



A Review on Management of Antibiotic Resistance: A Slow and Progressive Pandemic

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ABSTRACT

Resistance in microbes against antibiotics is a slow but a constant process which can occur via different modes according to the type and strain of the particular organism; from one species to other thus influencing selection of antibiotic to treat the infection, resulting into exposure of variety of antibiotics providing a competitive advantage for mutated as well as non-mutated strains. Resistance in microbes against antibiotics can occur via different modes depending upon the type and strain of that particular organism. In certain types of microorganism natural resistance can be found which was present before the discovery of antibiotics; certain types of microbes undergo genetic mutations over the time and hence develop resistance also some of them have been evolved as superbugs. Antibiotics Resistance is a continuous process from one species to other thus influencing selection of antibiotic to treat the infection, resulting into exposure of variety of antibiotics providing a competitive advantage for mutated as well as non-mutated strains. World Health Organization has taken several steps to avoid resistance chances. In this review an attempt has been made to figure out this alarming threat about antibiotic resistance, how can we preserve the antibiotics which are still non-resistance and ideal approaches to manage those disease which have been already reported to resistance to many of the available antibiotics. Medical professionals across the globe should follow the good practices while prescribing antibiotics, following the guidelines by WHO. Though in tough time several initiatives have been made between government, public and private sectors for the development of newer antibiotics.

Keywords: Antibiotics, Resistance, Mutated & non-mutated strains, World Health Organization.

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INTRODUCTION

Before the beginning of the 20th Century (pre-antibiotic era), almost every infectious disease were the main culprits for higher morbidity and mortality globally. The estimated life span of humans at that time was approximately 47 years. At that time diseases due to infection such as tuberculosis, pneumonia, smallpox, cholera, diphtheria, typhoid fever, syphilis, typhus, etc. were pandemic, similar to SARS, Ebola virus and Corona virus in recent times¹.

At that time healthcare professionals had no medication to cure such infection and as a result, human suffering was massive. Tackling with the bacterial diseases was such a difficult job to deal with beside having human body's own disease-fighting immune system, they were most of the times fatal and millions of populations died just because of a single bacterial infection.

With the advancement in medicine field a pool of antibiotics often referred as lifesaving drugs came into existence. These drugs had done wonders against those

life-threatening tiny creatures, but with the time they slowly mutate themselves against many of these lifesaving agents and apart from that somehow the malpractice and overuse of these drugs also contributes into this direction and now it has been emerging as an alarming threat to life that today we known it as "Antibiotic Resistance".

The data generated over the years reveals that approximately 700,000 people die every year globally due to infection caused by antimicrobial-resistant (AMR)⁽²⁾.

- About 19,122 patients were died due hospital-acquired infection as a result of multidrug-resistant bacteria during 2010 in Thailand.
- In 2015. due to first line antibiotic resistance, about 2,14,000 infants died because of infection resistant towards first line antibiotics out of which aminoglycosides and β - lactams were the highest reported worldwide.
- In the European Union region around 670,000 people have developed resistance against antibiotics which result into 33,000 deaths. The overall mortality was highest among infants and geriatrics.
- In South Africa (2018), it was found that a commonly located blood bacterium that is *Klebsiella pneumoniae* has been resistant to common antibiotics like β - lactams. It was also found that out of 12 isolates of bacterium, one case was reported to be resistant against carbapenems.



- In 2019, due to carbapenem-resistant (CR) infection high mortality rate was reported among the patients having bloodstream infection (BSIs) across African and Asian continent ².

Antimicrobial resistance is not just a setback that affects the healthcare sector, but it is an economical and global issue too that will impact future also. An estimation is made by World Bank about the heavy losses to global economy due to Antimicrobial resistance by 2050.

