

Antibiotic Resistance: Epidemiology and Strategies for Prevention

Pages with reference to book, From 18 To 23

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Introduction

Bacterial resistance to antimicrobial agents is an important public health problem in both the developing and the developed countries and has plagued clinicians for years, The community and the hospital face this problem both for gram positive and gram negative bacteria. Many of these organisms are multiple drug resistant, i.e., resistant to two or more antibiotics to which the bacteria is usually susceptible¹, Though bacterial resistance creates many difficulties for physicians and patients, it has received less attention than a number of other infectious diseases. This paper clarifies the misconceptions pertaining to the topic of antimicrobial resistance and describe the settings most affected by it. The policy and infection control issues including approaches to the control of resistance, are discussed in detail.

Some Facts about Antimicrobial Resistance

Antimicrobial resistance is a biologic phenomenon occurring as a result of antimicrobial drug use. The belief, that resistant organisms exist but they do not cause infectious disease, is not true². These organisms can cause severe untreatable infections³. High incidence and mortality of enterococcal septicemia has been observed in some studies³. These resistant organisms can cause infections of the urinary tract, central nervous system and pelvic and abdominal regions². Consequently, antibiotic resistance should not simply be considered a laboratory phenomenon. The belief that synthetic antimicrobial agents will not select resistance because these compounds are not exposed to the microorganisms is also misleading. Resistance to quinolone, which is a synthetic antibiotic, has been reported⁴. It is believed that antibiotics that target specific metabolic components of bacteria will not develop resistance. However, the resistance of enterococcus to vancomycin (which targets a vital bacterial enzyme system), has been observed and is in contrast to the above belief⁵. Resistance of Staphylococcus to vancomycin is also emerging⁶.

Resistance can also develop if antibiotic is applied locally. An example of this is Gentamycin, which when applied topically over bum wounds, develops resistance quickly to the organisms that come in contact².

Settings Corn m only Affected by Antimicrobial Resistance

Resistance of common pathogens is an important nosocomial problem and is of significant importance in community acquired infections⁷. In tertiary care facilities, the incidence of drug resistant gram positive infection has increased, especially with Staphylococcus aureus, coagulase negative Staphylococci, Corynebacteria, and Enterococci⁸. Drug resistance in gram negative organisms such as Pseudomonas, Serratia and Acinetobacter species, still continues to be a problem in hospital settings⁹. Recently, Mycobacterium tuberculosis strains have been isolated that are resistant to antibiotics from AIDS patients, illegal drug addicts and prison populations⁷. In industrialised countries, the major impact of antimicrobial resistance is felt in the hospital setting. However, in less industrialised countries, the outpatient acquired infections due to multiresistant organisms create major therapeutic problems¹⁰. Examples are Streptococcus pneumoniae, H. influenzae, Shigella and certain species of Salmonella¹⁰. In the United States, several other settings such as nursing homes and extended-care

facilities have problems with antimicrobial resistance¹¹. Day Care Centres in the US have high rates of antimicrobial resistance particularly among children in diapers¹². Pencillin resistant pneumococci outbreaks have been reported¹³. Studies of trimethoprim resistant *Escherichia coli* have also shown extensive colonisation and transmission of these organisms from one child to another^{12,14}. Animal feedlot is another setting for antimicrobial resistance¹⁵. Resistant *Salmonella* from cattle herds have been shown to spread to people in distant communities¹⁶. Several studies have shown that antibiotic resistant organisms can also spread from one country to another¹⁷⁻²¹.

