ANTIBIOTIC USE AND ACQUIRED BACTERIAL RESISTANCE

by

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Abstract

The extensive, and sometimes inappropriate, use of antibiotics has contributed to development of antibiotic-resistant bacterial strains. Antibiotics can act as strong forces in encouraging the growth of rare bacterial strains which resist the effects of drugs. Some strains have developed resistance to all available drug agents, while development of new agents has not kept pace. Health care professional and patient treatments of common diseases with antibiotics include practices which encourage the development of resistant strains. Review of professional literature illustrates the development of resistant bacteria in response to antibiotics. The increases reported in numbers of resistant bacteria correspond with continuously increased antibiotic use. Health care providers are responsible for following practice guidelines which minimize their contribution to this problem. The risk of encouraging resistance development must be considered in routine treatment decisions. Continuing education of professionals and the public regarding the problem is an urgent need. Public policy greatly affects the use of antibiotics and requires health care professional involvement. Ongoing research efforts aimed at understanding and monitoring antibiotic resistance are needed. Research into continued antibiotic development, as well as alternative treatment approaches, is warranted. These combined efforts are needed to minimize development of resistant bacteria, and to maintain antibiotics as effective infectious disease treatment.

INTRODUCTION

Statement of the Problem

"Infectious diseases remain the leading cause of death worldwide and a major cause of morbidity and mortality in the United States" (McGowan, 1994, p. 1). Consequently, antibacterial drug agents have played a major role in modern medical care since their first significant use in the 1940's. They have been used globally with great variation in regimens and availability. Their effectiveness once suggested a future free of bacterial disease.

Unfortunately extensive, sometimes inappropriate, antibiotic use by health care professionals and the public threatens the usefulness of these drug agents. Antibiotic use and misuse contributes to the development of drug-resistant strains of bacteria. Strains of common pathogenic organisms have developed resistance to multiple drugs. The incidence and prevalence of disease caused by resistant bacterial strains have grown with the ongoing development of antibiotics. Treatment of these illnesses has become increasingly difficult. The future of infectious disease control is unsure.

The purpose of this report is to contribute to the continuing education of health care providers concerning bacterial resistance to antibiotics. The report focuses on provider practices and patient behaviors which can affect the growth of this problem. Factors which influence the development of bacterial resistance, particularly antibiotic use and mis-use in health care, will be examined.

Information regarding increased bacterial resistance to antibiotics is often fragmentary or geared toward in-patient care. Though data is from scattered sources, the trends are clear. This study provides a synopsis of current information to describe the phenomenon, and reports the link between health care practices and the increase in the development of resistance. The resulting recommended guidelines for community practice and action will help minimize provider, patient, and public contributions to this problem.

Definition of Terms

To facilitate understanding of a complex problem, a number of terms commonly used in describing the phenomenon of bacterial resistance are defined as used in this report.

Antibiosis: The association between organisms in which one is harmful to the other (Thomas, 1993).

Antibiotics: "... a substance produced by a microorganism, or a similar substance produced wholly or partly by chemical synthesis, which in low concentrations inhibits the growth of other microorganisms" (Joklik, Willett, Amos, and Wilfert, 1992, p. 154). In this report, the terms antibiotic, antimicrobial, and anti-bacterial all refer to drugs used to treat bacterial infections.

Resistance: "Resistant organisms are those bacteria with higher MICs (minimum inhibitory concentrations for a given drug), suggesting that less than optimal results might be anticipated if the tested drug was utilized in the treatment of an infection resulting from these organisms" (Dipiro, et al., 1993, p.1492). This report

utilizes literature which recognizes the minimum inhibitory concentration of an antibiotic as the standard measure for evaluating its ability to limit the growth of susceptible bacteria. The bacteriostatic, or reproduction inhibiting, effects of a drug often vary with its dose. Doses useful in therapy are those whose side effects are tolerable. An organism is considered resistant to a drug agent when the MIC required for its treatment exceeds the safe dosage limits of that particular agent's use (Dipiro, et al., 1993).

Intrinsic resistance: For the purposes of this report, intrinsic is that which is part of the essential nature of an organism (Thomas, 1993). Antibiotic development and use have shown that even on initial exposure, some bacteria will demonstrate resistance to a given drug or class of drugs. For example, anaerobic bacteria have always shown resistance to aminoglycoside antibiotics (Murray, 1991).

Acquired resistance: The resistance that occurs in an organism which is not innate (Thomas, 1993). The development of acquired resistance involves genetic changes in an organism which are passed on to subsequent generations or other individuals. The genetic changes may occur as a result of mutations or more commonly, the transfer of genetic material between organisms (Murray, 1991).

Selection: Selection is the Darwinian concept that certain individuals, groups, or populations of organisms have a survival and reproductive advantage over similar organisms. A different genetic makeup accounts for an alteration in an organism's behavior, structure, or physiological characteristics which enables it to survive and reproduce in greater numbers than those not possessing the alteration. The altered

organisms, in this case bacteria, pass the genetic advantage to their progeny or other bacteria (Stansfield, 1977).

An altered organism's survival and reproductive advantages can be significantly increased by environmental conditions (Stansfield, 1977). The presence of antibiotics are an extremely powerful force in selecting for the growth of resistant bacteria by eliminating competing, drug susceptible strains.

Background of the Problem

Recognition of the naturally occurring process of antibiosis led to the discovery and use of antibiotics. The phenomenon of antibiosis is routinely observed among microbes. They produce a variety of substances toxic to other organisms in their immediate environment. Bacteria have evolved mechanisms for protection from the effects of these toxins. Antibiotics, often the natural products of microbes, may be rendered ineffective by these same mechanisms.

Intense selective pressures have been applied to populations of bacteria through the use of antibiotics, resulting in the rapid appearance of strains resistant to previously effective drug regimens. Newly developed antibiotics frequently are more costly and have greater side-effects. The future holds the potential prospect of inadequate new drug development while pathogen strains become increasingly unaffected by available antimicrobial drugs (Cohen, 1992).