In this review we tried to figure out this alarming threat about antibiotic resistance, how can we preserve the antibiotics which are still non-resistance and ideal approaches to manage those disease which have been

already reported to resistance to many of the available antibiotics. As we know that it has been long ago while a new class or new antibiotic drug have ever been discovered. We will try to focus on the good hospital practices to access the antibiotics efficiently in an optimised manner and also the need of surveillance system to monitor their usage. This review also highlights the major initiatives taken by various autonomous healthcare bodies, Governmental and private bodies.

History of Antibiotic

The decade of 1950 - 1960 is designated as the “Golden age of antibiotic” discovery, as half of the antibiotics that we use today were discovered.

Table 1: Timeline of Introduction of Antibiotics Classes

Year of Introduction	Antibiotic Class	Year of Introduction	Antibiotic Class	Reference
1935	Sulphonamides	1956	Glycopeptides	3
1941	Penicillin's	1957	Rifamycin's	
1944	Aminoglycosides	1959	Nitroimidazoles	
1945	Cephalosporins	1962	Quinolones	
1949	Chloramphenicol	1968	Trimethoprim	
1950	Tetracyclines	2000	Oxazolidinones	
1952	Macrolides/Lincosamides/streptogramins	2003	Lipopeptides	

Antibiotics and Origin of Resistance

In 1942, Selman Waksman gave the term "antibiotic" meaning “against life” that is against the microbes and that is defined as any substance produced by microorganisms which is capable to restrict the growth of other microorganisms at higher strength. Antibiotics, also called as antibacterial or antimicrobial drugs that are particularly known to treat bacterial infection ⁴.

Antibiotics can be of different types like - antibacterial, antifungal, antiviral and antiparasitic etc.

- Broad-spectrum antibiotics are those which are effective against many infectious microbes, while narrow spectrum antibiotics are effective against few microorganisms.
- With advancement in medicinal chemistry, original compounds found in nature can be - modified chemically and hence semi-synthetic antibiotics are obtained, as is the case with β -lactams (example penicillin - produced by fungi – penicillium; cephalosporins, and carbapenems).
- Some antibiotics are synthesised from living microbes for example aminoglycosides, while some are purely synthesised synthetically like sulphonamides, oxazolidinones and quinolones.

Additionally, antibiotics can also be categorised into two broad classes based upon their action on microbes – Bactericidal agents which are capable of killing bacteria and bacteriostatic agents are known to inhibit the bacterial growth. But the major threat after this remarkable feat is the “antibiotic resistance”, that is the inability of these agents to treat/inhibit the infectious diseases caused by microorganisms for which they are discovered for.

Resistance in microbes against antibiotics can occurs via different modes depending upon the type and strain of that particular organism. In certain types of microbe's natural resistance can be found which was present before the discovery of antibiotics; certain types of microbes undergo genetic mutations over the time and hence develop resistance which is a continuous process from one species to other thus influencing selection of antibiotic to treat the infection, resulting into exposure of variety of antibiotics providing a competitive advantage for mutated as well as non-mutated strains. Substandard dosing, malpractice and misuse of antibiotics also promotes resistance. Major examples of resistant pathogens across the world are Methicillin-Resistant *Staphylococcus aureus* (MRSA), Multiple-Drug-Resistant Gram-Negative Bacilli (MDRGNB), Penicillin-Resistant *Streptococcus pneumonia* (PRSP), and Vancomycin-Resistant Enterococci (VRE) ¹.