Use and Misuse of Antibiotics

By means of synthetic changes we have been able to improve antibiotics usefulness in many ways by reducing the toxicity and increasing effectiveness. Concomitant with antibiotic use has been the appearance of resistant bacteria which seem to emerge as rapidly as new antibiotics are introduced. Fortunately most infections are still responsive to treatment by present day antibiotics. However, there is a disturbing worldwide increase of resistance genes in reservoirs of non-pathogenic bacteria and an emergence of resistance pathogens which were previously susceptible. The result is treatment failure, high cost and deaths. The emergence of new drugs will remain useful only if they are reserved for the hard to treat infections. The only way to curtail resistance genes and resistance organisms is to decrease and control the indiscriminate use of antibiotics. In view of the widespread misuse and overuse of antibiotics in the world, such reduction need not compromise health. Hospital acquired infections are recognized as a factor in mortality and the escalating cost of health care. The gravity of the underlying disease processes found among hospitalized patients, as well as the invasiveness of modern interventions, are major factors in susceptibility to infection. At the same time, nosocomial infections have become increasingly associated with the changing patterns of opportunistic organisms found in the hospital environment. Thirty years ago, hospital-acquired infections were mainly caused by gram positive *Staphylococci*, but now, gram negative bacilli and *Enterococci* have emerged as the primary etiological agents of nosocomial morbidity and mortality²². Bacteremia due to gram negative organisms, for example, affects about 1% of hospitalized patients each year and is fatal in 30-50% of cases²³. Although it is not clear if these microorganisms are actually more virulent, it is certain that the disease processes associated with these agents are especially difficult to treat due to their ability to acquire resistance to antibiotics. The emergence of resistant strains and species of bacteria is a natural consequence of antimicrobial usage²⁴. When older chemotherapeutic agents are inadequate, new drugs are required which are often more costly and toxic than their predecessors. As resistant microbes continue to emerge from the use of these substances, the question of whether medication therapy will continue to be effective becomes paramount. It has been noted, however, that the process by which antibiotic resistance occurs can be slowed if the use of antimicrobial agents is limited²⁵. This has led to numerous investigations of antibiotic usage patterns to determine if the present extensive reliance on these drugs is always necessary. About 30% of hospitalized patients receive systemic antibiotics²⁶ and this accounts for 25-30% of the cost of all pharmacological agents administered in hospitals²⁷. Studies reviewing patterns of antibiotics treatment in this setting have shown that up to one-half of all therapy is inappropriate and revealed alarming tendencies of both excess and misuse²⁸. Antibiotics are often given for surgical prophylaxis in instances where they have not been shown to be needed to prevent infections and even when given under appropriate circumstances, treatment has continued for an extended period rather than only pre-operative period²⁹. Antibiotics are also administered to medical patients for prophylactic purpose even though their ability to prevent infections in immunosuppressed or anatomically compromised patients is limited²³. When ordered for an actual infection, antibiotics are sometimes prescribed that are not the most effective (or least expensive) agent for the identified pathogen. The use of a medication with a broader spectrum of activity than is necessary for treatment is

another example of antibiotic abuse. Furthermore, these drugs are occasionally administered by an improper route, at an incorrect dose or for resistant microorganisms. Antibiotics are also misused in the treatment of suspected infections when most efficacious agent is not prescribed with consideration of the site of infection and the pathogens most likely to be present.

Medications such as the aminoglycosides, the third generation cephalosporin, ticarcillin-carbenicillin and amikacin, need to be held in reserve for the systemic treatment of life threatening infections for which there are no alternative antimicrobial agents.

Unnecessary exposure to antibiotics is a direct consequence of their overuse and misuse. In addition to extra cost, overuse of antibiotics may cause adverse effects in about 10-20% of the hospitalized patients to whom they are administered³⁰. These untoward actions may include gastrointestinal disturbances, infusion phlebitis, organ damage (nephrotoxicity, ototoxicity etc.), bone marrow dysfunction and hypersensitive or even anaphylactic reactions. Moreover, superinfection can occur due to disturbances in the normal flora of the host. Together, these factors result in greater morbidity, mortality and expense of treatment

Strategies for Prevention

Education

Education will play a substantial role in promoting the appropriate use of antibiotic therapy. This will include more comprehensive instruction in both medical schools and postgraduate training programmes on the diagnosis of infections and antimicrobial treatment principles.

Interactions between Hospitals, Physicians and Pharmaceutical Companies

There is also a need to control interaction between physicians and pharmaceutical manufacturers who use aggressive advertising campaigns to sell their products. Medical personnel need to have access to unbiased information on medication benefits as well as limitations. While the industry has been chastised for being a part of the problem, it is also a part of the solution in that new and useful antimicrobial agents have been discovered under its direction²⁷.

Experts have recommended that hospitals adopt policies to control meetings between staff and pharmaceutical company representatives, including the requirement that manufacturers register with the pharmacy, not enter patient care areas, restrict the time and location of advertising displays and limit the dispensing of product samples²⁸.

The Development of a Formulary System

Hospitals should maintain a formulary system that restricts the number of antimicrobial drugs to essential items and provides for the addition or deletion of agents based on therapeutic clinical rationales. The formulary may also state protocols for choosing the most effective and least expensive drug of a particular class. Similarly, the microbiology laboratory, if staffed by qualified experts, can assist doctors in selecting appropriate pharmacologic agents based on sensitivity tests tailored to the specific pathogen identified by culture and by the site of infection. Restrictions may be placed on reporting of sensitivity test for high cost or toxic drug therapies unless special requests are made.

Furthermore, both the pharmacy and the laboratory should use generic terminology for all antibiotic ordering, labelling and reporting.

The importance of maintaining a strong hospital formulary system cannot be overstated because of the increasing numbers of new broad spectrum antibiotics available and the complexities of their use. The decision to add new antimicrobials onto formulary list is a task requiring thoughtful investigation. Effectiveness, toxicity and cost are primary considerations in determining whether or not an agent should be included in the formulary, but it is important to point out that new drugs are not granted approval for marketing based on criteria of greater efficacy, safety or cost effectiveness than already established medications. Therefore, an antibiotic is not necessarily better simply because 'it is new. Other factors to consider in making formulary decisions are the results of in vitro susceptibility testing and possibly unique pharmacokinetics actions. In this regard, however, it must be emphasized that in

in vitro activity does not always correlate with in vivo effectiveness and conclusion based on pharmaceutical manufacturer's studies may be biased in favour of a newly marketed agent. If questions remain or differences in efficacy are noted, a hospital might choose to perform its own laboratory or clinical studies³¹.