Early antibiotics, the sulfonamides, were discovered in the 1930's and used with some success, particularly against blood-borne *Streptococcus* infections. However,

they were ineffective against other organisms and often had significant adverse side effects. The existence of organisms which showed minimal or no response to the use of these agents demonstrated the concept of intrinsic resistance. These microbes already possessed the mechanisms necessary to render sulfonamides useless in the treatment of disease caused by their presence. Some of these organisms, particularly *Staphylococcus* species, were sensitive to the exciting new drug penicillin.

Paul Ehrlich, a 19th century chemist, is credited with coining the phrase "magic bullet" (Levy, 1992, p. 6) in searching for a drug which could kill microbial invaders without harming the body. While organisms with intrinsic resistance to penicillin existed, penicillin seemed to be the epitome of the concept of an effective anti-bacterial agent and was soon labeled a miracle drug for its abilities. It became available orally, and it was not until the mid-1950's that a prescription was required for its purchase in the United States. The new wonder drug was widely marketed and advertised to the general public. Alexander Fleming, a British bacteriologist, discovered penicillin in 1928 and had been concerned about the effects of such easy access to the drug from the beginning of its use (Levy, 1992).

During development of penicillin in the laboratory, Alexander Fleming observed altered bacterial strains. These appeared to be produced by growing normally drug-susceptible bacteria in varying amounts of penicillin. The altered strains were found to be resistant to levels of the drug normally circulating in the blood during treatment (Levy, 1992). Unlike organisms which demonstrated intrinsic resistance to sulfonamides, the bacteria observed by Fleming acquired resistance to penicillin

through its presence in their environment. Antibiotic use strongly selected for growth of the altered strains. He recognized the danger of producing penicillin-resistant strains, particularly through self-medication and inadequate doses, and warned the medical community.

Subsequently, evidence of acquired bacterial resistance to antibiotics was reported in 1940 in Nature magazine where Abraham and Chain reported the existence of a penicillin-destroying enzyme produced by strains of *Escherichia coli*, cited in Neu (1993). These rare, naturally occurring resistant bacterial strains were favored by selection when exposed to penicillin, allowing their populations to flourish.

In a 1944 Science article, *Staphylococcus aureus* was identified as producing an enzyme that destroyed penicillin, cited in Neu (1993). The subsequent increase in numbers of these penicillin resistant strains was encouraged by the extensive use of the antibiotic. Again, the presence of penicillin provided a tremendous survival advantage to the resistant bacteria.

Despite these early warnings, society and the scientific community have become complacent about the problem of bacterial resistance to antibiotics. The development of over 150 new antibiotics over the last three decades has contributed to belief in an endless supply of new drugs. The rate of new drug development however, has declined markedly (Neu, 1992). The public and health care providers have continued to view antibiotics as miracle drugs. The concept of an untreatable bacterial disease is difficult for many to comprehend. However, the incidence of disease caused by antibiotic resistant organisms has increased significantly in both the hospital and

community settings. Some organisms which had not been significant pathogens have become serious problems due to their acquired resistance (Neu, 1993).

Historically, new drugs or drug combinations have become available in time to combat organisms developing resistance to previously effective antibiotics. This trend has contributed to the increased development of multiple-drug-resistant organisms. In 1941 virtually all strains of *Staphylococcus aureus* were susceptible to penicillin G, but by 1944 they commonly produced the enzyme penicillinase which destroyed penicillin. By 1992, 95% of strains worldwide exhibited resistance to penicillin (Neu, 1992). Methicillin was synthesized in response and was effective until the 1980's, when methicillin-resistant *Staph. aureus* became a problem.

After developing resistance to penicillin and methicillin, *Staph. aureus* was treated successfully with fluoroquinolones. After less than a year of their use, the rates of resistance to the new agents were as high as 79% (McGowan, 1994). What was once an easily treated pathogen has become a disturbingly resistant organism with very limited choices for treatment. "The pattern of discovery, exuberant use, and predictable obsolescence has been repeated after the introduction of each new antimicrobial drug" (Kunin, 1993, p. 557).

Vancomycin has been an effective last-line-of-defense drug against multiple-drug-resistant organisms, particularly enterococci. However, evidence shows increasing numbers of vancomycin resistant organisms with the potential for causing bacterial disease unresponsive to current antibiotic therapy (Cohen, 1992).

Significance

Although all studies do not concur, the mortality rates of patients with drug-resistant infections have been estimated to be more than twice those of patients infected with susceptible strains (Murray, 1991; Pallares, R. et al., 1995). Resistant bacteria increase the incidence of disease when failed treatment allows their spread to uninfected hosts (Cohen, 1992). Data on the economic burden of antibiotic resistant bacteria, while limited, has indicated up to $30 billion per year is spent in the United States alone in treatment of resistant pathogens (Phelps, 1989).

Medical care has increased the longevity of chronically ill patients and the numbers of immunocompromised patients. Increased antibiotic use in these patients and in the growing elderly population has contributed to the development of resistant bacterial strains. The problem is not limited to hospital based infections. Nursing homes and long-term care facilities are experiencing an increase in the incidence of resistant bacterial infections. Communities have seen "...increased colonization of children and their families, including those never treated for infections, with multiple-drug-resistant organisms. When a patient is infected by a resistant organism, treatment is likely to be prolonged, more expensive and associated with a greater risk of failure" (McGowan, 1994, p. 3). Additionally, multiple drug therapies and newer agents, if effective, carry a greater likelihood of adverse side effects (McGowan, 1994).

The inappropriate use of antibiotics is frequently linked with the increasing incidence of resistant strains of bacteria. The factors influencing inappropriate

antibiotic use are widespread and common. The expectations and behaviors of both patients and health care professionals appear to be significant factors in the growth of this problem. Many health care clients want antibiotics as treatment for illnesses which do not warrant antibiotic use. It is difficult for practitioners to resist prescribing what many consider to be a wonder drug. Clients' propensity to not finish prescribed courses of antibiotics is notorious, and the prescribed duration and dosage of treatment varies. Further, practitioners may unknowingly prescribe antibiotics which enhance the development of resistant strains among pathogens once easily treated.