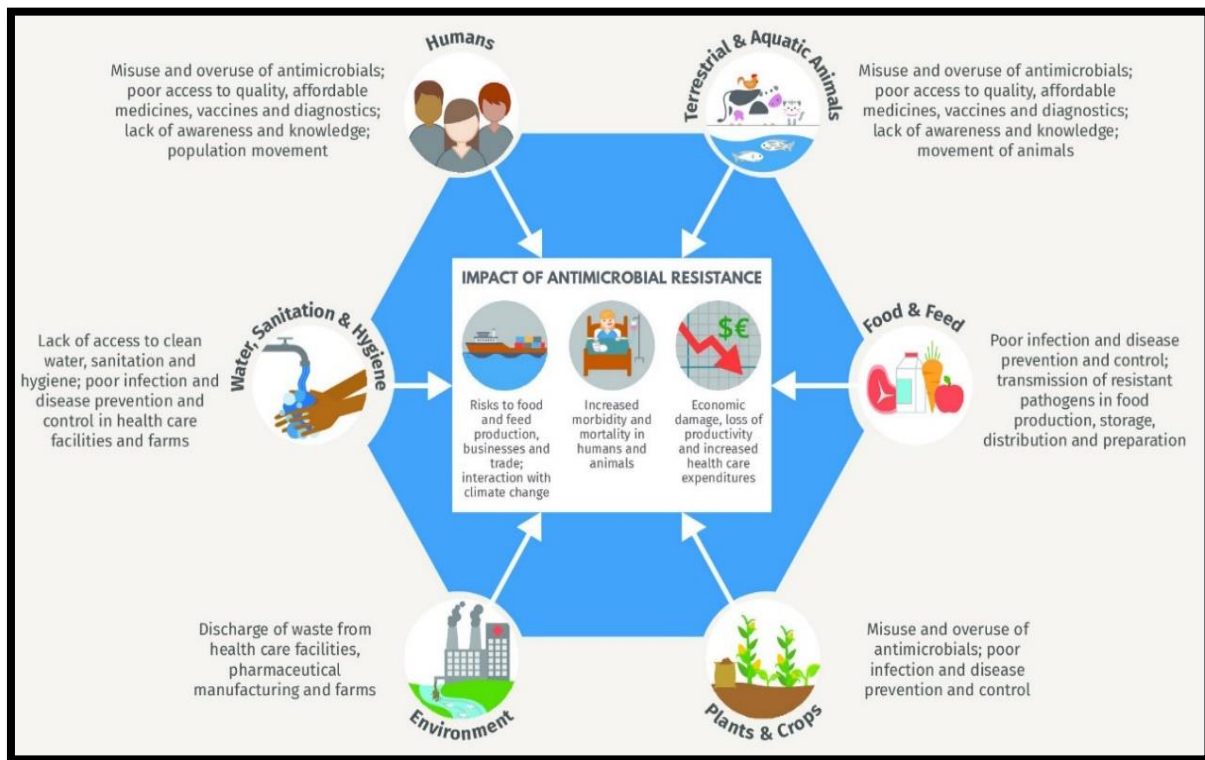


Figure 1: Drivers of Antibiotic resistance⁴²

Mechanism of Antibiotic Targets and Resistance

Antibiotics essentially targets the bacterial cell physiology and biochemical processes, resulting into inhibition of

their growth or cell death. The major antibiotic targets and resistance are:

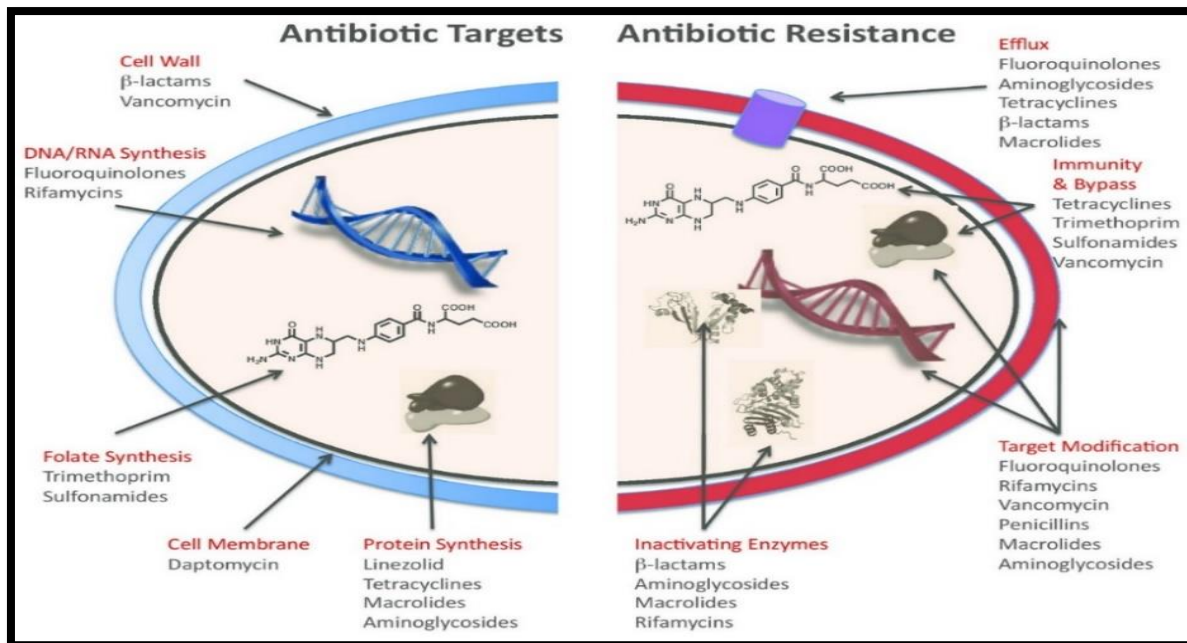


Figure 2: Mechanism of antibiotic targets and resistance⁴³

In eukaryotic cells (including those of humans), the bacterial cell targets are in dissimilar pattern or sometimes non-existent which means that antibiotics are comparatively nontoxic drugs. For example, antibiotics such as penicillins (β-lactam), carbapenems and cephalosporins blocks the bacterial cell wall synthesis, which is necessary for bacteria to survive but it is absent in

some of the higher organism. Antibiotics such as tetracycline, macrolide, aminoglycoside, and some other antibiotics mainly targets bacterial ribosome which is adequately different from that of eukaryotic ribosome hence, probability of cross-inhibition occurrence is minimal or negligible^{5,6}.

Table 2: Mode of Action and Resistance of Commonly Used Antibiotics

S.no	Antibiotic	Examples	Target	Mode(s) of resistance	References
1.	β -Lactams	Penicillins (ampicillin), cephalosporins (cephamycin), penems (meropenem), monobactams (aztreonam)	Peptidoglycan biosynthesis	Hydrolysis, efflux, altered target	5, 6
2.	Aminoglycosides	Gentamicin, streptomycin, spectinomycin	Translation	Phosphorylation, acetylation, nucleotidylation, efflux, altered target	
3.	Glycopeptides	Vancomycin, teicoplanin	Peptidoglycan biosynthesis	Reprogramming peptidoglycan biosynthesis	
4.	Tetracyclines	Minocycline, tigecycline	Translation	Monooxygenation, efflux, altered target	
5.	Macrolides	Erythromycin, azithromycin	Translation	Hydrolysis, Glycosylation, phosphorylation, efflux, altered target	
6.	Lincosamides	Clindamycin	Translation	Nucleotidylation, efflux, altered target	
7.	Streptogramins	Synercid	Translation	Acetylation (type A streptogramins), C-O lyase (type B streptogramins), efflux, altered target	
8.	Oxazolidinones	Linezolid	Translation	Acetylation (type A streptogramins), efflux, altered target	
9.	Phenicols	Chloramphenicol	Translation	Acetylation, efflux, altered target	
10.	Quinolones	Ciprofloxacin	DNA replication	Acetylation, efflux, altered target	
11.	Pyrimidines	Trimethoprim	C ₁ metabolism	Efflux, altered target	
12.	Sulfonamides	Sulfamethoxazole	C ₁ metabolism	Efflux, altered target	
13.	Rifamycins	Rifampin	Transcription	ADP-ribosylation, efflux, altered target	
14.	Lipopeptides	Daptomycin	Cell membrane	Altered target	
15.	Cationic peptides	Colistin	Cell membrane	Altered target, efflux	