Automatic Stop Orders

Other practices that encourage only essential antibiotic use include the requirement of automatic stop orders for prophylactic therapy and the use of certain newly developed or toxic drugs that need to be held in reserve. It is imperative, however, that the patient receives an uninterrupted medication supply if continued treatment is necessary. Therefore, the physician must reassess pharmacologic therapy at regular intervals and reorder antibiotics as needed. Cooperation may be obtained from nursing and pharmacy staff in alerting doctors to the need for treatment review.

Antibiotic Ordering Forms

Special antibiotic ordering forms that specify the reason for treatment can also be helpful in monitoring the use of these drugs. Many researchers have recommended consultation with the infectious disease service before initiating therapy using certain chemotherapeutic agents that are toxic, expensive or promote the emergence of resistant organisms. This expert advice may continue throughout the course of therapy³².

Infection Control Programmes

Finally, the need for antibiotic usage may further decline in the presence of an active programme of infection control which emphasizes the prevention of nosocomial infections. Even if the issue of excess is effectively addressed, antibiotic therapy can be expected to be heavily employed and the emergence of resistant microbes will continue. Close epidemiological monitoring of the types and distribution of resistant organisms is essential and infection control practices that prevent, detect and eliminate nosocomial infections due to these agents are critical. Careful monitoring of the microbiology laboratory for the early detection of outbreaks involving antibiotic resistant organisms, will be required to control the spread of these microbes and eliminate their reservoirs¹. The hospital should have programmes which regularly review the antibiotic usage in order to monitor safety and effectiveness of therapy. Policies may restrict the use of newly marketed or toxic, broad spectrum antibiotics to only those situations where their use is deemed absolutely essential in order to limit the emergence of resistant microorganisms and to prolong their usefulness.

Review of Antibiotic Usage and Medical Audits

Studies have shown that restricting antibiotic usage is generally helpful in controlling nosocomial infection outbreaks due to multiple resistant organisms. In a few extreme instances, the total or near complete discontinuation of all antibiotics has led to the resolution of significant and persistent epidemics²². However, it is not practical to use this method. Instead, experts agree that policies promoting more rational use of antibiotics is essential. The implementation of such regulation requires flexibility in recognizing a doctor's responsibility in the treatment of patients. Rigid prescriptions that mandate specific therapeutic protocols are not appropriate solutions because they fail to take into account legitimate differences in view concerning optimal medical management or to address the constraints under which physicians perform their daily practice. Yet even though prescribing doctors will be ultimately responsible for controlling their use of antibiotic drugs, the increasing complexities of infectious disease treatment makes this a formidable task for physicians to accomplish individually and furthermore, many doctors have been slow to realize that the decision to order an antibiotic has potentially widespread ecological implications²². The ability to evaluate these guidelines and assess compliance with them, requires ongoing commitment³³. An organized antibiotic review committee may be established independently to facilitate this purpose. The committee should be staffed and chaired by doctors specializing in infectious disease medicine. Pharmacists, microbiologists and infection control personnel may provide additional support in issues involving antibiotic usage. The committee should

meet regularly to review and formulate policies and make recommendations to the medical staff for adoption into practice. Additionally, the committee may also examine matters related to the hospital formulary and standards or practices in the microbiology laboratory that concern antibiotic sensitivity testing.

Medical audits are quality assurance activities that compare practices to accepted standards of care. Similarly, antibiotics audits are used to evaluate the actual patterns of drug prescriptions against guidelines for their use. The antibiotic review committee may monitor medication usage by an auditing system to ensure that therapy is effective and consistent with medical standards. Audits may also be undertaken to assess the incidence of adverse reactions and the cost of drug treatment. Rather than attempting to monitor all antibiotic ordering, the committee may concentrate on specific concerns, such as the use of expensive, toxic agents or prophylactic treatment. In reviewing the therapeutic to empiric prescribing of antibiotics, attention should be focussed on circumstances for which general standards of care exist²². Other areas of concern which may be monitored, in conjunction with the infection control committee are antimicrobial resistance patterns and the distribution or types of organisms associated with nosocomial infections. Additionally, the antibiotic review committee can play a major role in disseminating information concerning development in the field of antimicrobial therapy and planning in service education.