The education of both primary care practitioners and the public concerning appropriate antibiotic use in the treatment of common infections is now more important than ever. Nurses have traditionally served as public educators and, with increasing numbers of advanced level nurse practitioners providing primary care, nurses are in a unique position to assist in fighting this growing problem. Essential steps include (a) comprehension of the mechanisms of resistance development, (b) recognition of the influence of health care practice and public policy on the problem, and (c) acknowledgement of guidelines to effective care. By instituting practices consistent with these steps, health care can provide more effective treatment of bacterial illness without inadvertently contributing to a serious problem.

Project Goal

The goal of this project is to provide a synopsis of current information and to identify and explain factors which affect the development of bacterial resistance. The

emphasis is on health care's contribution to the problem, primarily through the use or misuse of antibiotics. Guidelines to effective antibiotic use in primary care are presented, with recommendations on avoiding poor practice choices. Resources for current antibiotic information and resistance data, practices for accurate diagnoses and drug sensitivity, and suggestions for patient education are reflected in the guidelines.

Numerous factors contribute to the ongoing development of bacterial resistance to antibiotics. The primary care provider has the opportunity to directly influence many of these factors in practice, and to encourage change elsewhere to combat continued development of bacterial resistance to antibiotics. The frequency of antibiotic use in the routine practice of primary care carries a significant responsibility. Patients now expect antibiotics in the treatment of a wide range of common ailments due to their well publicized effectiveness. Often this antibiotic use is not warranted in the treatment of self-limiting illnesses. The lack of routine culturing to determine pathogen existence, type, and sensitivity to antimicrobial agents contributes to inappropriate antibiotic use.

Primary care practitioners must assume responsibility for educating themselves and their patients, so that antibiotics are prescribed on the basis of sound diagnostic and therapeutic criteria. An understanding of the basics of antimicrobial action and the development of resistance mechanisms among bacteria is essential to carrying out this responsibility. The necessity of practices which minimize the inadvertent selection of resistant strains is clear. These practices need to be implemented and a plan developed for public education. Finally, health care professionals must be active in establishing

public policy which maximizes the fight against infectious disease while minimizing the effects of resistant bacteria.

REVIEW OF THE LITERATURE

History of Modern Antibiotic Use

A brief history of the development of penicillin use serves to illustrate how antimicrobials came into prominence in the treatment of bacteria caused disease. Penicillin's first and most significant clinical trial in the U.S. was its use following a catastrophic fire at the Cocoanut Grove nightclub in Boston on November 28,1942. More than 400 were killed and 200 were severely injured. At the time of the fire penicillin remained a guarded secret, reserved for military use (Levy, 1992).

Penicillin had been discovered in England and proven in treatment of casualties of war. The new drug was introduced to the U.S. in 1941 when its large scale development was precluded by Britian's war economy. However, before the Cocoanut Grove fire, fewer than 100 people had been treated with the new drug. In addition to being reserved for military use, it continued to be difficult to purify and questions regarding its toxicity remained. Treatment of the Boston fire victims showed it to be effective in combatting infections caused by *Staphylococcus aureus*, a bacterium responsible for frequently fatal blood infections and skin graft failures common to burn injuries. Sulfonamides were ineffective in treating these infections. Penicillin's success in the treatment of Cocoanut Grove fire victims was crucial in the U.S. government's decision to back large scale production of the new drug by pharmaceutical companies (Levy, 1992). Penicillin was heralded as an unmatched

resource in the treatment of bacterial illness. Its initial, dramatic success ushered in the modern era of commercial pharmaceuticals. The public's perception of penicillin as a wonder drug, and its ready availability, led to widespread use. It represents the first episode in a pattern of drug discovery, overuse, and subsequent development of acquired resistance in previously susceptible organisms.

Mechanisms of Antibiotic Action

Antibiotics act to inhibit bacterial growth and/or kill bacteria by a variety of mechanisms. Their effects may damage, or alter the synthesis of bacterial cell walls or cytoplasmic membranes. They may inhibit the synthesis or metabolism of nucleic acids, the building blocks of DNA. Some interfere with protein biosynthesis by bacteria, or act to modify energy metabolism in bacteria (Neu, 1992).

Each of these mechanisms of action requires the antimicrobial drug to bind to specific bacterial cell wall structures, or to enter the cell intact in order to interfere with usual metabolic processes. The precision with which these substances must act allow bacteria a number of means to thwart the effects of antimicrobials.

Mechanisms of Bacterial Resistance

Intrinsic resistance exists if a microbe is routinely unaffected by a drug on initial exposure. Acquired resistance is demonstrated when organisms previously susceptible to an antibiotic become resistant to its effects following exposure. This resistance conveys a powerful survival advantage to these organisms in the presence of

the antibiotic, resulting in significant increases in their numbers.

A number of basic mechanisms have been recognized by which bacteria are resistant to the effects of antibiotics. The most common and well recognized is the enzymatic inactivation or modification of the antibiotic. The classic example of this is the bacterial production of beta-lactamase which renders penicillin and the other beta-lactam agents inactive. Organisms have also shown resistance to erythromycin, tetracycline, and the aminoglycosides via enzymatic modification or inactivation (Murray, 1991; Neu, 1992).

The production of these enzymes by bacteria is of two main types. Constitutive enzyme production occurs at a constant rate. Inducible enzyme production is initiated and increased by the presence of the enzyme's target (Stent, 1971). The target in this instance is the antibiotic.

