Antimicrobial Resistance: A Global Public Health Threat

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The 60 years of the antibiotic era has been marked by cycles of discovery of new antibiotics and the subsequent emergence of drug resistance. Imprudent use of antibiotics has lead to the development of resistance which has reached a grave situation.

The factors which increase bacterial resistance to antibiotics are the overuse and misuse of antibiotics (1, 2) The relationship between the amount of antimicrobials consumed in human communities and the frequency of resistance is well established. (3) A significant number of prescriptions written for antibacterial drugs in ambulatory care settings are for treatment of acute respiratory tract infections (common colds, acute bronchitis, and acute uncomplicated sinusitis) (3). There are geographic differences in proportion of resistance. A recent study from Europe by- Goossens(4) has shown a higher rate of antibiotic resistance in high consuming countries of Southern and Eastern Europe than in Northern Europe. A shift from the old narrow-spectrum to newer broad spectrum antibiotics has also been noted. Infections caused by resistant bacteria are not only confined to hospitalized patients but are now wide spread in the community. Antibiotic use in animal feeds adds to the risk of developing strains of bacteria that are resistant to agents commonly used to treat humans. Finally, with dwindling development of new antibiotics by pharmaceutical companies that favor production of drugs for chronic diseases like hypertension, lipid disorders, etc. which lead to higher profits, are leading to difficulty in treating bacterial infections (5). Antibiotic resistance is a global threat and has reached epidemic level. It won't be too long before we reach a time when we will not have effective antibiotics to combat serious infections caused by resistant bacteria. A comprehensive strategy is needed for the control of antimicrobial use. A number of industrialized countries and World Health Organization (WHO) have taken strong measures. In the United States, an interagency task force on antibiotic resistance (CDS, FDA, and NiI-I) is addressing issues of overuse and/or misuse of antibiotics. Recently the Council for Appropriate and Rational Therapy (CARAT) has developed criteria for appropriate and accurate antibiotic selection. (6,7).

Antimicrobial resistance is costly.and difficult to quantitate accurately as is the economic impact worldwide (7) .Estimates of the excess annual cost related to antimicrobial resistance in the USA is more than $30 billion and worldwide more than $105 billion. What is worst is the cost of drug discovery to licensure and marketing which exceeds $600 million in the USA. This takes 8 to 10 years, during which time multi-drug resistance may occur to the class of drug developed making the new drug ineffective before it is marketed.

In this article the problem of antimicrobial resistance in developing countries is briefly discussed, however, the objective is to discuss the major determinants of antimicrobial resistance and discuss in detail guidelines of use of antimicrobial drugs and in general tackle the control measures.

Mechanism of Antimicrobial Resistance

Some species of bacteria are innately resistant to one or more class of agents. However, the great concern of acquired resistance is that an initially susceptible bacteria become resistant to an antimicrobial and spreads under the selective pressure of the agent. The different mechanisms of resistance are shown in the figure below. 1). Organisms acquire genes encoding enzymes like beta lactamase that destroy the antibiotic; 2) Organisms acquire efflux pumps that remove the agents from the cell before reaching the target site, 3) Organisms alter the binding sites.

Antimicrobial Resistance in Developing Countries

Recently developed drugs are scarce in developing countries. Even in the tertiary referral hospitals first line drugs are ampicillin, chloramphenicol, erythromycin, gentamicin, penicillin, and tetracycline. Antibioitic use is unregulated and may be purchased in pharmacies or general stores with and without prescriptions. Locally produced antibiotics in some cases have low potency. Because laboratory facilities are not widely available, most patients are treated empirically using antibacterials in acute diarrheal disease sand respiratory tract infections even though in a good number of cases these are viral infections. Increasingly, problems of resistance in pneumococcal infections, tuberculosis, typhoid fever, sexually transmitted diseases, and nosocomial infections occur. (8).

Managing the problem of antimicrobial resistance in developing countries should include the following, 1) Improved access to diagnostic laboratories, 2) Surveys to detect the emergence of resistance, 3) Regulation of the use of antibiotics, 4) Train prescribers of antibiotics, and 5) Education of the public.

