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Change in Antibiotic Regimen Due to Inappropriate Selection of Antimicrobials

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FPHAMIN.P.PHILIPOSE[1], LAYANA ROY[1], ABEL ABRAHAM THOMAS*[2]

[1]Fifth Year PharmD. Department of Pharmacy Practice. Nazareth college of Pharmacy, Kerala, India

[2] Assistant Professor Department of Pharmacy Practice. Nazareth college of Pharmacy, Kerala, India

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ABSTRACT

Antibiotic, is a chemical substance produced by a living organism, generally a microorganism that is detrimental to other microorganisms. Antibiotics either kills the bacterium or slows down bacterial growth and thus it can be used for the prevention and treatment of bacterial infections. Irrational use of antibiotic includes unnecessary use where an antibiotic is not indicated and there is no health benefit for the patient, inappropriate use where timing, antibiotic choice, dose, route, frequency of administration or duration of treatment is incorrect. Inappropriate selection of antibiotic include choice of an antibiotic with an unnecessarily broad-spectrum or too narrow spectrum, either dose is too high or too low compared to what is indicated for that patient, duration is greater than 24 hours for surgical prophylaxis (except where guidelines endorse longer duration), treatment is not streamlined or changed when microbiological culture data become available and poor patient adherence to the prescribed treatment. This can lead to antibiotic resistance. It mainly occurs due to chromosomal mutation. The consequence of antibiotic resistance leads is delay in providing the effective therapy. Therefore, a change in antibiotic regimen is required. Example for the change in regimen include, combination therapy which has been particularly effective for preventing resistance in microbes where spontaneous mutation leads to the evolution of resistance, notably in the treatment of tuberculosis.

INTRODUCTION

Antibiotic, is a chemical substance produced by a living organism, generally a microorganism, that is detrimental to other microorganisms.[5] Antibiotics came into worldwide prominence with the introduction of penicillin in 1941[5]. Since then they have revolutionized the treatment of bacterial infections in humans and other animals. They may either kill or inhibit the growth of bacteria.[6] Antibiotics are not effective against viruses such as the common cold or influenza; drugs which inhibit viruses are termed antiviral drugs or antivirals rather than antibiotics. Inappropriate antibiotic practices include: lack of consultation with healthcare professionals, purchase of antibiotics without prescription or refilling of the previous prescription, sharing of antibiotics with others, improper dosage regimens and early cessation of antibiotic therapy and use of empirical therapy without performing culture sensitivity test and not individualizing the antibiotic regimen.

Antimicrobial resistance is a broader term, encompassing resistance to drugs to treat infections caused by other microbes as well, such as parasites (e.g. malaria), viruses (e.g. HIV) and fungi (e.g. *Candida*). Antibiotic resistance is how bacteria protect themselves against the effects of an antibiotic. Two common ways to overcome resistance are pumping the antibiotic out of the bacterial cell or producing molecules that can destroy the antibiotic.

ANTIMICROBIAL RESISTANCE

There are mainly two types of antimicrobial resistance that is natural and acquired resistance. Natural resistance may be intrinsic (always expressed in the species), or induced (the genes are naturally occurring in the bacteria but are only expressed to resistance levels after exposure to an antibiotic). Intrinsic resistance may be defined as a trait that is shared universally within a bacterial species, is independent of previous antibiotic exposure, and not related to horizontal gene transfer. The most common bacterial mechanisms involved in intrinsic resistance are reduced permeability of the outer membrane (most specifically the lipopolysaccharide, LPS, in gram negative bacteria) and the natural activity of efflux pumps. Acquired resistance is possible through all of the main routes by which bacteria acquire any genetic material: transformation, transposition, and conjugation. Plasmid-mediated transmission of resistance genes is the most common route for acquisition of outside genetic material; bacteriophage-borne transmission is fairly rare.

There are four mechanisms through which bacteria become resistance to antibiotics:

1. Enzymatic inactivation: An existing bacterial enzyme is modified to interact with an antibiotic in order to make them inactive towards bacteria. It is due to the transfer of the antibiotic resistance gene carried on plasmids. The most significant examples are beta-lactamase enzymes, which hydrolyze beta-lactams (penicillins, cephalosporins).