The rise of 'Superbugs'

Resistance against multiple antibiotics is termed as multiple drugs resistance bacteria also referred to as superbugs. Bacteria shares their genetic information via different modes and develops this phenomenon which is most difficult to manage any of the infection caused by them. The different modes for the rise of superbugs are –

- Two bacteria make contact with each other and exchange their genetic material via pilus. This is called conjugation.
- A phylogram is a phylogenetic tree that has branch lengths proportional to the amount of character change.
- Bacteria have the habit to share the genes with each other, whenever a bacterium dies, they

release their genetic material in their surroundings which is so picks up by the other bacteria, having the genetic information about the causes of their death and so does they modify themselves further.

- They also share their genetic material with the help of viruses (via those viruses which do not cause any harm to bacteria) that is viral pass mechanism – virus infect a bacterium and harvests some of the genes to another bacteria, that's how they incorporate those genes into their body and develop additional resistance features.

Strategies to Optimize the Use of Key Antibiotics

Before prescribing to any antimicrobial therapy at first identify that the disease is caused by microbes or not and/or whether it is infectious or not –

Then following proceedings can be made -

- Initiate the examination with the clinical diagnosis and other tests like gram staining can be performed to get the précised results.
- Identify the infection and its causative organism.
- Check the suitable antibiotic agent active against the so identified microbes causing infection or illness. Look for the spectrum of activity of so prescribed antibiotic also the chances of drug resistance, if any.
- Look for the factor that can affect the selection of drug and dose, like renal function, drug/food interactions, allergy, pregnancy and lactation ⁽⁷⁾.
- Ensure that therapeutic dose is prescribed. In case of any doubts, seek the advises of specialists - clinical microbiologist or infectious diseases Physician. Formularies can also be used as reference.
- Estimate the extent of treatment.
- Monitor whether the treatment given is effective or not.

Selection of Antibiotics

Selecting an antibiotic against any infection have always been the matter of special attention as wrong choices and improper dosing is like an open and free invitation to infectious microorganisms. Therefore, the choice of antibiotic depends upon the exposure of that to the causative organism. But there exists some of the infection that can be treated by not just one but of several drugs. For such cases the selection can be made based on drug's efficacy, toxicity, rapidity of action, pharmacokinetics and cost. The antibiotic treatment chosen must be based on diagnostic data regarding the nature of disease ⁸. In case of disease caused by a single microorganism to which the clinical diagnosis is well understood by the physician suitable choice of antibiotic medication can be made based upon the data so available e.g., scarlet fever, typhoid, anthrax, etc ⁹.

However, for the diseases which are caused by the spectrum of bacteria such as pneumonia, meningitis and urinary tract infection, the physician must rely on the bacteriological diagnosis and initiate the therapy accordingly.

Good Practices for Emergency Situations

When the causative agent is unknown and where any delay in initiating the therapy can cause serious illness or risk to

life, antimicrobial therapy can be given based upon clinically defined infection that can be justifiable ¹⁰.

Following directions can be considered:

- Do not run for the treatment immediately.
- Gather all the possible necessary information about microbial causes and specimens before proceeding to any therapy.
- Try to attain synergy.
- Look for all the possible drug interaction with other drugs and food.
- Revision of diagnosis and medication so given should be reviewed on a regular basis.
- Proper communication and availability of microbiological data should be provided if any alteration or cessation to the therapy is made.
- Less costly drugs should be used wherever possible ⁸.

Further the need of antibiotic therapy should be reviewed each day. As most of the antibiotic therapy infection requires only 5 – 7 days of therapy (simple UTI can be effectively treated with 3 days of medication) ¹¹.

Moreover, following practices should also be follow up –

If required intravenous (IV – broad spectrum) antibiotics can be given for 48 – 72 hours without any review and considering oral alternatives ^[10]. When fever defervescence (within 24 hours) or any other prominent clinical improvement is observed, then at this stage antibiotic therapy can be switched to IV narrow spectrum or oral antibiotic(s), any other suitable alternatives, or therapy can be halt in case if no infection is seen only after proper monitoring and diagnosis of the patient ¹².