In the tropics there are well known problems with antimicrobial multiple resistance in Shigella spp, Salmonella spp, Mycobacterium tuberculosis to first-line therapy and penicillin resistance to N. gonorrhoeae and Streptococcus pneumoniae.

Data on resistance, prevalence and antimicrobial use is lacking in developing countries. In addition, there are constraints to the development of effective surveillance because of lack of laboratory facilities among other factors. Strategies for managing,

antimicrobial resistance in developing countries require improved surveillance of antimicrobial resistance that will contribute to providing relevant data to prescribers and aid in developing disease control strategies (9)

Africa suffers from AIDS and other devastating epidemics, but a more incidious threat is the spread of antimicrobial resistance. There is an increase first-line treatment resistance (more than 85%). in major infectious disease causes death in Africa and globally are acute respiratory infections, diarrheal disease, malaria, and tuberculosis. The danger is an impending loss of broad-spectrum, low-cost antimicrobials such as ampicillin, chloramphenicol, tetracycline, and fluoroquinolones. Among the factors for resistance problem in Africa are lack of laboratory facilities, unavailability or short supply of crucial antibiotics, rudimentary hospital infection control and poor public health practices with crowding from urban migrants creating breeding grounds for resistance

Determinants of Antimicrobial Resistance and Future Control

Review of data from 74 published studies (10) has revealed common risk factors for acquiring various resistant organisms due to nosocomial colonization caused by methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant enterococcus (VRE), extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacilli, Clostridium difficile and Candida species.

The determinants are put in 4 categories (11):
1) Molecular characteristics of pathogens i.e. virulence, transmissibility and survival fitness, 2) Prescribing habits, 3) Consumers characteristics, and 4) Health care environment (regulatory policies, infection control practice, promotional activities by industry).

Potential control measures/interventions can be done for each of these determinants (See table):

1) Improving diagnosis of microbial infection with rapid diagnostic tests.

2) Discontinuing antimicrobial therapy inpatients who do not have a bacterial infection, shortening duration of treatment, and to some degree using guidelines .During the last 10 years, several countries in Europe and North America but also Chile, South Korea and Taiwan have decreased antimicrobial prescriptions, especially in ambulatory settings,

3) Increase immunizations, hand hygiene, barrier precautions and public information campaigns. Knowing or recognizing the risk factors for acquiring resistance organisms that have common risk factors can help on in establishing effective control measure for all resistant organisms. The most likely risk factors are advanced age, underlying disease, severity of illness, extended length of stay in hospital, inter-hospital transfer of patients and admission from nursing home, invasive procedures or devices and antibiotics use.

Strategy for Control of Antimicrobial Resistance

Several strategies have been tried. The most common one is to lower antibiotic consumption. This has been shown to be a successful in Finland and Iceland but has yet to be a general rule in practice. Antibiotic cycling (like crop rotation) programs to remove antibiotic pressure place the resistant(s)organisms at a selective disadvantage. However, compensatory mutation can arise. More feasible ways with this issue are discussed below. Examples of managing three drug-resistant infections are also given below.

Restricting antibiotic use in animals is another strategy. Many outbreaks of disease due to Salmonella species and E.coli have been shown to be associated with the use of antibiotics like fluoroquinolones in poultry. This practice is one cause of bacterial antibiotic resistance. Prohibiting use of such drugs is an important strategy to reduce resistance.

Treatment Strategies to Reduce Antimicrobial Resistance

1) The CDC 12 steps to prevent antimicrobial resistance

These include four major components namely, 1) Prevent infection, 2) Diagnose and treat infection, 3) Use antimicrobials wisely, and 4) Prevent transmission as detailed in following table.