2. Drug extrusion by efflux pumps: Those proteins, which are able to extrude a wide variety of compounds (including antibiotics) out of the cell, are overexpressed by the bacteria to extrude the antibiotic. This is an important mechanism of resistance in *P. aeruginosa* and *Acinetobacter* spp.

3. Decreased uptake by changes in the outer membrane permeability or by presence of porins.

4. Modification of the drug target: These changes impede the binding of the antibiotic and limit its potency.

Bacteria have two alternative pathways to acquire all types of resistance:

• Random changes in the bacterial DNA (mutations) may provide resistance by chance.

• Alternatively, they can receive resistance genes from other bacteria nearby.

If a resistance mechanism gives an advantage to the bacterium it may be maintained and will be passed on to coming generations as the bacterium divides or be passed along by horizontal transfer by human contact, in food and water, sometimes by respiratory droplet and across borders through travel and trade.

Antibiotic resistance is a natural and acquired problem. The evolution of resistant strains is a natural phenomenon that occurs when microorganisms replicate themselves erroneously or when resistant traits are exchanged between them. Antibiotics function by disrupting essential processes or structures in the bacterial cell. This either kills the bacterium or slows down bacterial growth. Depending on these effects an antibiotic is said to be bactericidal or bacteriostatic. A bactericidal antibiotic kills the bacteria while the bacteriostatic antibiotics reduce bacterial growth. There are several different classes of antibiotics. These can have

completely different bacterial targets or act on the same target but at a different site. There are three main antibiotic targets in bacteria:

• The cell wall or membranes that surround the bacterial cell.

• The enzymes that synthesizes the nucleic acids DNA and RNA.

• The machinery that synthesizes proteins (the ribosome and associated proteins).

These targets are absent or different in the cells of humans and other mammals, which means that the antibiotics usually do not harm our human cells but are specific for bacteria.

The clinical impact of resistance on antimicrobial therapy include it leads to a delay in the administration of microbiologically effective therapy, which may be associated with adverse outcomes. Infections caused by antimicrobial-resistant organisms may require more toxic therapy that can lead to adverse outcomes. The use of colistin for highly resistant *Pseudomonas* or *Acinetobacter* infections is associated with a high risk of renal dysfunction. In addition, some agents used to treat the resistant strain of an organism are less effective than the agents used to treat the susceptible strain of the organism—for example, vancomycin for the treatment of deep-seated methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Patients infected with organisms that are resistant to all available antimicrobials often require surgical procedures to remove the nidus of infection and also patients with infections that are not amenable to surgical debridement have high mortality rates.

ANTIMICROBIAL STEWARDSHIP TO TACKLE ANTIBIOTIC RESISTANCE

Antimicrobial stewardship is defined as ensuring that every prescriber or provider prescribes the right antibiotic for the right indication, in the right patients, at the right time, with the right dose and route, causing the least harm to the patient and future patients. The goals of the program are improving patient care by providing optimal therapy, reducing collateral damage thus reducing antimicrobial use and reducing the cost involved in it.

Being an important tool in the treatment of many infections, antibiotics produce a desired and immediate effect of inhibiting the growth of bacteria are highly prevalent in the present scenario but it is also associated with a very important undesired effect of promoting the evolution of resistance [4]. According to the new researchers a new strategy has been evolved

by which different antibiotic ombinations can be used to deal with bacterial growth and selecting against resistant mutants [4]. By exploiting certain specific interactions between drugs we can increase the sensitivity of the bacteria [3]. In the present scenario development of high rate of antibiotic resistance and the decreasing rate of drug discovery.It is necessary to device new strategies for antimicrobial treatment to redirect or limit or even reverse the course of resistance [1].