Bacteria may resist the activity of antibiotics by limiting or preventing a drug's access to the target site at which its effects are produced. Several mechanisms are important. The production of substances by the bacteria may inhibit the approach of antibiotics to the bacterial cell. Outer membrane porins, electro-chemical channels, allow penetration of antibiotics into the cell. They may be altered to prevent entry of enough drug to affect the cell. An active transport mechanism may develop which causes efflux of the antibiotic out of the bacterial cell. These mechanisms are important in the intrinsic resistance of gram-negative bacteria to vancomycin, and in the acquired resistance of some organisms to tetracycline and beta-lactams (Murray, 1991; Neu, 1992).

The target site of an antibiotic's action may be altered in such a way that the drug has limited or no effect on the bacteria. A new, unreactive target site with enhanced affinity for an antibiotic may develop within the bacterial cell. The lack of drug binding to the usual target site results in correspondingly decreased effectiveness. These mechanisms have been shown to be active in the resistance to sulfonamides and trimethoprim found in multiple-drug-resistant staphylococci (Murray, 1991).

Bacteria may employ one or more of these mechanisms of resistance, and the strategies may augment one another synergistically (Jacoby and Archer, 1991). The routes by which bacteria acquire the genetic coding for these mechanisms vary.

Routes of Acquired Resistance

"Most drug-resistant microbes emerge as a result of genetic change and subsequent selection by antimicrobial drugs" (Jawetz et al., 1989, p. 147). A number of genetic mechanisms accomplish the change necessary for resistance to develop, and population selection to occur. Spontaneous mutations in the chromosomes of bacteria can occur in the genes coding for the structural receptors of antibiotics, altering the target site. Although rare, these changes provide the organisms a tremendous survival advantage for population growth in the presence of antibiotics (Jawetz, et al.).

Resistance information coded in genetic material can be passed among bacteria. Several mechanisms exist for this transfer. Plasmids are extrachromosomal genetic elements which often carry genes for resistance. They can be passed between bacteria of the same or different genera through the process of conjugation, which is an

exchange of genetic material between bacteria. Often a series of closely linked genes which code for resistance to more than one drug are passed on simultaneously during the process of conjugation. Multi-drug resistance is believed to pass among different genera of gram-negative bacteria as well as gram-positive cocci via this process (Jawetz, et al., 1989).

Plasmid DNA is sometimes transferred from one bacterium to another by its inclusion in bacterial viruses, known as transduction. This process has been recognized in the transfer of resistance among *Staphylococcus* and the salmonellae (Jawetz, et al., 1989).

Transformation is the term used to describe the direct transfer of genetic material between lysed bacteria and other intact organisms. Once believed to occur only during laboratory manipulation, it now appears to occur spontaneously within bacterial populations as well (Jawetz, et al., 1989). Additionally, at least one investigator believes that preparations of antibiotics may unintentionally contain free bacterial genetic material that passes on resistance to organisms during antibiotic treatment (Robinson, 1994).

Transfer of short DNA sequences called transposons between plasmids or between plasmids and bacterial chromosomes is known as transposition. It also is a recognized means by which bacteria acquire resistance from one another. This form of genetic recombination is believed to be a significant mechanism for the evolution of plasmids conferring antibiotic resistance (Joklik, Willett, Amos, and Wilfert, 1992).

All of these mechanisms are active in the development of antibiotic resistance

in previously susceptible strains. The genetic material coding for resistance can be passed between different bacterial species and genera. Once resistance is established, the use of antibiotics applies tremendous selective pressures encouraging the growth of the resistant strains. What were once odd anomalies among bacterial populations can become the prevalent strain.

Evidence of Increased Resistance

Reports of increasing incidence and prevalence of resistant strains of relatively common pathogens are widespread. *Neisseria gonorrhoeae* was once effectively treated with low doses of penicillin. Doses were increased to reflect rising minimum inhibitory concentrations, [MICs], but since the 1970's the prevalence of strains resistant first to penicillin, and then to tetracycline, has increased. Center for Disease Control surveillance showed significant increases in resistant *N. gonorrhoeae* prevalence between 1988 through 1991. Data showed over 32% of strains resistant to either penicillin or tetracycline (Centers for Disease Control and Prevention, [CDC], 1993). Today, because of the frequency of strains resistant to these drugs, the treatment of choice is a third generation cephalosporin (Cohen, DiNubile, Dudley, and Shlaes, 1994).

Haemophilus influenzae causing otitis media have demonstrated a similar increase in resistance to ampicillin. One study showed an increase of nearly 35% in resistant strains over a two year period ending in 1977 (Schwartz, Rodriquez, Khan, and Ross, 1978).

Haemophilus influenzae strains responsible for meningitis, once susceptible to ampicillin, had levels of resistant organisms as high as 32% by 1986 (Wenger, Hightower, Facklam, Gaventa, and Broome, 1990). Subsequent resistance to oral and intravenous chloramphenicol has developed. Today the primary treatment is again a third-generation cephalosporin (Cohen, et al., 1994).

A 1994 study of children in the Memphis area identified *Streptococcus pneumoniae* in cultures of 31% of otitis media cases in those under age six. Twenty-nine percent of bacterial isolates in those cases were penicillin resistant (CDC, 1994).

Hospitals participating in surveillance studies have reported resistant streptococcal strains increasing from less than 0.02% in 1979 to over 16% in 1992, particularly among children (Breiman, Butler, Tenover, Elliot, and Facklam, 1994).

Other community acquired bacterial pathogens showing signs of increasing resistance include various *Salmonella* and *Shigella* strains as well as Group A *Streptococci* (Cohen, et al, 1994). One study in 1986 found 32% of *Shigella* isolates had developed resistance to ampicillin, then a common treatment choice for shigellosis (Tauxe, Puhr, Wells, Hargrett-Bean, and Blake, 1990).

Center for Disease Control studies found the prevalence of *Salmonella* isolates resistant to one or more of a group of antibiotics increased from 16% to 32% over a ten year period. One epidemiological study linked the resistance found in human *Salmonella* strains to antibiotic use in food animals (Cohen and Tauxe, 1986).

