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Review Article

Rational Use of Antibiotics: An Area of Concern

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ABSTRACT

Most of the IPD (Inpatient department) and OPD (Outpatient department) patients receive a course of antibiotics either for treatment or prevention of infection or during discharge. The therapeutic outcome with an antibiotic depends mostly on choice of appropriate agent. The selection of antibiotic depends on causative agent, patient factors, clinical pharmacology of antibiotics and its cost effectiveness. Antimicrobial resistance (AMR) occurs when microbes like bacteria, parasites, viruses and fungi become resistant to antimicrobial drugs that are used for treatment of various diseases leading to decreased effectiveness, difficulty in treatment of disease and hence requiring multiple therapeutic options. Antimicrobial stewardship is a coordinated intervention, designed to improve and measure the appropriate use of antimicrobial agents, by promoting the selection of optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration. To strengthen the implementation of rational antibiotic use and reduction of antimicrobial resistance, WHO (World Health Organisation) in 2019 introduced "AWaRe" classification of antibiotics that includes details of 180 antibiotics classified as Access, Watch or Reserve, their pharmacological classes, Anatomical Therapeutic Chemical (ATC) codes and WHO Essential Medicines List status. One health approach is the collaborative effort of multiple health science professions to attain optimal health for people, domestic animals, wildlife, plants, and environment. Recently, WHO issued new guidelines regarding the use of antimicrobials in animals producing food, recommending the restricted use of such medicines in growth promotion or prevention of disease in healthy animals. Hence rational use of antibiotics is important for successful treatment outcome and prevention of emerging drug resistance for broader community.

Key words: Antibiotics, Antibiotic resistance, Antibiotic stewardship, AWaRe Classification, One health approach.

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INTRODUCTION

Recently, antibiotics are that group of drugs which are often prescribed, both in IPD and OPD. Most of the IPD patients receive a course of antibiotics either for treatment or prevention of infection; this is also true during discharge. The antibiotics share a major part of hospital's drug budget. Rational use of antibiotics is therefore extremely important to achieve desired patient outcome, prevent appearance of antibiotic resistance and increased cost of health care.

RATIONAL PRESCRIBING OF AN ANTIBIOTIC - THE ISSUES

Necessity of Antibiotics

Bacterial infections are always treated by an antibiotic. One must remember that infection is one of the many causes of fever and not all infections are caused by bacteria. A considerable portion of infections seen in general practice are of viral origin and antibiotics have no role in these patients. Even after establishment of bacterial infections, not necessarily an antibiotic is required because some bacterial infections resolve spontaneously.[1]

Selection of most appropriate antibiotic

The therapeutic outcome with an antibiotic depends mostly on choice of appropriate agent. This appropriate selection of antibiotic depends on causative agent, the patient factors, the clinical pharmacology of antibiotic and cost effectiveness of the antibiotics.

Determination of the causative agent depends on a combination of clinical skill (and a knowledge of both universal and local sensitivity patterns that helps in starting empirical therapy) and laboratory support. Laboratory reports should always be viewed in the light of clinical findings to distinguish normal flora, colonizers or contaminants from true pathogens.[2]

The patient factors which are taken into consideration while selecting an antibiotic are age, pregnancy, allergic history, organ function, genetic factors and compliance. For example, chloramphenicol is unsafe in neonates, tetracyclines and quinolones may cause adverse effects in growth of tissues and organs in children. Aminoglycosides leads to nephrotoxicity in elderly patients. Antibiotics selection in pregnancy is a major area of concern to safeguard the growing fetus. Allergy history should always be taken before selecting an appropriate antibiotic. Safer antibiotics selection and dosage modifications should be done for patients with hepatic or renal impairment. Genetic factors can raise the risk of adverse reaction (e.g. the acetylation and G6PD status).[3] The patient's adherence and compliance to antibiotics are important factors required to achieve desirable outcome and preventing resistance. Generally, compliance is better with once daily dosing and shorter duration regimen.[4]