Various procedures by which antibiotics usage can be monitored have been described in the literature and each method has advantages and drawbacks. Ideally, the audit process should be easily accomplished, relatively inexpensive and provide accurate information. The ability to standardize auditing procedures can also render data that may be compared with other institutions²⁸. Pharmacy records can give general information in the use and cost of specific pharmacologic agents and may identify broad trends. If patients can be identified by hospital service, patterns indicating potential problems in general areas may be seen. The use of pharmacy records is cost effective, but the data obtained is retrospective and cannot always highlight specific trouble spots. The use of special antibiotic ordering forms, that include the type of therapy prescribed and the reason for treatment, can be an invaluable source of specific data and encourages doctors to consider the appropriateness of their prescriptions³³. The use of a separate sheet in ordering antibiotics requires cooperation from the medical staff and consideration in making the form easy to complete is essential to its success. Yet the benefits of providing current information on actual prescribing practices related to therapy, empiric usage and prophylaxis, make this an especially helpful tool for auditing purpose. The results may even show the effects of differing antibiotic prescriptions on the emergence of bacterial resistance. Moreover, the data obtained can be used for confidential feedback to physicians on the appropriateness of their prescribing habits and allows comparison of their practice with those of their peer³⁰. An antibiotic review must be performed under the direction of doctors who have a special interest in the field. Medical control of the process can ensure that the evaluation of antibiotic usage is accomplished by experts and that feedback to prescribing physicians comes from an authoritative source. In this way, an antibiotic audit is a peer review process, rather than an administrative directive. In undertaking an auditing procedure, evaluations are performed to ensure that practices conform with accepted standards and to maintain high quality in care. Therefore, the ultimate goal of an antibiotic audit is to determine that the most effective and least toxic drug is given and to minimize the emergence of resistant microorganisms, while holding down the cost of therapy. When instances are discovered that do not conform with the standard policies, it must not be immediately concluded that the treatment given is incorrect.

Surveillance

Surveillance by international agencies, such as the World Health Organization is a necessary component of controlling global antibiotic abuse and the emergence of resistant microorganisms in developing countries and in hospitals around the world³⁴. W.H.O. has developed a list of essential

drugs and supplies for use in local dispensaries and provides educational materials for the development of national drug policies³⁵.

Other Measures

In addition to surveillance, other measures can be initiated to help limit the use of antibiotics, including the undertaking of sanitation projects which improve the quality of drinking water and immunization programmes to prevent diseases, such as meningococcal infection in areas where this is prevalent.

Antibiotic Resistance in Developing Countries

Twenty percent of the worldwide supply of antimicrobials goes to the developing countries³⁶. These countries still have the highest rates of resistance to antimicrobial drugs³⁷. Children are most commonly affected as they are frequent victims of respiratory and gastrointestinal infectious diseases^{36,38}. This indiscriminate use of antimicrobial therapy has been responsible for the emergence of antibiotic insensitive infections, including those caused by sulphonamide-resistant *Neisseria meningitidis*, ampicillin-resistant *Shigella dysenteriae* and multiple-resistant *Serratia marcescens*. Beta-lactamase producing strains of *Neisseria gonorrhoeae* require the use of more expensive and toxic antibiotics. To further complicate matters, world travel has helped to spread antibiotic resistant infections to distant geographical locations.

Table. Factors promoting drug resistance in developing countries

Large population

Lack of Primary Health Care

Inappropriate use of anti-microbials

Heavy burden of infectious diseases

Rapid spread of infections through

i) crowding

ii) poor sanitation

iii) sexual contact

Self prescribing

Antibiotics purchase without prescription

Irrational mixtures of vitamins, stimulants and steroids

Lack of responsibility of domestic pharmaceutical firms

Lack of proper education (patients, pharmacists, doctors etc.)

Corruption in political system

Table lists the factors that can promote drug resistance in developing countries³⁹⁻⁵⁴. Silverman, Lydecker and Lee in *Bad Medicine, The Prescription Drug Industry in the Third World*⁵⁵ have reported that "in their promotion of drug products in developing countries, the major offenders were originally the

big multinational companies based in the United States, Europe and more recently, Japan. By the end of 1980s, however, the situation has changed remarkably. More and more, it was the multinationals which had discovered that they could tell the truth and still make money. Instead it was the local or domestic firms, many with enormous political power, that were telling lies, defrauding and endangering the lives

of their fellow citizens". The solution of restricting antibiotic use, however, may not be practical in places where there are few, if any, medical facilities and trained personnel to administer these life saving medications. Under these circumstances, limiting the availability of antibiotics to the general population can result in higher instances of illness and death⁵⁶. Yet developing nations are already experiencing morbidity and mortality due to resistant infections that is disproportionate to their industrial counterparts and therefore, timely action is needed. The situation in developing countries will not improve unless governments become more stable, the living standards are improved and adequate medical as well as preventive care are provided³⁶. The governments should strengthen their national drug policies, restrict licensing to safe and effective drug products and administer rules and regulations aimed at rational use of the available drugs by physicians and consumers³⁶.

