasal discharge that lasted one day. Only about one third of family practitioners and pediatricians waited until day 7 of illness to prescribe antibiotics for these same symptoms (Schwartz & Freij et al., 1997). A randomized clinical study done on the benefits of antibiotic treatment for purulent rhinitis showed no benefit from placebo 36% versus 31% respectively (Todd, Todd, Damato, & Todd, 1984).

Sinusitis is diagnosed only in the presence of prolonged nonspecific upper respiratory signs and symptoms (e.g., rhinorrhea and cough without improvement for >10-14 days), or more severe upper respiratory tract signs and symptoms (e.g., fever >39
C with purulent nasal discharge, facial pain or tenderness, periorbital swelling) (see Figure 2) (Wald, 1992). The usual etiologic pathogens include Streptococcus pneumoniae 31%, H. influenzae 21%, especially in heavy smokers with a greater than 25-pack year history, and M. catarrhalis 2%.

Initial antimicrobial treatment of acute sinusitis should be with the most narrow-spectrum agent, which is active against the likely pathogens. Oral amoxicillin with clavulanate (Augmentin) 875/125mg two times a day is considered first-line treatment for community-acquired sinusitis, which has a higher rate of beta lactamase-producing organisms (Gilbert et al., 1998; Wald, 1992). A twice-a-day formulation of Augmentin has reduced the incidence of its most common side effect, diarrhea (Fitzgerald, 1998). The shortest effective treatment course should be used. Clinical improvement should occur in 2-3 days. Patients who do not respond to treatment in 2-3 days should return to the clinic. Treatment should continue for 7 days after symptoms improve or resolve (usually 10-14 day course) (O’Brien et al., 1998).

The Judicious Treatment of Pharyngitis

Eighty-five percent of sore throats are caused by viral agents (Tanz & Shulman, 1995). Only 15% of pharyngitis cases are caused by group A streptococci. Clinical findings alone do not distinguish streptococcal versus non-streptococcal pharyngitis (Poses, Cebul, Collins, & Fager, 1985). Research has shown that even the best clinical scoring system shows poor predictive value (p=65%) (Reed, Huck, & French, 1990). Diagnosis of group A streptococcal pharyngitis should be made using a laboratory test in conjunction with clinical and epidemiological findings (see Figure 3) (CDC, 1999; Schwartz et al., 1998). Antigen tests (rapid strep kits) or culture should be positive
before beginning antibiotic treatment. Negative results on antigen tests should be confirmed with a culture. By following these guidelines antibiotic prescriptions could be reduced by 7 million, a 50% reduction (CDC, 1999). Penicillin V 25-50/mg/kg/day q6h for 10 days is the drug-of-choice for group A streptococcal pharyngitis (Schwartz, Marcy, Phillips, Gerber, & Dowell, 1998; Shulman, Gerber, Tanz, & Makowitz, 1994; Tanz & Shulman, 1995). Erythromycin may be used if the patient is penicillin allergic. Group A streptococci has yet to show resistance to penicillin. Treatment is 90% effective at eliminating streptococci, and may be even more effective in preventing acute rheumatic fever. Carriers of group A streptococci are at a very low risk for both acute rheumatic fever and spreading infection (Shulman et al., 1994). Accurate diagnosis is the key to judicious antimicrobial use (Denson, 1995). It is very important to remember that most cases with clinical signs of streptococcal infection, like exudate and adenopathy, are viral.