The physician should have proper knowledge of the pharmacokinetic profile of the prescribed antibiotic, especially its ability to attain therapeutic concentrations at the site of infection. For example, moxifloxacin and gemifloxacin are not effective for the treatment of urinary tract infections, as they do not achieve adequate concentration in urine. Concentration dependent killing (CDK), time dependent killing (TDK), post antibiotic effect (PAE) and bactericidal-bacteriostatic

interaction are also the area of concern. The drug-drug interactions of antibiotics with other non-antibiotic drugs may produce barrier in optimum response.[5]

Nevertheless, a major concern remains the cost burden caused by prescribed antibiotics. While calculating costs, one should consider the total cost of therapy rather than the unit value of antibiotic i.e the cost per dose. In addition to this, the cost of drug administration, the requirement for performing TDM and the duration of hospital stay must also be taken into consideration.

Appropriate regimen of antibiotics (dose, route, frequency and duration of use)

In patients who are unable to take oral treatment, parenteral therapy is obviously indicated. But preferring parenteral treatment for severe sepsis, is not always true when antibiotics having good oral bioavailability are readily available (eg. Linezolid has 100% bioavailability). Studies showed that oral antibiotics are as good as parenteral antibiotics in specific infections.[6] The dose, frequency and duration depend on PK of drug, CDK or TDK, MIC and PAE.

Oral therapy has several advantages. This eliminates the risk of intravenous access related bacteraemia, phlebitis and pulmonary embolism, ancillary costs related to intravenous injections apart from pain. Oral therapy reduces the duration of hospitalization and the cost of treatment.[7]

The ideal term of antibiotic treatment is unclear in many situations. Most of the antibiotics are usually prescribed for a span of 5-7 days. However, it is unreasonable to stop the prescribed therapy, if the patient's symptoms have resolved, even after 3 to 5 days.[8]

Monitoring of effectiveness of therapy

An early evaluation (preferably 3rd or 4th day of treatment) of the response is essential to ensure if the patient is receiving suitable treatment and to further determine whether to stop, continue, change, modifying the dose or regimen. If the patient is responding well there is no necessity to change antibiotic even if the laboratory reports a resistant organism (the isolate may be a colonizer or a contaminant). On contrary, if there is no improvement in patient's condition, then a change in antibiotic should be considered, even if the laboratory reports claims it as sensitive organism. Sometimes, a patient might not respond to an antibiotic due to incorrect diagnosis and improper antibiotic selection, resistant strain, secondary infection, non-compliance to treatment etc. Whenever feasible intravenous therapy should be changed to oral therapy and vice versa if the patient's condition warrants it without hesitation.[9] The oral antibiotic should be selected based on clinical and laboratory findings.

Four types of changing from intravenous (IV) to oral treatment are:[10]

- ***Streamlining*** - here the IV antibiotic is changed to one with narrower spectrum which specifically targeting the offending pathogen confirmed by culture-sensitivity reports e.g., a third generation cephalosporin is changed to cloxacillin for staphylococcal infection.
- ***Sequential*** - the use of oral formulation of the IV antibiotic without any loss in potency e.g., changing from IV to oral ciprofloxacin.
- ***Step-down*** – Here, the IV antibiotic is changed to an oral agent of the same or different class of similar antibiotics with a reduction in potency e.g., changing from IV cefuroxime to oral cefuroxime axetil.
- ***Switch*** - here the IV antibiotic is changed to an oral formulation of another antibiotic without any loss in potency e.g., changing from IV ceftazidime to oral ciprofloxacin.

ANTIBIOTIC RESISTANCE

Antimicrobial resistance (AMR) takes place when microbes (like bacteria, parasites, viruses and fungi) become resistant to antimicrobial drugs that are used for treatment of various diseases. Irrational use (over use, under use, miss use and abuse) of antibiotics not only expose the patients at risk for therapeutic failure and serious adverse events but also endanger the entire globe by introducing antimicrobial resistant pathogens. Once the microbe develops resistance, the effectiveness of some common antimicrobials is decreased and even completely ineffective, the disease becomes difficult to treat, requires different/multiple therapeutic options that could be more toxic and expensive. In addition to this, lack of clean water, improper sanitation and continuous environmental exposure of pharmaceuticals and personal care products (PPCPs) also increases the chances of resistance. Treatment of common infections like pneumonia, diarrhoea, gonorrhoea, tuberculosis, HIV/AIDS and malaria, get affected due to this AMR. WHO has declared AMR as top 10 global public threats that need to be addressed urgently.