Future Research

Further research in the field of infectious disease is needed to ensure the continued availability of effective treatments. Specific areas of priority are the development of new tests which can more rapidly identify infective microbes and their antibiotic sensitivities, as well as methods that will decrease or eliminate the spread of factors that enhance antibiotic resistance among microorganisms. The development of new vaccines which confer immunity to bacterial diseases could be invaluable and substitute for antibiotic supplements in animal feed will have to be found. The effect of discontinuing antibiotic therapy on resistant patterns is another area of study that will provide useful information in controlling future epidemics. In this area, the information provided by antibiotic audits may provide good starting reference points. The development of a community formulary in which local pharmacists play a role in encouraging rationale prescribing practices is another area of investigation. Finally, programmes that educate doctors in appropriate antibiotic administration and the study of factors that promote the acceptance of peer review recommendations in medical practice, will continue to be the cornerstone of limiting global antibiotic abuse.

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Resistance can also develop if antibiotic is applied locally. An example of this is Gentamycin, which when applied topically over bum wounds, develops resistance quickly to the organisms that come in contact².

Settings Commonly Affected by Antimicrobial Resistance

Resistance of common pathogens is an important nosocomial problem and is of significant importance in community acquired infections⁷. In tertiary care facilities, the incidence of drug resistant gram positive infection has increased, especially with Staphylococcus aureus, coagulase negative Staphylococci, Corynebacteria, and Enterococci⁸. Drug resistance in gram negative organisms such as Pseudomonas, Serratia and Acinetobacter species, still continues to be a problem in hospital settings⁹. Recently, Mycobacterium tuberculosis strains have been isolated that are resistant to antibiotics from AIDS patients, illegal drug addicts and prison populations⁷. In industrialised countries, the major impact of antimicrobial resistance is felt in the hospital setting. However, in less industrialised countries, the outpatient acquired infections due to multiresistant organisms create major therapeutic problems¹⁰. Examples are Streptococcus pneumoniae, H. influenzae, Shigella and certain species of Salmonella¹⁰. In the United States, several other settings such as nursing homes and extended-care

facilities have problems with antimicrobial resistance¹¹. Day Care Centres in the US have high rates of antimicrobial resistance particularly among children in diapers¹². Pencillin resistant pneumococci outbreaks have been reported¹³. Studies of trimethoprim resistant *Escherichia coli* have also shown extensive colonisation and transmission of these organisms from one child to another^{12,14}. Animal feedlot is another setting for antimicrobial resistance¹⁵. Resistant *Salmonella* from cattle herds have been shown to spread to people in distant communities¹⁶. Several studies have shown that antibiotic resistant organisms can also spread from one country to another¹⁷⁻²¹.

Use and Misuse of Antibiotics

By means of synthetic changes we have been able to improve antibiotics usefulness in many ways by reducing the toxicity and increasing effectiveness. Concomitant with antibiotic use has been the appearance of resistant bacteria which seem to emerge as rapidly as new antibiotics are introduced. Fortunately most infections are still responsive to treatment by present day antibiotics. However, there is a disturbing worldwide increase of resistance genes in reservoirs of non-pathogenic bacteria and an emergence of resistance pathogens which were previously susceptible. The result is treatment failure, high cost and deaths. The emergence of new drugs will remain useful only if they are reserved for the hard to treat infections. The only way to curtail resistance genes and resistance organisms is to decrease and control the indiscriminate use of antibiotics. In view of the widespread misuse and overuse of antibiotics in the world, such reduction need not compromise health. Hospital acquired infections are recognized as a factor in mortality and the escalating cost of health care. The gravity of the underlying disease processes found among hospitalized patients, as well as the invasiveness of modern interventions, are major factors in susceptibility to infection. At the same time, nosocomial infections have become increasingly associated with the changing patterns of opportunistic organisms found in the hospital environment. Thirty years ago, hospital-acquired infections were mainly caused by gram positive *Staphylococci*, but now, gram negative bacilli and *Enterococci* have emerged as the primary etiological agents of nosocomial morbidity and mortality²². Bacteremia due to gram negative organisms, for example, affects about 1% of hospitalized patients each year and is fatal in 30-50% of cases²³. Although it is not clear if these microorganisms are actually more virulent, it is certain that the disease processes associated with these agents are especially difficult to treat due to their ability to acquire resistance to antibiotics. The emergence of resistant strains and species of bacteria is a natural consequence of antimicrobial usage²⁴. When older chemotherapeutic agents are inadequate, new drugs are required which are often more costly and toxic than their predecessors. As resistant microbes continue to emerge from the use of these substances, the question of whether medication therapy will continue to be effective becomes paramount. It has been noted, however, that the process by which antibiotic resistance occurs can be slowed if the use of antimicrobial agents is limited²⁵. This has led to numerous investigations of antibiotic usage patterns to determine if the present extensive reliance on these drugs is always necessary. About 30% of hospitalized patients receive systemic antibiotics²⁶ and this accounts for 25-30% of the cost of all pharmacological agents administered in hospitals²⁷. Studies reviewing patterns of antibiotics treatment in this setting have shown that up to one-half of all therapy is inappropriate and revealed alarming tendencies of both excess and misuse²⁸. Antibiotics are often given for surgical prophylaxis in instances where they have not been shown to be needed to prevent infections and even when given under appropriate circumstances, treatment has continued for an extended period rather than only pre-operative period²⁹. Antibiotics are also administered to medical patients for prophylactic purpose even though their ability to prevent infections in immunosuppressed or anatomically compromised patients is limited²³. When ordered for an actual infection, antibiotics are sometimes prescribed that are not the most effective (or least expensive) agent for the identified pathogen. The use of a medication with a broader spectrum of activity than is necessary for treatment is