Strains of *Enterococci* have recently been found to be resistant to vancomycin. Multiple-drug-resistant strains of gram negative rods have also been identified (Cohen,

1992).

The appearance of multiple-drug-resistant *Mycobacterium tuberculosis* is increasing. Isolates collected in 1991 showed 3.1% of strains were resistant to both isoniazid and rifampin. This represents an increase from 0.5% in 1986. Specific geographical areas may show much higher resistance figures (Cohen, 1992).

In summary, many common pathogens have demonstrated increased resistance to antibiotics over time associated with antibiotic use. They have developed resistance to many previously effective antibiotics. No reliably effective antimicrobial treatment exists for some of these organisms, including use of drugs like vancomycin (McGowan, 1994). The existence of these rare but increasingly encountered microbes has led some investigators to believe we have already entered a "post-antimicrobial era" (Cohen, 1992, p. 1050). This concept implies that antibiotics will cease being effective as treatment for bacterial disease.

Contributing Factors

Various aspects of antibiotic use are related to the increase of resistant strains of bacteria. The use of broad spectrum antibiotics, when agents with a narrower range of activity could be effective, increases the selective pressure on resistant organisms (Cohen, DiNubile, Dudley, and Shlaes, 1994). This points out the importance of identifying the responsible pathogen through culturing, and the need for sensitivity studies in choosing the most appropriate antibiotic. Antibiotic samples provided by pharmaceutical companies are commonly dispensed without regard for their spectrum

of activity due to their convenience to providers and patients.

The effects of duration of antibiotic therapy on the emergence of resistance can vary greatly. If treatment is too short, only the most susceptible members of the bacterial population are affected, leaving behind a higher prevalence of resistant organisms. However, the extended antibiotic treatment of some diseases, including acne and urinary tract infections, is linked with the development of multiple-drug resistant bacteria (Levy, 1993). Research comparing the efficacy of different common treatment regimens of even susceptible organisms is sorely lacking (Schmidt, 1990). This makes choice of treatment agent and duration even more difficult.

The common practice of patients discontinuing their antibiotic therapy before finishing the prescribed length of treatment mimics the potential effects of improper treatment duration. Similarly, individuals self-medicating with antibiotics left over from old prescriptions or sharing antibiotics with others promotes opportunities for the development of resistant strains as the treatment is likely to be inappropriate.

The use of antibiotics in the treatment of viral illness is a frequent contributor to the development of resistant bacterial strains. In the absence of large populations of target pathogenic bacteria, antibiotic use heavily selects for the growth of rare, resistant bacteria by eliminating normal, benign flora. The increased prevalence of resistant organisms results in disease difficult to treat, leading to more antibiotic use, common particularly during childhood. This scenario may account for the increased proportion of children to adults seen with illness related to resistant organisms (Breiman, et al., 1994).

Tremendous amounts of antibiotics are used in the animal husbandry industry and more recently in the growing fish-farming industry. They are used in a continuum of concentrations from sub-therapeutic to enhance growth, to full therapeutic levels for treatment of infectious disease among animals. Evidence is emerging that not only are antibiotics contributing to the development of populations of resistant organisms within animals, but that the genetic basis for the resistance is being transferred to human bacterial populations (Cohen and Tauxe, 1986; Schmidt, 1990). Additionally, evidence is accumulating that multiple-drug-resistant food-borne pathogen incidences are increasing as a direct result of the extensive use of antibiotics in animals (Young, 1994). Food contaminated with resistant organisms is readily shipped from one part of the globe to another, compounding the problem.

Inappropriate use of perioperative, prophylactic antibiotics is considered to increase the development of resistant strains (Cohen, et al., 1994). Both the extended use of agents in the absence of signs of infection and the use of last line-of-defense agents like vancomycin for prophylaxis set the stage for the selection of resistant populations.

Sexually transmitted disease is increasing in incidence, often among segments of the population who are less likely to practice disease control behaviors. With the increased use of antibiotics to treat these diseases, susceptible populations of organisms are being eliminated while resistant strains are increasing (Cohen, et al., 1994).

The extensive use of day care for pre-school children is a relatively recent

trend in the U.S. and has produced an ideal breeding ground for resistant organisms. The close proximity of children in these settings and the difficulties in maintaining adequate hygiene practices encourages the routine spread of pathogens. The numerous courses of antibiotics children often undergo are during the day care years and the resistant organisms developed are easily transferred among individuals (Schmidt, 1990).

The spread of resistant bacteria is occurring around the world. Antibiotic use in developing and some industrialized nations often does not require a prescription, yet supplies are frequently inadequate to provide full recovery from bacterial illness. The lack of public education in antibiotic use encourages behaviors which contribute to the development of resistant strains. The increasing mobility of the world's population facilitates the spread of these strains (Cohen and Tauxe, 1986).

Potential for increased development of resistant bacteria exists through many common circumstances. Health care providers have a responsibility to recognize their contribution to the problem, and to practice accordingly. Providers must educate themselves and the public concerning antibiotic use and its effects on bacterial resistance. Efforts to control infectious disease must continue. Guidelines for proper antibiotic use and suggestions for community action are essential.

GUIDELINE RECOMMENDATIONS

Introduction to Recommendations

The development of antibiotic resistant bacteria is a growing problem in the treatment of infectious diseases. Organisms which were once benign or easily treated are becoming troublesome pathogens. The incidence of previously rare, resistant strains is growing. Bacteria possess numerous mechanisms for the transfer of resistance between individuals, species, and genera. Resistant organisms are spreading around the globe from their sites of origin. Strains of bacteria are increasingly resistant to multiple drugs, with the potential for becoming unresponsive to any available treatment. The link between antibiotic use and misuse, and the development of resistance is clear.

The safe and effective use of antibiotics starts with wise practice choices by primary care practitioners. The public relies on health care professionals to develop plans for public education and community action concerning health issues. Practitioners' influence on public and industrial policy can be significant. The responsibility to address and control the development of bacterial resistance to antibiotics must be accepted by the health care and scientific communities.