Guiding Principles for Some Specific Strains (Multi-Drug Resistant Bacterial Pathogens)

There are several microbial strains which have gone almost resistant to all the typical and classical antibiotics that are mostly used. In order to manage infection caused by such strains several antibiotics are used which are specially meant to treat such, these antibiotics are called as 'reserved antibiotics' ¹³.

India has very high resistance rates to some of the broad-spectrum anti-microbials.

- The drug of choice (DOC) against the infection due to Methicillin- Resistant *S. aureus* (MRSA) is the glycopeptides i.e., Vancomycin and Teicoplanin ¹⁴.
- Linezolid is indicated for skin and soft tissue infection caused by MRSA can be used, also indicated for Vancomycin Resistant Enterococcus (VRE) -blood stream infection ¹⁵.



- For complicated skin infection due to MRSA, Daptomycin is indicated (not approved for treatment of VRE infection) ¹⁶.
- For nasal MRSA infection Mupirocin local application (intranasally bid x 5 days) is applicable.
- Doxycycline: Not a first line therapy for VRE infection. For susceptible isolates, not for bacteremia or endocarditis. It should not be used as monotherapy ¹⁷.
- Tigecycline has in vitro activity against a broad spectrum of Gram-positive and -negative bacteria, anaerobes as well as multidrug-resistant pathogens such as MRSA and VRE ¹⁸.

Following are the few combinations available to manage infection caused by *Carbapenem-Resistant Enterobacteriaceae* (CRE) strains -

- Polymyxins (Colistin and Polymyxin B).
- Tigecycline and Minocycline.
- Ceftazidime-avibactam.
- Ceftolozane-tazobactam ¹⁹.

Treatment with Antibiotic Combinations

It is advisable to opt for mono therapy wherever possible so as to avoid multiple drug antagonism and to minimise the undesirable side effects ²⁰. However, for some situations, combination therapy is required and that can be opted in order to -

- Avoid the development of resistance in case of long-term therapy for instance the treatment of tuberculosis, malaria, typhoid etc.
- Achieve synergistic effect, for example infective endocarditis.
- Manage multiple infection, when one drug is not effective against the pathogen.

- To reduce the dose of potentially toxic drugs.
- The choice of the drug should be that they act synergistically. The following combinations are synergistic –
 - β -lactam and Aminoglycoside antibiotic.
 - β -lactam antibiotic and β -lactamase inhibitor.
 - β -lactam antibiotic and Glycopeptide (vancomycin/teicoplanin).
 - Sulphamethoxazole and Trimethoprim ²¹.

Combination Therapy

Whenever there is any event of serious infection, it is always recommended to initiate the therapy with the combination of various broad – spectrum antibiotic drugs. The basic principle behind opting for the combination therapy is to prevent resistance, better therapeutic output and quick recovery from the infection ²².

Dose Optimization

The dose optimization approach reduces nephrotoxicity, length of hospital stays and mortality ²³. To optimise the dose several factors should be considered which includes PK/PD – characteristics, patient physiological data, infective agent(s) (microorganism) and site of infection ²⁴. PK data examination and regulation program lower the cost as well as reduce the events of adverse effects. It is advised to implement PK monitoring for aminoglycosides and vancomycin ²⁵.

Duration Optimization

Evidences suggests that optimising the duration of therapy with respect to the type of infection can produce effective therapeutic effects also facilitates to avoid automatic 10-14-day course of therapy ¹⁰, following is the recommended duration of therapy -

Table 3: Recommended Optimised Duration of Therapy for Various Infection

S. No.	Infection	Duration of Therapy	References
1.	Uncomplicated UTI	5 days	(12)
2.	Community acquired pneumonia	7 days	
3.	Ventilator associated pneumonia	8 days	
4.	CR-BSI Coagulase negative staphylococci	7 days	
5.	Acute Hemosteomyelitis in children	21 days	

Monitoring the Treatment

Before proceeding with the antibiotic drug therapy other options of therapy should also be considered with respect to therapeutic effect of treatment. As in some cases antibiotic treatment can be ineffective like drainage of pus, septic shock and hypoxia ²⁶.