The major steps to tackle antibiotic resistance include:

Motivation to improve outcomes for patients with infections, prevent avoidable harm related to antimicrobial prescribing and a recognition of the potential and actual impact of antimicrobial resistance; this motivation needs to be present at many levels in an organisation – both from healthcare professionals but also shared by the senior executive team, those with the power to implement/support/fund the scheme, or capable of being persuaded of the benefit of the scheme (whether in terms of the benefits listed above, or purely financial/operational benefits).

The stewardship program is established with clear lines of accountability and there is a structure within the organization that can allow the implementation of a stewardship program to take place, support the scheme, monitor its performance and hold it to account for performance and outcome measures.

There needs to be both clinical and executive leadership provided to and by the scheme, it needs to have high level support and input from a senior management team, as well as clinical supporters.

Antimicrobial Stewardship committee:

A stewardship committee is fundamental to any stewardship scheme as it will provide the strategic direction, guidance, manpower, intelligence, resources etc. for any stewardship activities. It may be a stand-alone group or it may be a sub-committee or part of a larger group such as an infection prevention and control committee or a drugs and therapeutics committee.

Composition of a stewardship committee: A successful committee will be one which includes representatives of key staff groups involved in antimicrobial prescribing, and which is representative of the organisation it is a part of.

Educate and train:

Education is a key part of antimicrobial stewardship, but it can be extremely time consuming, especially when the sheer number of healthcare professionals who need to be educated is considered. Developing educational resources can be challenging, especially in resource limited settings.

Antibiotic resistance is the unresponsiveness to antimicrobial therapy [1]. It is mainly due to spontaneous mutation and horizontal gene transfer [1]. Spontaneous mutations can lead to resistance to an antibiotic by modifying the target of action or its expression level, or by up-regulating resistance genes [2]. Antibiotic resistance mainly occurs due to chromosomal mutation [3]. The transmission of resistance essentially occurs vertically from the organism in which the mutation appears to its descendants, and therefore a progressive increase in resistance is observed rather than a rapid outbreak [2]. A direct way to bypass the resistance is to inhibit the mechanism that works behind it [4]. Eg, the strategy of delivering β-lactam antibiotics along with β-lactamase inhibitors allows the antibiotic to kill both the susceptible and resistant strains [4].

Antibiotic resistance leads to delay in the administration of effective therapy. One of the important factors in delaying effective therapy is the mismatch between empirical therapy and the antibiotic susceptibility test results [3]. The impact of multi- drug resistant organism is not just to the patients who are infected but to all patients who are being treated with empiric antibiotic regimen [2]. This leads to the loss of the use of narrow spectrum agents even for the treatment of common diseases. Due to this we are compelled to use older agents with reduced efficacy and high toxicity [3]. In human health, antibiotic resistance is responsible for the loss of effectiveness of antibacterial agents to the degree that they are not used empirically, worse outcomes from infection, treatment and prophylaxis failure and secondary costly effects on both healthcare delivery and therapeutic options [1].

REVIEW OF STUDIES CONDUCTED

Friedman N.D, Temkin. E and Carmeli. Y did a review on the topic "negative impact on antibiotic resistance". The study was conducted in Barwon Health, Geelong, Vic., Australia and Division of Epidemiology, Tel Aviv Sourasky Medical Centre, Tel Aviv, Israel. In this study they reached the conclusion that the emergence of resistant strains and MDR bacteria is more apparent in the last 20 to 30 years. The underestimated values of the actual magnitude of causative organism are reported as the majority of treated infections are not microbiologically diagnosed. It may affect the success of empiric therapy. Loss of effectiveness of antibacterial agents to the degree that they are not used empirically, worse outcomes from infection, treatment and prophylaxis failures and secondary costly effects on both healthcare delivery and therapeutic options.