There are many ways advanced level nurse practitioners can provide leadership and collaboration in these efforts. Presented here are recommendations for treatment and surveillance of bacterial disease. The importance of education and community

action are stressed.

Treatment Guidelines

Treatment of Viral and Self-limiting Illness

The practice of prescribing antibiotics in the absence of clear signs or symptoms of bacterial illness is well known (Schmidt, 1990). Many times practitioners are satisfying their patients' demands for these drugs in fear of losing them to more obliging providers. Antibiotics may be prescribed in the belief that little harm can come from their use. Practitioners may feel the need for covering all possibilities and prescribe antibiotics despite lack of clear indications for their use.

The dangers of these practices are now apparent. The differential signs of viral and bacterial illness must be recognized through the patient's history and examination. Continued research efforts into objective measures designed to differentiate viral and bacterial illness should be encouraged. Practitioners must resist the temptation to prescribe antibiotics when not indicated, despite pressure from patients.

Patients should be educated concerning common disease etiology. They should understand that the use of antibiotics for viral illness is not only ineffective but possibly hazardous in its contribution to the development of resistant bacteria. Both individual patients and the public at large need education in this matter. Education should include information on recognition of the signs and symptoms differentiating bacterial from viral illness and the treatment likely to be effective. Patients should be taught general, red-flag symptoms which necessitate medical attention regardless of etiology.

The formation of collaborative, trusting relationships with patients will limit shopping for doctors, while patient education and reliable follow-up care will relieve anxiety and promote safety. Development of collaborative information networks with other community providers can encourage standard prescribing practices and ensure consistent application. One futuristic model which could promote the sharing of information necessary for prudent antibiotic use involves personal integrated circuit cards. In use in a number of locations in Japan, these cards have been tested as portable medical records, providing instant medical history access to providers (Akaho, Armstrong, and Fujii, 1996).

Patients should be encouraged to use alternative treatments to antibiotics when appropriate. The importance of adequate hydration, and treatment of mild symptoms with antipyretics, and common analgesics should be stressed. Patient education in the possible complications, for example Reye's syndrome, in the treatment of viral illness must be addressed.

Use of herbal or other alternative treatments may be encouraged based on the practitioner's expertise in their use and the patient's expectations. Continued research into the efficacy of these treatments should be encouraged and their use advocated when appropriate.

Controversy surrounds the use of antibiotics in the treatment of common, often self-limiting childhood illness acknowledged to be caused by bacteria. Otitis media is routinely treated with antibiotics despite equivocal findings about the treatment's ability to limit the course of the illness or even the occurrence of complications

(Schmidt, 1992; Goldfarb, 1995). With the emergence of resistant organisms linked to antibiotic use, the provider must weigh the benefit to the individual against the possible risk to the public (Kunin, 1985). Treatment decisions need to reflect the severity of the infection and the practitioner's judgement. Knowledge of current American Academy of Pediatricians guidelines for treatment of childhood illness is essential.

The ability of a parent to adopt a wait-and-see approach to the treatment of a child with an earache depends on their trust in the provider. Providing education, recommending effective pain control measures, and ensuring followup availability enhances that trust.

Diagnosis and Treatment of Serious Bacterial Illness

When initial diagnosis is unclear but bacterial illness is suspected, steps should be taken to positively identify the pathogen responsible. Practitioners should not rely on empiric therapy if pathogen identification is possible. Efforts should be made to obtain an adequate specimen for gram stain, culture, and sensitivity tests. Patients concerned about the accompanying inconvenience, expense, and/or discomfort can be reassured through an explanation of the importance of a definitive diagnosis for effective treatment.

The provider should be aware of local laboratory procedures. Standardized procedures in accordance with guidelines of the National Committee for Clinical Laboratory Standards enhance result reliability (McGowan, 1994). Labs should be encouraged to run a full range of susceptibility tests, not relying on the drug

susceptibility patterns found on organisms in the past. The emergence of resistant organisms has limited the value of previously predictable susceptibility patterns. Local sensitivity patterns can be ascertained and help guide drug selection. Additionally, information on individual antibiotics should be provided. One drug's effectiveness is an unreliable indicator of the effectiveness of its antibiotic class, as organisms adopt very specific resistance mechanisms (Cohen, et al., 1994). Continued research is necessary to identify and track resistance mechanisms to increase the cost-effectiveness of sensitivity testing. When resistance is known to exist in a geographic area, sensitivity assessment of organisms not routinely tested may be required as well as procedures to test for specific resistance mechanisms (McGowan, 1994).

Once a positive or likely bacterial diagnosis is obtained and the need for treatment recognized, the choice of antibiotic and regimen is made. The use of broad spectrum agents should be avoided due to the increased likelihood of the selection of resistant organisms. If a broad spectrum agent was prescribed empirically while awaiting culture and sensitivity results, the patient should be switched to a narrower spectrum antibiotic, even if the original appears to be working well (Cohen, et al., 1994). Conversely, providers should remain flexible and ready to prescribe a different antibiotic if signs and symptoms indicate poor response to treatment.

Use of combination agents designed to avoid common resistance mechanisms is encouraged, particularly in patients with recurrent illness or in local areas known to harbor resistant organisms. Multiple agent treatment of some infections, for example *H. pylori*, has shown significant reductions in the incidence of recurrence attributed to

acquired resistance (Fennerty and Melnyk, 1995).

When appropriate, the use of topical antibiotic preparations to treat skin infections should be encouraged. Topical application limits a drug's systemic effects and reduces the chance of contributing to resistance.

The practitioner is encouraged to consult authoritative sources of antibiotic treatment recommendations, including doses and duration of treatment, often compiled in professional journals. The choices are not always clear. Particularly culture and sensitivity information should be utilized in the decision, as well as consideration of the location of infection. When a significant incidence of resistant organisms is recognized locally, or in other difficult treatment situations, the practitioner is encouraged to consult with infectious disease specialists and clinical pharmacists. As new agents are developed specifically for treatment of resistant organisms, it is very difficult for the provider in general practice to be fully informed regarding their use.