Summary

The threat of a post-antibiotic era looms. Antimicrobial resistance will continue to be a problem far into the 21st century. The health care community is faced with resistant microorganisms for which there are no adequate therapies. Research is greatly needed to evaluate the economic benefits of antibiotics, the costs of bacterial resistance, and the relative importance of resistance as a cause of mortality and morbidity. Further, the relationship between resistance and consumption of antibiotics should be reexamined. As health care providers, we need to audit our prescribing practices and institute many of the guidelines presented in this paper as well as keeping up-to-date on current recommendations through the Centers for Disease Control and Prevention (CDC).
(www.cdc.gov) and the Alliance for Prudent Use of Antibiotics (APUA)
(www.apua.org) to help in the fight against antimicrobial resistance.
## TABLE 1
Mechanisms of Resistance

| 1. Decreased cell permeability. |
| 2. Drug efflux. |
| 3. Enzymatic neutralization. |
| 4. Alterations of the target site. |
| 5. Creation of new metabolic pathways. |

Danziger & Pendland, 1995; Fraimow & Abrutyn, 1995; Kujdych, 1999; Liu, 1999; Moellering, 1998; Murray, 1992; Volk et al., 1986.
TABLE 2
Contributing Factors to Antimicrobial Resistance

- Inappropriate or imprudent prescribing practices due to patient pressures, time limitations, and legal liability concerns.
- Inconsistent infection control techniques: failure of health care providers to wash hands and wear gloves when in contact with patients.
- Inadequate insurance coverage for narrow spectrum antimicrobials and the use of broad spectrum complimentary drug samples.
- Fear of treatment failures due to antibiotic-resistant pathogens which has lead to increased empiric use of broad-spectrum antibiotics.
- Pharmaceutical companies promote the wide use of antimicrobials without the development of new major antimicrobial agents.
- The public’s lack of knowledge about appropriate antibiotic use in bacterial versus viral illnesses, importance of following a therapy regimen, sharing of prescriptions, and “shopping” around for providers who will prescribe antimicrobials.
- Availability of antibiotics without prescriptions in many parts of the world.
- The use of antimicrobial agents in agriculture on crops, added to livestock, used in aquaculture, and used in a variety of veterinary settings.

Acar et al., 1997; Bauchner et al., 1999, Bauchner & Phillip, 1998; Bax, 1997; Billstein, 1994, CDC, 1999; Fitzgerald, 1998; Goldmann & Huskins, 1997; Hamm et al., 1996; Hancock, 1997; Joshi & Milfred, 1995; Kujdych, 1999; Kunin, 1993; Levy, 1998; Levy et al., 1987; Liu, 1999; McCaig & Hughes, 1995; Moellering, 1998; Murray, 1992; O’Brien, 1992; Palmer & Bauchner, 1997; Reece, 1999; Schwartz, Bell, & Hughes, 1997
**TABLE 3**

Recommendations for the Control of Antimicrobial Resistance

1. **Judicious Use of Antibiotics:**
   - Keeping abreast of local data on antimicrobial resistance, observe and report suspected resistance, keep in contact with microbiology laboratories, and to consult with experts on infectious disease.
   - Antimicrobials should not be used for prophylactic purposes in settings where the likelihood of infection is low (e.g., URI).
   - Cultures should be obtained to treat the appropriate organism.
   - The most appropriate narrow spectrum antibiotic should be used.
   - The full dose of an antibiotic should be used for the shortest course.
   - Use antibiotics with little or no resistance potential found on restricted or rotating formularies, computer directed antibiotic selection programs, or on the WHO Model List of Essential Drugs.

2. **Infection Control and Prevention:**
   - Good hand washing technique before and after patient contact.
   - Wear gloves and change between patient visits.
   - Follow universal precautions and aseptic techniques.
   - Instruct patients on good hand washing techniques, encourage to rinse off fruits and vegetables before eating, and cook meats thoroughly.

3. **Susceptibility Surveillance**
4. **Continuing Education**
   - Education of health care personnel, veterinarians, users in the agriculture sector, and the public about the importance of the rationale use of antimicrobial drugs.

5. **Pharmaceutical Research and Development**
   - Chemical modification of currently known agents.
   - Inhibitors of bacterial cell wall synthesis.
   - DNA inhibition.
   - Potentiators of known antimicrobials.
   - Immunization therapy.
   - Immune function enhancers and cytokines.