another example of antibiotic abuse. Furthermore, these drugs are occasionally administered by an improper route, at an incorrect dose or for resistant microorganisms. Antibiotics are also misused in the treatment of suspected infections when most efficacious agent is not prescribed with consideration of the site of infection and the pathogens most likely to be present.

Medications such as the aminoglycosides, the third generation cephalosporin, ticarcillin-carbenicillin and amikacin, need to be held in reserve for the systemic treatment of life threatening infections for which there are no alternative antimicrobial agents.

Unnecessary exposure to antibiotics is a direct consequence of their overuse and misuse. In addition to extra cost, overuse of antibiotics may cause adverse effects in about 10-20% of the hospitalized patients to whom they are administered³⁰. These untoward actions may include gastrointestinal disturbances, infusion phlebitis, organ damage (nephrotoxicity, ototoxicity etc.), bone marrow dysfunction and hypersensitive or even anaphylactic reactions. Moreover, superinfection can occur due to disturbances in the normal flora of the host. Together, these factors result in greater morbidity, mortality and expense of treatment

Strategies for Prevention

Education

Education will play a substantial role in promoting the appropriate use of antibiotic therapy. This will include more comprehensive instruction in both medical schools and postgraduate training programmes on the diagnosis of infections and antimicrobial treatment principles.

Interactions between Hospitals, Physicians and Pharmaceutical Companies

There is also a need to control interaction between physicians and pharmaceutical manufacturers who use aggressive advertising campaigns to sell their products. Medical personnel need to have access to unbiased information on medication benefits as well as limitations. While the industry has been chastised for being a part of the problem, it is also a part of the solution in that new and useful antimicrobial agents have been discovered under its direction²⁷.

Experts have recommended that hospitals adopt policies to control meetings between staff and pharmaceutical company representatives, including the requirement that manufacturers register with the pharmacy, not enter patient care areas, restrict the time and location of advertising displays and limit the dispensing of product samples²⁸.

The Development of a Formulary System

Hospitals should maintain a formulary system that restricts the number of antimicrobial drugs to essential items and provides for the addition or deletion of agents based on therapeutic clinical rationales. The formulary may also state protocols for choosing the most effective and least expensive drug of a particular class. Similarly, the microbiology laboratory, if staffed by qualified experts, can assist doctors in selecting appropriate pharmacologic agents based on sensitivity tests tailored to the specific pathogen identified by culture and by the site of infection. Restrictions may be placed on reporting of sensitivity test for high cost or toxic drug therapies unless special requests are made.

Furthermore, both the pharmacy and the laboratory should use generic terminology for all antibiotic ordering, labelling and reporting.

The importance of maintaining a strong hospital formulary system cannot be overstated because of the increasing numbers of new broad spectrum antibiotics available and the complexities of their use. The decision to add new antimicrobials onto formulary list is a task requiring thoughtful investigation. Effectiveness, toxicity and cost are primary considerations in determining whether or not an agent should be included in the formulary, but it is important to point out that new drugs are not granted approval for marketing based on criteria of greater efficacy, safety or cost effectiveness than already established medications. Therefore, an antibiotic is not necessarily better simply because 'it is new. Other factors to consider in making formulary decisions are the results of in vitro susceptibility testing and possibly unique pharmacokinetics actions. In this regard, however, it must be emphasized that in

in vitro activity does not always correlate with in vivo effectiveness and conclusion based on pharmaceutical manufacturer's studies may be biased in favour of a newly marketed agent. If questions remain or differences in efficacy are noted, a hospital might choose to perform its own laboratory or clinical studies³¹.

Automatic Stop Orders

Other practices that encourage only essential antibiotic use include the requirement of automatic stop orders for prophylactic therapy and the use of certain newly developed or toxic drugs that need to be held in reserve. It is imperative, however, that the patient receives an uninterrupted medication supply if continued treatment is necessary. Therefore, the physician must reassess pharmacologic therapy at regular intervals and reorder antibiotics as needed. Cooperation may be obtained from nursing and pharmacy staff in alerting doctors to the need for treatment review.