Practitioners must be cautious in the use of antibiotic samples provided by pharmaceutical companies. They may be inappropriately utilized due to their convenience and cost savings to providers and patients. The same scrutiny should be applied to their spectrum of activity and culture/sensitivity match as is applied to any other antibiotic.

Although the value of post treatment cultures for proof-of-cure following antibiotic treatment is not universally accepted, providers are encouraged to schedule follow-up visits and repeat cultures if indicated. The patient's reports of symptom changes and/or the physical examination may give clues to the effectiveness of

treatment and the possibility of the presence of resistant organisms. The failure of treatment or the recurrence of illness may indicate a resistant organism etiology. Adequate culture and sensitivity studies then become even more essential for making effective treatment choices.

Finally, patients must be educated about the treatment they have been prescribed. Information on side-effects, a frequent cause of patients discontinuing therapy, should be provided. Patients should be instructed in ways of limiting adverse reactions, commonly nausea, to encourage full treatment duration. They should be encouraged to contact the provider if troublesome reactions occur so that an alternative regimen can be prescribed if necessary. Symptoms of allergic reactions should be described and instructions given for actions to be taken if they occur. The provider or some other information resource should be available to the patient should questions arise.

The importance of finishing the duration of treatment even after cessation of symptoms should be emphasized. Patients should be cautioned about sharing antibiotics or using drugs left over from previous treatments. The contribution of these behaviors to the development of resistant organisms should be explained to patients. Patients should be encouraged to question why an antibiotic is being prescribed instead of demanding their use (Levy, 1993).

Surveillance Recommendations

Global surveillance systems of infectious disease continue to expand and coordinate their efforts. The World Health Organization, the International Network for Rational Use of Drugs, the Department of International Health Care Research, and the International Clinical Epidemiology Network are a few of the agencies tracking the global development of infectious disease. Specific concern over antibiotic resistance was behind the formation of the Alliance for Prudent Use of Antibiotics (Kunin, 1993).

These organizations track infectious disease on a global level, and the Center for Disease Control monitors activity in the U.S.. However, the need exists for tracking resistance patterns on a local level, particularly in rural areas where available data are scant. The importance of recognizing local trends in the choice of antibiotic therapy has been discussed. Practitioners are encouraged to form collaborative relationships with other area providers as well as public health departments to provide sources of data on local disease characteristics. The surveillance of reportable diseases should be strengthened, with additional focus on diseases due to resistant organisms (CDC, 1994).

Local laboratories should be encouraged to track the incidence of resistant organisms, and this information should be made available to providers. A community system for reporting illness outbreaks should be encouraged. Emphasis should be placed on sites where conditions encourage the development of resistant organisms.

These sites include nursing homes, day care centers, and community hospitals (McGowan, 1994). Providers must have ready access to this information and utilize it in decisions regarding antibiotic treatment. Cooperation between providers, laboratories, and community health departments can assist the local surveillance of infectious disease and assist providers in making informed treatment choices.

Education Recommendations.

The appropriate and continued education of health care providers about bacterial resistance is essential. Providers' knowledge of infectious disease, antibiotics, and resistance must be improved. Educational content for primary care practitioners should include training in microbiology, infectious disease, epidemiology, and antimicrobial therapy with emphasis on diagnosis and management (Kunin, 1985).

Providers need to continue their education on resistance through postgraduate programs, journal articles, and consultation with infectious disease experts. Postgraduate education programs should be independent of pharmaceutical industry influence. It is not unusual for programs to involve new drug clinical research, with procedures slanted towards use of a new agent. The use may be unwarranted and may encourage providers to use the drug in questionable circumstances (Kunin, 1985).

Education of medical laboratory personnel should provide state-of-the-art training in diagnostic evaluation to ensure surveillance of emerging resistant organisms (CDC, 1994). Collaboration between labs, microbiologists, pharmacists, and epidemiologists can assist comparative research into the importance of different

resistance mechanisms. This information will make measures to control the spread of resistance more efficient (McGowan, 1994).

The increase in managed care settings places administrators in the position of making practice decisions (Goldfarb, 1995). They must be educated in the appropriate use and choice of antibiotics. The continuing education of all health care workers involved in the treatment of infectious disease is essential in addressing the problem of resistant organisms.

Community Action Recommendations

Health care providers are in a position to encourage action on many fronts in the battle against infectious disease and the development of resistant bacteria. The influence on public, industrial, and foreign policy has tremendous potential for affecting the problem.

Prevention of disease should receive top priority. Providers have a responsibility to continue efforts aimed at reducing the incidence of all infectious disease. Encouraging domestic and foreign policy which improves living conditions around the world remains paramount. Safe water and food supplies are frequently inadequate. Poor sewage disposal causes contamination and the spread of disease. Malnutrition, particularly among children, makes them susceptible to disease. Supplies of antibiotics in developing nations are often insufficient to adequately treat many diseases, despite the vast array of drugs frequently available over the counter in these nations (Kunin, 1985). The paucity of health care workers in rural U.S. areas and undeveloped nations is well known. Health care professionals must continue efforts to

address these issues.

Providers must encourage policies that ensure adequate staffing and hygiene in nursing homes and child care facilities. The importance of proper hand-washing techniques in these and other sites, including clinics and providers offices, cannot be overstated (Neu, 1993). Collaboration between providers and public health departments can assist in promoting communicable disease prevention strategies.

Education of the public concerning the occurrence and spread of sexually transmitted diseases [STDs] must be advocated. The increased incidence of resistant STDs, particularly in the vulnerable adolescent population, precludes the moral arguments against sex education in public schools and elsewhere.