6. **Laboratory Research and Development**
7. **Global Regulation**

APUA, 1999; CDC, 1999; Couper, 1997; Cunha, 1998; Danziger & Pendland, 1995; Dowell et al., 1998; Dowell et al., 1999; Giebink, 1994; Hancock, 1997; Jones, 1999; Kessler, 1997; Kujdych, 1999; Kunin, 1993; Liu, 1999; Moellering, 1998; Murray, 1992; Neu, 1993; O'Brien et al., 1998; Obrien, 1997; Pulcini, 1999; Reece, 1999; Rossen, 1999; Schwartz et al., 1998; Stelling & O'Brien, 1997; Stephenson, 1996; WHO, 1995.
Figure 1: The Judicious Treatment of Acute Otitis Media

<table>
<thead>
<tr>
<th>Pneumatic otoscopy or tympanometry to confirm middle ear effusion</th>
</tr>
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<tbody>
<tr>
<td>Effusion Present</td>
</tr>
<tr>
<td><strong>YES</strong></td>
</tr>
<tr>
<td><strong>NO</strong></td>
</tr>
<tr>
<td><strong>Signs or symptoms of AOM (ear pain, fever, and bulging</strong></td>
</tr>
<tr>
<td><strong>yellow or red TM)</strong></td>
</tr>
<tr>
<td><strong>YES</strong></td>
</tr>
<tr>
<td><strong>NO</strong></td>
</tr>
<tr>
<td><strong>AOM</strong></td>
</tr>
<tr>
<td><strong>Treatment:</strong> Amoxicillin 80-90/mg/kg/day for children and 1.5-3/g/day for adults for 10 days.</td>
</tr>
<tr>
<td><strong>Recurrent AOM (≥ 3 distinct, well documented episodes in 6 months (or ≥ 4 in 12 months)).</strong></td>
</tr>
<tr>
<td><strong>YES</strong></td>
</tr>
<tr>
<td><strong>NO</strong></td>
</tr>
<tr>
<td><strong>OME</strong></td>
</tr>
<tr>
<td><strong>Treatment:</strong> Antibiotics are not required.</td>
</tr>
</tbody>
</table>

- Tympanocentesis for culture and sensitivity.
- Consider prophylactic therapy with Amoxicillin 20/mg/kg/day for ≤ 6 months.
- Consider surgical intervention (i.e., myringotomy, tympanostomy tubes, adenoidectomy, tonsillectomy) for recurrent AOM if prophylactic failure, bilateral hearing loss of at least 20dBs, child attends a large day care, and/or bacterial resistance is prevalent in the community.

Adapted from the CDC, 1999.
Figure 2: The Judicious Treatment of Rhinitis and Sinusitis

Mucopurulent rhinitis, (i.e., thick, opaque, or discolored nasal discharge) cough, and/or fever > 39°C, facial swelling, and/or facial pain for 10-14 days without improvement.

**YES**

Sinusitis

Treatment: Augmentin 875/125mg b.i.d. for 10-14 days.

**NO**

Viral rhinosinusitis

Treatment: Symptomatic (decongestants, (i.e., pseudoephedrine dimetapp), humidification).
Figure 3
The Judicious Treatment of Pharyngitis

Rapid Strep Test

- **POSITIVE**
  - Penicillin V potassium 25-50/mg/kg/day q6h for 10 days with salt water gargles, lozenges that contain benzocaine, analgesics and anti-inflammatory agents (i.e., aspirin or acetaminophen).

- **NEGATIVE**
  - Await culture results

  - **POSITIVE**
  - Treatment: Salt water gargles, lozenges that contain benzocaine, analgesics and anti-inflammatory agents (i.e., aspirin or acetaminophen)

  - **NEGATIVE**
References


Stephenson, J. (1996). Icelandic researchers are showing the way to bring down rates of antibiotic-resistant bacteria. *JAMA, 275*(3), 175.

Pediatric Infectious Disease Journal, 13(11), 1069-73.