Antibiotic Ordering Forms

Special antibiotic ordering forms that specify the reason for treatment can also be helpful in monitoring the use of these drugs. Many researchers have recommended consultation with the infectious disease service before initiating therapy using certain chemotherapeutic agents that are toxic, expensive or promote the emergence of resistant organisms. This expert advice may continue throughout the course of therapy³².

Infection Control Programmes

Finally, the need for antibiotic usage may further decline in the presence of an active programme of infection control which emphasizes the prevention of nosocomial infections. Even if the issue of excess is effectively addressed, antibiotic therapy can be expected to be heavily employed and the emergence of resistant microbes will continue. Close epidemiological monitoring of the types and distribution of resistant organisms is essential and infection control practices that prevent, detect and eliminate nosocomial infections due to these agents are critical. Careful monitoring of the microbiology laboratory for the early detection of outbreaks involving antibiotic resistant organisms, will be required to control the spread of these microbes and eliminate their reservoirs¹. The hospital should have programmes which regularly review the antibiotic usage in order to monitor safety and effectiveness of therapy. Policies may restrict the use of newly marketed or toxic, broad spectrum antibiotics to only those situations where their use is deemed absolutely essential in order to limit the emergence of resistant microorganisms and to prolong their usefulness.

Review of Antibiotic Usage and Medical Audits

Studies have shown that restricting antibiotic usage is generally helpful in controlling nosocomial infection outbreaks due to multiple resistant organisms. In a few extreme instances, the total or near complete discontinuation of all antibiotics has led to the resolution of significant and persistent epidemics²². However, it is not practical to use this method. Instead, experts agree that policies promoting more rational use of antibiotics is essential. The implementation of such regulation requires flexibility in recognizing a doctor's responsibility in the treatment of patients. Rigid prescriptions that mandate specific therapeutic protocols are not appropriate solutions because they fail to take into account legitimate differences in view concerning optimal medical management or to address the constraints under which physicians perform their daily practice. Yet even though prescribing doctors will be ultimately responsible for controlling their use of antibiotic drugs, the increasing complexities of infectious disease treatment makes this a formidable task for physicians to accomplish individually and furthermore, many doctors have been slow to realize that the decision to order an antibiotic has potentially widespread ecological implications²². The ability to evaluate these guidelines and assess compliance with them, requires ongoing commitment³³. An organized antibiotic review committee may be established independently to facilitate this purpose. The committee should be staffed and chaired by doctors specializing in infectious disease medicine. Pharmacists, microbiologists and infection control personnel may provide additional support in issues involving antibiotic usage. The committee should

meet regularly to review and formulate policies and make recommendations to the medical staff for adoption into practice. Additionally, the committee may also examine matters related to the hospital formulary and standards or practices in the microbiology laboratory that concern antibiotic sensitivity testing.

Medical audits are quality assurance activities that compare practices to accepted standards of care. Similarly, antibiotics audits are used to evaluate the actual patterns of drug prescriptions against guidelines for their use. The antibiotic review committee may monitor medication usage by an auditing system to ensure that therapy is effective and consistent with medical standards. Audits may also be undertaken to assess the incidence of adverse reactions and the cost of drug treatment. Rather than attempting to monitor all antibiotic ordering, the committee may concentrate on specific concerns, such as the use of expensive, toxic agents or prophylactic treatment. In reviewing the therapeutic to empiric prescribing of antibiotics, attention should be focussed on circumstances for which general standards of care exist²². Other areas of concern which may be monitored, in conjunction with the infection control committee are antimicrobial resistance patterns and the distribution or types of organisms associated with nosocomial infections. Additionally, the antibiotic review committee can play a major role in disseminating information concerning development in the field of antimicrobial therapy and planning in service education.

Various procedures by which antibiotics usage can be monitored have been described in the literature and each method has advantages and drawbacks. Ideally, the audit process should be easily accomplished, relatively inexpensive and provide accurate information. The ability to standardize auditing procedures can also render data that may be compared with other institutions²⁸. Pharmacy records can give general information in the use and cost of specific pharmacologic agents and may identify broad trends. If patients can be identified by hospital service, patterns indicating potential problems in general areas may be seen. The use of pharmacy records is cost effective, but the data obtained is retrospective and cannot always highlight specific trouble spots. The use of special antibiotic ordering forms, that include the type of therapy prescribed and the reason for treatment, can be an invaluable source of specific data and encourages doctors to consider the appropriateness of their prescriptions³³. The use of a separate sheet in ordering antibiotics requires cooperation from the medical staff and consideration in making the form easy to complete is essential to its success. Yet the benefits of providing current information on actual prescribing practices related to therapy, empiric usage and prophylaxis, make this an especially helpful tool for auditing purpose. The results may even show the effects of differing antibiotic prescriptions on the emergence of bacterial resistance. Moreover, the data obtained can be used for confidential feedback to physicians on the appropriateness of their prescribing habits and allows comparison of their practice with those of their peer³⁰. An antibiotic review must be performed under the direction of doctors who have a special interest in the field. Medical control of the process can ensure that the evaluation of antibiotic usage is accomplished by experts and that feedback to prescribing physicians comes from an authoritative source. In this way, an antibiotic audit is a peer review process, rather than an administrative directive. In undertaking an auditing procedure, evaluations are performed to ensure that practices conform with accepted standards and to maintain high quality in care. Therefore, the ultimate goal of an antibiotic audit is to determine that the most effective and least toxic drug is given and to minimize the emergence of resistant microorganisms, while holding down the cost of therapy. When instances are discovered that do not conform with the standard policies, it must not be immediately concluded that the treatment given is incorrect.