Table 1: The Centers for Disease Control: 12 Steps to Prevent Antimicrobial Resistance

Prevent Infection
* Vaccinate
* Remove catheters

Diagnose and Treat Infection Effectively
* Target the pathogen
* Access the experts

Use Antimicrobials Wisely
* Practice antimicrobial control
* Use local data when available
* Treat infection, not contamination
* Treat infection, not colonization
* Know when to say no to vancomycin
* Stop treatment when infection is cured or unlikely Prevent Transmission
* Isolate the pathogen
* Break the chain of contagion

Adapted from: Centers for Disease Control Campaign to Prevent Antimicrobial Resistance. CDC, Atlanta, Spring, 2002.

2) Stages for use of antimicrobial drug include the following steps — initial broad spectrum therapy, followed by modification of antimicrobial

therapy after determiñing the etiology and drug susceptibility and progression to early discontinuation after ensuring appropriate therapy. Antimicrobial therapy should aim for rapid and maximal reduction in bacterial load with ultimate objective of eradication. This recommendation has been forwarded by a consensus group (12). Recurrent infection with multi-resistant bacteria occurs with longer antimicrobial use. Improvement of diagnosis by early identification of pathogens using techniques such as PCR's, etc. Antibiograms can be useful, but may not reflect the current susceptibility of the organism or organisms in the present situation. Using automated, susceptibility methodology results may be back at the same time the pathogen is identified.

Appropriate empirical antibiotic treatment can be associated with better survival and decrease in hospital stay (13).
MIC's are preferred than "sensitive""intermediate" and resistance" in some important pathogens like pneumococci and alph-hemolytic streptococci in blood vs penicillin, Pseudomonas spp. vs fluoroquinolones and aminoglycosides, Staphylococcus species vs vancomycin, and enteric gram negative rods vs cephalosporin.

3) Antimicrobial stewardship strategies. This is one the important parts of the multifaceted approach to preventing emergence of antimicrobial resistance. Strategies include prescriber education, formulary restriction, prior approval, antibiotic cycling, etc. These approaches can result in improved appropriateness of antibiotic use, cure rates, lower cost and reduced rates of C.difficile associated diarrhea and VRE infections(14). These include educational guidelines, formulary restriction of selected antibiotics to certain indications, surveillance amid prospective intervention, computerized decision analysis. Pharmacists are key person in antimicrobial stewardship programs. However, these strategies are sophisticated programs can be successfully done in only industrialized countries.

4) Infection control. This includes standard precautions, universal precautions (designed to reduce the risk of transmission of blood-borne pathogens) and body substance isolation (designed to reduce the risk of transmission of pathogens from moist body substances). Additional components are personal protective equipment, patient p1acement, handling of soiled linens, hand hygiene, decontamination of environmental surfaces and prevention of sharps injuries.

Solution for pressure by patients
Physicians say they often over prescribe antibiotics because of patient demand. The following are suggestions how to say "No" to' patient demands for antibiotics.

I) Make patients understand about their illness. Studies have shown that patient satisfaction is more related to having their physician spending time to help them understand their illness and using educational materials. Written information accompanied by physician's counsel is more effective.

2) Use simple terms to explain about dangers of overuse of antibiotics, like inappropriate prescribing will later affect patient's ability to fight bacterial infection next time he or she has one. These include adverse effects, allergic reactions and cost in addition to development of antibiotic resistance.

3) Use simple terms to explain diagnosis, like "runny nose" and "chest cold" that give impression of a mild viral infection rather than "bronchitis" and sinusitis".

4) Use of office staff and space for patient education. The staff can tell patients about chest colds/viral infections amid give reading material (brochures) that explain dangers of inappropriate prescribing. Educational materials are available from the CDC, The American Academy of Pediatrics and American Society for Microbiology.

5) Discuss what measures patients can take to decrease illness. These are hand washing to decrease transmission of microbes and vaccination.