Many new initiatives have been launched by various agencies in India to combat this problem like Indian Clinical Epidemiology Network (Clen) has produced some quality data on antibiotic resistance in pathogens like pneumococcus, *H. influenzae* across the country, Indian Initiative for Management of Antibiotic Resistance (IIMAR started in March 2008) for promoting the rational use of antimicrobials, INSAR (Indian Network for Surveillance of Antimicrobial Resistance) consisting of 20 private and public laboratories generates quality data on AMR all over the country etc. An ICMR expert committee was formed in 2009 to combat the problem of antibiotic resistance, while an Indo-Swedish workshop was organised in New Delhi on 2 February 2010 to evaluate a joint strategy for confinement of AMR.

ANTIMICROBIAL STEWARDSHIP

"It is a coordinated intervention, designed to improve and measure the appropriate use of antimicrobial agents, by promoting the selection of optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration" (definition by SHEA, IDSA, PIDS – April 2012).[11]

An effective antimicrobial stewardship program relies on appropriate

- appropriate drug selection,
- optimum dosing,
- suitable route of administration and,
- proper duration of antimicrobial therapy,

For a successful antibiotic stewardship program, a team work of knowledge regarding scope and areas of unmet needs, effective strategies and updated recommendations as well as guidelines, are required. Pharma industries, international organizations and governmental health policy makers have all those competency and skills for implementing effective antimicrobial stewardship. When this antimicrobial stewardship program coupled with comprehensive infection control program it maximally curbs the emergence as well as transferal of antimicrobial resistant pathogens. WHO, national and international organization (like SHEA, IDSA, and PIDS), and government now strongly encourages healthcare institutions to develop stewardship programs.

In 2012, the first initiative was taken in India to combat antimicrobial resistance by formulating a document, known as the "Chennai Declaration", to improve the overall awareness regarding AMR. After this, ICMR started a program named "Antimicrobial Resistance Surveillance and Research Network" (AMRSN) in 2013 to accumulate nationwide evidence on antimicrobial resistance. Grounding on this data, in 2016, National Antimicrobial Treatment Guidelines document was released.

These guidelines were helpful in using antibiotics more judiciously and have strengthened the antimicrobial stewardship practices.

In these upcoming years, other stewardship programs like Indian Clinical Epidemiology Network, and IIMAR (in collaboration with WHO) have been launched to generate more standard data on antimicrobial resistance. Initiatives were also taken to get rapid diagnostics which could be affordable in combating AMR. India has also implemented National Action Plan (NAP) on Antimicrobial Resistance, from 2017 to 2021, for improving antibiotic prescribing by doctors and health care workers. Another step that was taken in this respect, was by the hospital accreditation bodies like National Accreditation Board for Hospitals (NABH), Joint Commission International (JCI), etc., i.e these bodies are to implement Antimicrobial Stewardship Program (AMSP), which is now an essential prerequisite for a hospital to get accredited.

AWARE CLASSIFICATION

Rational use of antibiotics, through antimicrobial stewardship, is one of the most relevant interventions that ensure appropriate treatment, limits further development and outspread of antimicrobial resistance.[12]

To strengthen the implementation of rational antibiotic use and reducing antimicrobial resistance, WHO in 2019 introduced the "AWaRe" (Access, Watch, Reserve) classification of antibiotics, those are in its Essential Medicines List. Total 180 antibiotics are classified as Access, Watch or Reserve, with details of their pharmacological classes, ATC (Anatomical Therapeutic Chemical) codes and WHO Essential Medicines List status. This classification can be used as an interactive tool for antibiotic stewardship, at national and international levels for adequate support of antibiotic monitoring and its appropriate use.[13]