Policies for the prudent use of antibiotics in food animal industries must be encouraged by providers. Tremendous amounts of antibiotics are used to enhance growth and fight infection in beef, pork, and poultry (Schmidt, 1990). Continued research is needed into the usefulness of antibiotics in the food industry, and the adverse effects of their use. A collaborative effort needs to promote the use of those agents least likely to contribute to the development of resistant organisms in animals (Cohen, 1992). The public needs to be educated about the consumer trade-off between limiting antibiotic use in food production versus resultant higher prices.

Providers must encourage the continued development of new antimicrobial agents by pharmaceutical companies. While not a panacea, new agents have a place in the treatment of infectious disease. In collaboration with health care workers, pharmaceutical efforts can be aimed at developing antibiotics specifically designed to

treat resistant organisms. Government policy should consider accelerated antibiotic programs to diminish the long and expensive process of new drug development (Murray, 1994). Marketing efforts should be aimed at infectious disease specialists most likely to promote wise use, instead of generalists or surgeons who may find the promise of a new agent irresistible and use it poorly (Kunin, 1985). Advocates should urge development of programs designed to eliminate the great disparity in drug prices which sometimes leads to inappropriate antibiotic choice.

Providers need to encourage the continued development of bacterial vaccines. The threat of the development of resistant strains through antibiotic use is reduced in proportion to bacterial vaccine use and effectiveness. Significant reductions in disease caused by *H. inlfuenzae* have been reported with the use of conjugated vaccine (CDC, 1994). As disease is brought under control, increasing frequencies of resistant organisms become less important (Cohen, 1994).

If these measures prove inadequate to stop excessive and inappropriate antibiotic use, providers may need to advocate for greater governmental control of antibiotic use. Limits on antibiotic use may be achieved in various ways. Formularies might be limited to the most efficacious drugs with the least side effects and lowest cost within an antibiotic class. Obsolete or duplicative drugs could be eliminated from formularies. The use of specialized antimicrobials could be limited to infectious disease consultants (Kunin, 1985).

Further control of antibiotic use could be achieved through protocols requiring specific conditions. Consultation with an infectious disease specialist could be required

prior to initiation of therapy. Additional consultation could be required for continued use (Kunin, 1985). While the prospect of restriction on antibiotics is alarming, it may be the only way to control their use. This is especially true of those antibiotics with limited indications that are likely to be prescribed inappropriately.

These guidelines represent a step toward maximizing the usefulness of antibiotics. Their implementation seeks continued effectiveness of antibiotic therapy in treating bacterial infection by helping limit the development of resistant organisms.

SUMMARY

The control of infectious diseases continues to challenge the world. History shows that an unintended result of extensive antibiotic use has been the increased prevalence of drug-resistant strains of bacteria. The continued development of new antibiotics has limited the impact of disease caused by these strains, but treatment is likely to be more difficult, expensive, and have a higher failure rate. Moreover, resistance patterns indicate that organisms can become resistant to any available antibiotic and are doing so in increasing numbers. The possibility of wide-spread disease caused by organisms with no known effective treatment is rising.

Bacteria exhibit many mechanisms which enhance the emergence of resistant strains. For example, a number of genetic alterations which convey drug resistance have been recognized in bacteria. Antibiotics place intense selective pressure on these organisms, enhancing their survival and growth. Additionally, the various genetic determinants of resistance are easily passed between bacteria, increasing the prevalence of resistant strains.

The careless use of antibiotics by health care providers, the public, and industry has contributed to the growth of resistance among bacteria. Patients expect a cure for illness, and antibiotics have been heralded as wonder drugs. The public is poorly educated about the etiology of common ailments and the inappropriateness of antibiotics in their treatment.

Practitioners may prescribe antibiotics for viral or mild self-limiting illness in the belief that their use poses little or no risk. Treatment varies greatly, reflecting lack of consensus on efficacious use. Insufficient or incorrect information leads to poor drug choices. Patients change the frequency and duration of treatment. While antibiotic use in health care continues to be invaluable, inappropriate practices promote the development of resistant organisms.

The extensive use of antibiotics in agriculture has led to the development of resistant bacterial strains in animals. These strains have been shown to spread beyond their animal hosts to humans.

Guidelines for the use of antibiotics seek to minimize the inadvertent development of resistant organisms, and reflect the conclusions of this report. Recommendations for health care provider actions are four-pronged and include (a) changing the routine use of antibiotics in practice, (b) increasing public awareness, (c) influencing public policy, and (d) research into antibiotic use, alternative treatments, and bacterial resistance development.

Providers must now consider the risk of contributing to the development of resistant bacteria when prescribing antibiotics. The risk-benefit equation that determines treatment choice must reflect this growing concern. It is essential that all available resources be utilized to reach appropriate treatment decisions.

The continuing education of health care professionals and the public is paramount in confronting this problem. The growth of the phenomenon demands attention. Providers have an obligation to be informed on this issue and are in a unique

position to educate others.

Public policies concerning antibiotic use must reflect awareness of the development of resistant bacteria. Health care professionals must take the responsibility to encourage public policies aimed at controlling infectious diseases and supporting prudent antibiotic use. Restrictive policies governing the use of antibiotics might become necessary.

Current research clearly defining signs and symptoms which differentiate bacterial from viral illness is needed. Recommendations concerning the efficacy of antibiotics in the treatment of common illnesses, especially among children, must be based on continuing research.

The effectiveness of alternative treatment modalities must be demonstrated to encourage acceptance of their use. Practitioners are justifiably reluctant to endorse treatments which lack supporting data.

Research into resistance mechanisms among bacteria must continue. The development of future antibiotics must be directed to overcome specific resistance expressions.

Research into antibiotic use and resistant bacteria must be continued and expanded. Increased surveillance of disease caused by resistant organisms, particularly in community and rural settings, is needed to provide accurate information useful to local providers.

Bacterial resistance to antibiotics threatens to limit effective treatment of infectious disease. A concerted effort by health care providers, the public, and

government is required to discourage antibiotic use which leads to development of resistant strains. The ability to understand and control the emergence and prevalence of these strains will determine future treatment of bacteria caused illness.

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