A combined community intervention and clinical decision support system (CD SS) has recently been conducted in rural primary care settings to reduce inappropriate prescribing of antimicrobial drugs for acute respiratory infections (15). The community interventions are designed for behavioral change modes — spread of educational materials with key message "Do not treat viral infections with antibiotics". The second part focuses on patient behavior rand includes how to self manage common respiratory infections and how to improve communication with clinicians. The CDSS included decision support tools for clinicians for management of acute respiratory tract infections including sinusitis, pharyngitis, otitis media, pneumonia, influenza and URTI paper-based and programmed in personal digit assistant (PDA) for diagnostic and therapeutic recommendation. This study was conducted in 2002 to 2003 (over a 21 month period). Communities were divided into two groups — community intervention only i.e. meetings, news releases, distribution of educational materials, etc. compared to another group i.e. community level as well as clinical decision support tool given to primary care clinicians either on paper or in an electronic

yersion through PDA. Over two years prescription of drugs declined by 10% In CDSS communities versus only 1% in community intervention.

Combating three common drug-resistant infections

Physicians or prescribers need to rethink their prescribing practices. The goals are to combat the growing threat of antibiotic resistance and avoid giving patients drugs that don't help in treating the infections. Such common infections are discussed below:

I)   Urinary tract infections (UTI's) . Escherichia. coli, the common cause of UTI has become increasing resistant to trimethoprim-sulfamethoxazole (TMP-SMX) that had been used for many years. Recent guidelines from Infectious Diseases Society of American (IDSA) guidelines indicate checking local resistance data. If prevalence of TMP-SMX resistance is 2% or more or reaches l0% in special cases as diabetics use alternative drugs. However, the local incidences of resistance is not known in most cases. A practical strategy is to consider using an alternative drug for UTI like fluoroquinolone if the a) severity of illness. b) presence of risk factors like hospital admission, use of bladdler catheters, undlerlying illness such as diabetes. Other drugs which may be used are nitrofurantoin or fosfomycin.

2)   Community-Acquired Pneumonia Strepto coccus.pneumoniae. This common cause of pneumonia has become increasingly resistant to many antibiotics all the world. In most cases, high doses of penicillins and cephalosporins may be used to treat pneumonia, but not meningitis caused by S.pneumoniae. In outpatient setting physicians may use amoxicillin, cefuroxime, azithromycin or clarithromycin, or a fluoroquinolone (normal dosages). For hospitalized patient who has pneumococcal pneumonia either of the following regiments may be used: Ampicillin with or without clavulanic acid, ceftriaxone/cefotaxime, vancomycin in only in beta-lactam antibiotic allergy. The newer quinolones (levofloxacine, gatifloxacin, moxifioxacin) need to be used only if other regimens have failed, the patient is allergic to above drugs or causative agent is highly resistant. Boosting dose of penicillin or cephalosporin is recommended for treatment of penicillin-resistant pneumococcal infections. This is not recommended to treat meningitis due to S. pneumoniae. Assume that a resistant strain may be the cause then treat initially with maximum doses of vancomycin plus ceftriaxone or cefotaxime.

3)   Gonorrhea. Penicillin and tetracycline resistant. Neisseria gonorrhoeae has become common since 1980's. Thus the drugs of choice are ceftriaxone and fluoroquinolone. In the last few years fluoroquinolone resistant strains of N.gonorrhoeae resistant have increased in Asian countries and California and Hawaii in United States. In such case the only recommended drugs are ceftriaxone or cefixime (the only oral drug if available). In those areas where fluoroquinolone-resistant strains are uncommon Ciprofloxacin and Levofloxacin can be used..

Concluding Remarks

Stuart Levy in his' book "The Antibiotic Paradox" has made a strong point that resistance is an inevitable outcome of the interplay between microbial evolution and overuse of antibiotics and belief in antibiotics as "Miracle Drugs" has lead to dangerous misconceptions. He adds, antibiotic resistance will not go away, but it will be a much more manageable problem.

The fact that antibiotic resistance is a major problem in the practice of medicine and in public health is fairly well recognized., It needs to be emphasized at all levels of knowledge from medical school and higher with the intention of decreasing resistance rates among antibiotics.

The bottom line is appropriate use of antibiotics!.

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