- Access group includes 48 antibiotics like amoxicillin, ampicillin, nitrofurantoin, doxycycline, gentamicin, clindamycin, metronidazole etc. These antibiotics are effective against numerous commonly susceptible microorganisms and have less resistance potential than antibiotics in the other two groups.
- The Watch group includes 110 antibiotics like azithromycin, cifixime, ceftriaxone, ciprofloxacin, vancomycin, meropenem etc. These antibiotics have higher risk of bacterial resistance and are recommended for some specific infectious disease, as an essential first or second-choice empiric treatment options. The antibiotics of this group should be regarded as the essential targets of stewardship programs and monitoring.
- Reserve group antibiotics should be used as "last resort" options. The antibiotics and antibiotic classes of this group should be reserved for the treatment of confirmed or suspected infections due to multi-drug-resistant organisms, to highly specific patients and situations when no suitable alternatives are available. For examples - linezolid, polymyxin etc.

ONE HEALTH APPROACH

This is worth mentioning, the emergence of antimicrobial resistance is not only due to irrational antimicrobial use in human, but also irresponsible use of antimicrobial in animal, live stocks and various environmental sectors; and then the dissemination of resistant bacteria between these sectors and across the world. This is because of similarity in antimicrobials (or antimicrobials classes) used in humans and animals. For example, the mass medication (for prevention or treatment) of animals with critically important antimicrobials for humans, like third-generation cephalosporins and fluoroquinolones; and the long-term use of medically important antibiotics, such as colistin, tetracyclines, and macrolides, for growth promotion. This overriding interconnecting source and spread of antimicrobial resistance, introduce the logical notion of 'One Health approach' to address this global threat.

"*One Health is the collaborative effort of multiple health science professions to attain optimal health for people, domestic animals, wildlife, plants, and our environment*" (Definition). This is aimed to safeguard the existing antimicrobials by (1) limiting their irrational use (by adopting regulation and policy, surveillance, stewardship etc), (2) implementing regulation and guidelines on animal husbandry (3) restricting propagation of infection (by improving sanitation and hygiene), (4) reduction of environmental pollution (from industrial, domestic, and farm contains antimicrobials waste); to reduce emergence of antimicrobial resistance, to achieve continuous and assured antimicrobial effectiveness and effective health outcomes.

Recently, focusing on 'one health approach', guidelines are introduced by WHO on use of therapeutically important antimicrobials in animal husbandry. This aims to prevent apperance of antimicrobial resistance and to protect effectiveness of antimicrobial, used in human disease. According to the recommendations, the antimicrobials used to promote growth and prevent disease in healthy animals, should be stopped.

CONCLUSION

Extravagant use of antibiotics has resulted in the rapid rise of multi-drug resistant bacteria - the so called "superbugs" whereas the production of newer antibiotics to combat those is till slower. The infections caused by these superbugs are difficult to treat, leading to increase complications and fatality rates. Recently, universal and national battles draw an attention globally to the rational use of the available antibiotics and antibiotic stewardship programs. The goal of these stewardship programs is to maintain the effectiveness of antibiotics by implementing their appropriate and optimum use. The therapeutic aim of antibiotics therapy is not limited to only the successful treatment outcome in a given patient, rather it also encompassing the prevention of emerging drug resistance for broad community. Recently WHO has issued new guidelines regarding the use of antimicrobials in animals producing food, recommending the restricted use of such medicines in growth promotion or prevention of disease in healthy animals. Therefore, it is essential to use the available antibiotics in an optimal manner to limit the spread of these superbugs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AMR: Antimicrobial resistance; **WHO:** World Health Organization; **ATC:** Anatomical Therapeutic Chemical; **IPD:** Inpatient department; **OPD:** Outpatient department; **CDK:** Concentration dependent killing; **TDK:** Time dependent killing; **PAE:** post antibiotic effect; **TDM:** Therapeutic drug monitoring; **MIC:** Mean inhibitory concentration; **PPCPs:** Pharmaceuticals and personal care products; **INSAR:** Indian Network for Surveillance of Antimicrobial Resistance; **AMRSN:** Antimicrobial Resistance Surveillance and Research Network; **ICMR:** Indian council of medical research; **NABH:** National Accreditation Board for Hospitals; **NAP:** National Action Plan; **JCI:** Joint Commission International; **AMSP:** Antimicrobial Stewardship Program.

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