Megraud F did a study on the topic "*H. pylori* antibiotic resistance prevalence, importance, and advances in testing". The study was a retrograde study conducted in the Northern and Southern parts of Europe. The study aim to review the prevalence of *H. pylori* resistance to various antibiotics, their clinical importance, and methods of testing, especially in light of the resistance mechanism. Triple therapy, including two antibiotics, amoxicillin and clarithromycin, and a proton pump inhibitor given for a week has been recommended as the treatment of choice. However, the above may fail due to various reasons. The main reason for failure was found to be *H. pylori* resistance to one of the antibiotics used (that is, clarithromycin). Then usage of metronidazole was found to be effective due to reduced risk for the development of resistance. Prevalence of *Helicobacter pylori* resistance to clarithromycin was studied. The essential risk factor for clarithromycin resistance is previous consumption of macrolides and if resistance is higher in children it is because there was increased prescription of these drugs, notably in children during the last decade essentially for respiratory tract infections. Prevalence of *Helicobacter pylori* resistance to amoxicillin was also conducted, in all of the surveys reported; resistance to amoxicillin is either null or less than 1%, indicating that it is very useful agent in treating *Helicobacter pylori* infections. Fortunately, plasmid-borne *beta lactamase* resistance to tetracycline is also very low, or even absent. Most of the studies Indicate the prevalence of double resistant strains. It was found that they were twice as frequent as expected resistance has never been encountered. The combination of proton pump inhibitor, amoxicillin and metronidazole has also been used.

For metronidazole susceptible strains, the eradication rate was similar to the association of amoxicillin – clarithromycin which is inferior to the combination with clarithromycin.

Kollef. H. M, Vlasnik. J, Sharples. l, Pasque. C, Murphy. D and Fraser did a study on "Scheduled Change of Antibiotic Classes- A Strategy to Decrease the Incidence of Ventilator-associated Pneumonia, to determine the impact of a scheduled change of antibiotic classes". The study was a T-test done on a sample size of six hundred and eighty patients. Used for the empiric treatment of suspected gram-negative bacterial infections, on the incidence of ventilator-associated pneumonia and nosocomial bacteremia. The study was conducted at a university-affiliated teaching hospital: Barnes-Jewish Hospital (900 beds). All patients undergoing cardiac surgery were included in the investigation. Patients were excluded if they were younger than 18year of age and if they were undergoing heart transplantation. In this patients were given with a third generation cephalosporin (ceftazidime) for the empiric treatment of suspected gram-negative bacterial infections before the surgery. After the surgery the patients were treated with quinolone (ciprofloxacin) for the same indication instead of empiric treatment with third generation cephalosporin. During the investigation, they demonstrated a scheduled change of antibiotic classes used for the empiric treatment of suspected gram-negative bacterial infections. It can significantly decrease the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. They also found a trend favoring a lower incidence of bacteremia attributed to antibiotic-resistant gram-negative bacteria among patients in the study group assigned to receive a scheduled change of antibiotic classes. They also observed there is no increase in lengths of hospital stay, or the development of multi organ dysfunction. It shows that patients receiving prior antimicrobial therapy had a greater incidence of ventilator-associated pneumonia caused by *Pseudomonas* species than did patients without previous antimicrobial therapy. Prior antibiotic exposure appears to increase the risk of ventilator-associated pneumonia by facilitating patient colonization with antibiotic-resistant pathogens. Therefore, it is biologically plausible that efforts directed at reducing such colonization could decrease the occurrence rates of ventilator-associated pneumonia caused by antibiotic-resistant bacteria. They concluded that reducing the use of third-generation cephalosporin may have decreased the occurrence of ineffective antimicrobial therapy for infections due to bacteria resistant to this class of antibiotics. Also the use of a quinolone class may have prevented the emergence of infections not previously suppressed by third-generation cephalosporins. This mechanism would be most important in patients colonized with gram-negative bacteria

resistant to the third-generation cephalosporins but sensitive to the quinolones. Also cannot exclude the possibility that the decrease in the overall rate of ventilator-associated pneumonia was due to factors other than the change in antibiotic classes. That is reintubation and the duration of mechanical ventilation was independently associated with the development of ventilator-associated pneumonia.