There are several conditions to which antibiotic therapy alone is not sufficient to treat an infection, for example infection can reappear due to obstructive lesions unless they are surgically removed. Also, in some cases antibiotic therapy is not sufficient to drain an abscess, eradicate sequestra or calculi. Sometimes treatment can also be failed due to development of resistance or poor tissue



penetration, when infection is caused due to superbugs or in case of mixed infection, e.g., phlebitis²⁷.

Effects of Treatment and Laboratory Control

In order to assess the effectiveness of the therapy clinical outcomes must be considered. It is good to determine that whether the organism causing the infection has been eradicated or not, for that repeated cultures are recommended^{26, 28}.

Antibiotic Cycling

“Antibiotic cycling” stands for the scheduled elimination and swapping of a specific antibiotic or a whole antibiotic class to avoid chances of development of resistance. Cycling is an effort at controlled heterogeneity of antimicrobial use to minimize antibiotic selection pressures. Concerns about allergies, adverse drug events and conflicts with national guidelines have led to 10%–50% of patients in cycling programs to receive “off-cycle” antimicrobials, resulting in poor outcomes and reduced effectiveness²⁹.

Antibiotic Use Measures

Antibiotic use can be measured by two strategies, days of therapy (DOT) and defined daily dose (DDD)³⁰.

- DOT is a cumulative sum of days for which any quantity of a specific antibiotic drug is administered/dispensed to a particular patient divided by a standardized denominator (patient days)³¹.

- DDD estimates the use antibiotic in hospitals by quantifying the total number of grams of each antibiotic purchased/dispensed/administered during a period of interest divided by WHO assigned DDD^{30,32}.

“Compared to DOT, DDD estimates are not appropriate for children and those with reduced drug excretion such as renal impairment.”

Swapping of Therapy: Parenteral to Oral

Antibiotic therapy for patients with serious infection/illness is usually starts with parenteral therapy after hospitalisation. The switching should be considered when there is a gram-negative bacteraemia, hospital acquired infection, intra-abdominal infection, pneumonia, skin and soft tissue infection and urinary tract infection. The individual physician can obtain appropriate culture before starting antibiotics and review antibiotic use after 48-72 hours¹⁰.

The swapping of IV to oral therapy decreases the risk of IV associated complications like thrombophlebitis, catheter related infection and improves the outcome of the patient. It also promotes earlier discharge and saves the health care costs³³.

Enhanced oral bioavailability among certain antibiotics—such as fluoroquinolones, oxazolidinones, metronidazole, clindamycin, trimethoprim-sulfamethoxazole, fluconazole, and voriconazole—allows switching to oral therapy once a patient meets defined clinical criteria¹².

Table 4: Some Antibiotic Drugs and Their Dosing IV v/s ORAL

S. No.	Antibiotic drug	Usual IV Dose	Usual Oral Dose	References
1.	Ampicillin	1-2 g IV QID	500 mg – 1 g oral TDS	(12)
2.	Azithromycin	500 mg IV daily	300 mg oral daily	
3.	Benzyl penicillin	1.2 g IV QID	500 mg oral QID	
4.	Cephazolin	1 g IV TDS	500 mg oral QID	
5.	Ciprofloxacin	200-400 mg IV BD	250-500 mg oral BD	
6.	Flucloxacillin	1g IV QID	500 mg oral QID	
7.	Lincomycin	600-900 mg IV TDS	300-600 mg oral TDS	
8.	Fluconazole	200-400 mg IV daily	200-400 mg oral daily	
9.	Metronidazole	500 mg IV BD	400 mg oral TDS	

Strategies to Manage the Spread of Multi-Drug Resistant Organisms (MDRO)

- Effective laboratory diagnosis and reporting of MDRO.
- Effective infection monitoring and control in ICUs
- Prevent spread of infection by using Gowns, face mask and gloves.
- Proper Hand Washing (alcohol based) and use of sanitizers.
- Restrict/ Limit the use of 3rd generation cephalosporins as much as possible³⁴.