Surveillance

Surveillance by international agencies, such as the World Health Organization is a necessary component of controlling global antibiotic abuse and the emergence of resistant microorganisms in developing countries and in hospitals around the world³⁴. W.H.O. has developed a list of essential

drugs and supplies for use in local dispensaries and provides educational materials for the development of national drug policies³⁵.

Other Measures

In addition to surveillance, other measures can be initiated to help limit the use of antibiotics, including the undertaking of sanitation projects which improve the quality of drinking water and immunization programmes to prevent diseases, such as meningococcal infection in areas where this is prevalent.

Antibiotic Resistance in Developing Countries

Twenty percent of the worldwide supply of antimicrobials goes to the developing countries³⁶. These countries still have the highest rates of resistance to antimicrobial drugs³⁷. Children are most commonly affected as they are frequent victims of respiratory and gastrointestinal infectious diseases^{36,38}. This indiscriminate use of antimicrobial therapy has been responsible for the emergence of antibiotic insensitive infections, including those caused by sulphonamide-resistant *Neisseria meningitidis*, ampicillin-resistant *Shigella dysenteriae* and multiple-resistant *Serratia marcescens*. Beta-lactamase producing strains of *Neisseria gonorrhoeae* require the use of more expensive and toxic antibiotics. To further complicate matters, world travel has helped to spread antibiotic resistant infections to distant geographical locations.

Table. Factors promoting drug resistance in developing countries

Large population

Lack of Primary Health Care

Inappropriate use of anti-microbials

Heavy burden of infectious diseases

Rapid spread of infections through

i) crowding

ii) poor sanitation

iii) sexual contact

Self prescribing

Antibiotics purchase without prescription

Irrational mixtures of vitamins, stimulants and steroids

Lack of responsibility of domestic pharmaceutical firms

Lack of proper education (patients, pharmacists, doctors etc.)

Corruption in political system

Table lists the factors that can promote drug resistance in developing countries³⁹⁻⁵⁴. Silverman, Lydecker and Lee in *Bad Medicine, The Prescription Drug Industry in the Third World*⁵⁵ have reported that "in their promotion of drug products in developing countries, the major offenders were originally the

big multinational companies based in the United States, Europe and more recently, Japan. By the end of 1980s, however, the situation has changed remarkably. More and more, it was the multinationals which had discovered that they could tell the truth and still make money. Instead it was the local or domestic firms, many with enormous political power, that were telling lies, defrauding and endangering the lives

of their fellow citizens". The solution of restricting antibiotic use, however, may not be practical in places where there are few, if any, medical facilities and trained personnel to administer these life saving medications. Under these circumstances, limiting the availability of antibiotics to the general population can result in higher instances of illness and death⁵⁶. Yet developing nations are already experiencing morbidity and mortality due to resistant infections that is disproportionate to their industrial counterparts and therefore, timely action is needed. The situation in developing countries will not improve unless governments become more stable, the living standards are improved and adequate medical as well as preventive care are provided³⁶. The governments should strengthen their national drug policies, restrict licensing to safe and effective drug products and administer rules and regulations aimed at rational use of the available drugs by physicians and consumers³⁶.

Future Research

Further research in the field of infectious disease is needed to ensure the continued availability of effective treatments. Specific areas of priority are the development of new tests which can more rapidly identify infective microbes and their antibiotic sensitivities, as well as methods that will decrease or eliminate the spread of factors that enhance antibiotic resistance among microorganisms. The development of new vaccines which confer immunity to bacterial diseases could be invaluable and substitute for antibiotic supplements in animal feed will have to be found. The effect of discontinuing antibiotic therapy on resistant patterns is another area of study that will provide useful information in controlling future epidemics. In this area, the information provided by antibiotic audits may provide good starting reference points. The development of a community formulary in which local pharmacists play a role in encouraging rationale prescribing practices is another area of investigation. Finally, programmes that educate doctors in appropriate antibiotic administration and the study of factors that promote the acceptance of peer review recommendations in medical practice, will continue to be the cornerstone of limiting global antibiotic abuse.

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