Baym. M, Stone. K.L, Kishony. R did a review on topic "Multidrug evolutionary strategy to reverse antibiotic resistance". In this they pointed that antibiotic treatment has two conflicting effects: the desired, immediate effect of inhibiting bacterial growth and the undesired, long-term effect of promoting the evolution of resistance. Resistance is frequently conferred by dedicated efflux pumps or antibiotic-degrading enzymes, which in turn can be countered by compounds that inhibit the resistance machinery. To use this strategy therapeutically, an antibiotic is delivered concurrently with resistance-inhibiting compounds; for example, a Beta-lactam antibiotic paired with an inhibitor of *beta-lactamase*. This allows the antibiotic to kill both resistant and susceptible strains, thereby potentiating the efficacy of the drug and diminishing the selective advantage of the resistance gene. Compounds have been discovered that inhibit a large variety of resistance mechanisms. The most clinically successful examples are the pairings of amoxicillin-clavulanic acid, ampicillin-sulbactam, and piperacillin-tazobactam to block serine *beta-lactamases*. Recently, this principle has been expanded to *Metallo-β-lactamases* with the discovery that *aspergillomarasmine A* inhibits *New Delhi metallo-beta-lactamase-1* and VIM-2, two clinically important enzymes that degrade β-lactams, including carbapenem antibiotics. Collateral sensitivity can occur directly through mutations in the antibiotic target. Drug pairs that target the same protein, such as quinolones and novobiocin (both DNA *gyrase* inhibitors); often show collateral sensitivity or cross-resistance. Here, the interaction occurs directly through the target: The amino acid changes that provide resistance to one drug increase or decrease sensitivity to the other. Collateral sensitivity can also occur through less direct means. It also highlighted the prevalent collateral sensitivity between aminoglycosides and other antibiotic classes. Both the import of aminoglycosides and the export of multiple antibiotics through intrinsic efflux pumps require the proton motive force. Therefore, when a strain evolves resistance to aminoglycosides by diminishing the proton motive force, it becomes more susceptible to other antibiotics, such as beta-lactams, quinolones, and tetracyclines, which are normally exported by the proton-force–dependent pumps. By adapting to the presence of one antibiotic, bacteria effectively specialize and can become less resilient to other antibiotics.

Ultimately, treating resistance will require a portfolio of strategies including drug discovery, resistance monitoring, and combinations of novel methods to invert the selection for resistance.

Daniel. A. E, Mekuria. A. Band Belachew. S. A did a review on the topic "Inappropriate use of antibiotics among communities of Gondar town, Ethiopia: a threat to the development of antimicrobial resistance". The study was based on cross-sectional survey and was conducted on a total of 650 participants in Gondar town, northwest Ethiopia from December 1, 2016 to January 30, 2017. The emergence of antimicrobial resistance, the main cause of morbidity and mortality from otherwise treatable infections, is largely attributed to the inappropriate use of antimicrobial. The study aim to document the extent of inappropriate use of antibiotics and its associated factors among the communities of Gondar, Northwest Ethiopia. Inappropriate use of antibiotics was found to be considerably high in the communities of Gondar, northwest Ethiopia. Taking into consideration the heightened importance of comprehensive knowledge in the rational use of antibiotics, different stakeholders working in the public health sectors should provide a comprehensive and customized education to the public to improve their knowledge about antibiotics. It is also essential to adopt a strong and explicit line of actions towards the accessibility of antibiotics without a valid prescription in community medicine retail outlets.

Kollef. H. M did a review on the topic "The Importance of Appropriate Initial Antibiotic Therapy for Hospital-Acquired Infections". An effective approach to antimicrobial de-escalation necessitates that clinicians be aware of the microorganisms that are most likely associated with infection and inappropriate antimicrobial treatment in their practice setting. This approach requires that hospitals have updated and accurate antibiograms reflecting the bacterial pathogens and their antimicrobial susceptibility encountered at the local level. Variability in the bacteria associated with hospital-acquired infections among hospitals, as well as within the wards of large hospitals, has been shown. Additionally, changing temporal patterns of nosocomial pathogens and antimicrobial susceptibility have been described, thus necessitating regular updating of these databases. Utilizing such data can improve the efficacy of antimicrobial therapy by increasing the likelihood that the appropriate initial antibiotic treatment will be prescribed. The de-escalation approach to empiric antibiotic treatment of patients with serious infections (e.g., severe sepsis, bloodstream infection, hospital-acquired pneumonia) also requires that clinicians be able to obtain culture

specimens before starting therapy. The subsequent culture results will allow the treatment to be narrowed appropriately once the pathogen responsible for infection and their susceptibility profiles are identified. Clinicians should consider initial treatment with combination antibiotic therapy to provide coverage for antibiotic- resistant bacteria if appropriate risk factors are present. These risk factors include prior therapy with antibiotics during the same hospitalization, the occurrence of the infection 5 or more days after hospital admission, having received intravenous antibiotic therapy at home, chronic hemodialysis or intravenous drug use, hospitalization in an acute care setting for 2 or more days in the 90 days before the current hospitalization, and residence in a nursing home or long-term care facility.

DISCUSSION

In order to control antibiotic resistance, certain steps have to be taken. They are as follows:

1) Countries where antibiotics are freely available without prescription a regulatory environment should be reformed. This reformation can be done by reclassification of antibiotics, whereby certain antibiotics in the watch list – which includes those antibiotics that are recommended as a first or second choice treatment for some infections – and all the reserved items. This means they would only be used in the most severe circumstances when all other alternatives have failed, for instance to treat life-threatening infections due to multidrug-resistant bacteria. To combat antibiotic resistance, antibiotic stewardship is another method. It is the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance. Hospital prescription audits, by an official regulatory body, should also be developed as critical entry points for improved antibiotic stewardship. Positive incentives and punitive measures should be introduced by regulators or hospitals following the antibiotic stewardship program to achieve prudent use. In the health-care sector, inappropriate use by professionals can be reduced with education and training, peer review and support, preauthorization of certain antibiotics by experts on infectious disease, better diagnostic tools, and use of resistance profiles.

2) Antibiotic should be used only for acceptable indication.

3) Culture sensitivity should be sought before determining the therapy.

4) Agents with greater spectrum of activity should be always selected and the dose and duration should be used for all antibiotic therapy.

5) Prophylactic use of antibiotics should be only used based on evidence based medicine.

6) Empirical use of antibiotics should be based on the local epidemiological data and its pattern of resistance.

7) Combination therapy using antibiotics should be indicated to extend the spectrum or to prevent emergence of resistant organisms.

In summary, the initial use of appropriate antibiotic therapy is an important determinant of outcome in hospitalized patients with infection. Treating physicians should work closely with their local infection control experts, clinical pharmacists, and infectious disease consultants to develop strategies aimed at optimizing the delivery of initial appropriate antibiotic treatment. Inappropriate use of antibiotics was found to be considerably high in the communities. Taking into consideration the heightened importance of comprehensive knowledge in the rational use of antibiotics working in the public health sectors should provide customized education for the public to improve their knowledge about antibiotics. It is also essential to adopt a strong and explicit line of actions towards the accessibility of antibiotics without a valid prescription in community medicine retail outlets. The hospital sector should improve stewardship through support and peer reviews, requiring preauthorization for certain antibiotics and ensuring that antimicrobial resistance profiles guide clinical decisions before and after the results of sensitivity tests. Finally, the right antibiotic for the right patient, at the right time, with the right dose, and the right route, causes the least harm to the patient and future patients.

CONFLICT OF INTEREST

There is no conflict of interest in our study.

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	***Ms. FPHAMIN. P. PHILIPOSE*** *FIFTH YEAR PHARM.D* *NAZARETH COLLEGE OF PHARMACY. THIRUVALLA P.O .KERALA .INDIA*
	***Ms. LAYANA ROY*** *FIFTH YEAR PHARM.D* *NAZARETH COLLEGE OF PHARMACY. THIRUVALLA P.O .KERALA .INDIA*
	***Dr. ABEL ABRAHAM THOMAS (corresponding author)*** *ASSISTANT PROFESSOR* *DEPARTMENT OF PHARMACY PRACTICE* *NAZARETH COLLEGE OF PHARMACY. THIRUVALLA P.O .KERALA .INDIA*