Steps to Slow Down the Spread of Resistance

The role of vaccination, safe sex, food hygiene, hand washing, clean water, and prudent use can prevent the spread of AMR.

Vaccination

Routine immunization is the foundation for stronger, resilient health systems and universal health coverage. Vaccines protect against more than 25 debilitating diseases, including measles, tetanus, meningitis, and typhoid and every disease that is prevented by vaccination is an antimicrobial medicine avoided⁷.



Safe Sex

Millions of sexually transmitted infections (STIs) are acquired every day worldwide due to proper precautionary measures. These can be simply avoided by the use of condoms which offers protection against STIs, including HIV and Gonorrhoea, as both of which are showing alarming levels of resistance to treatment globally ⁷.

Food Hygiene

Food can become contaminated at any point during slaughtering, harvesting, processing, storage, distribution, transportation and preparation. Inadequate food hygiene can lead to potentially fatal foodborne diseases and death. Improved education in the safe handling of food is a key measure in preventing these diseases as well as in containing the spread of antimicrobial resistance.

Hand Washing

Effective infection, prevention and control (IPC), including hand hygiene, is the basis of high-quality health care and one of the most effective ways of reducing the spread of antibiotic resistant organisms. This is particularly true in health-care settings, where vulnerable and sick patients are more susceptible to developing drug resistant infection. Every infection prevented through hand washing is a medicine avoided and the threat of resistance reduced ⁷.

Clean Water/Sanitation

Sanitation is a basic component of good healthcare. Despite this, levels of global sanitation are inconsistent. Poor sanitation often led to the transmission of diseases such as cholera, diarrhoea, dysentery and hepatitis A. It can also exacerbate the spread of antimicrobial-resistant infection. Lack of clean water further compromises sanitation levels.

Open defecation, discharge of untreated waste water from on-site sanitation systems and health-care facilities can lead to the release serious pathogens into environment which boosts deadly infection and ultimately led to use of antibiotics, that gives an exposure to bacteria to develop resistance thereby increasing levels of antimicrobial resistance. Also, at antimicrobial manufacturing plants, residues must be carefully handled and disposed-off to minimise the risk of polluting the environment and ecosystem ³⁵.

Practical Use

Although AMR is a natural part of evolution, the misuse and overuse of antimicrobials in people and animals, often without any professional oversight, is accelerating this process. Misuse includes people taking antibiotics for viral infection like colds and flu and healthy animals being given antimicrobials to promote growth or to prevent disease ⁽⁷⁾.

Use of Antibiotics during COVID – 19: Present Scenario

With the outbreak of global pandemic Novel Corona Virus Disease (nCOVID-19), which is mainly affecting the

respiratory tract and having no specific treatment or any other medication available yet, this disease is being somehow managed completely on the basis of symptoms by the use of various antibiotics. The confusion and uncertainty arise with COVID-19 pandemic as it mainly targets the respiratory system so the patients with mild symptoms of COVID-19, acute bronchitis, common cold or flu and some other infectious diseases associated with the system, they received antibiotic medications although knowing the fact that most of them are caused due to viruses.

The collected data across different countries reveals that the use of antibiotics have been increased rapidly which is contributing towards the exposure of various antibiotics among different populations which will somehow ultimately leads to long term antibiotics resistance. Several factors like encouraging the use of antibiotic in the absence of proper clinical treatment about COVID-19 infection, premature type surrounding possible therapies for COVID-19, by some media reports and other sources by promoting the use of antibiotics like azithromycin in combination with the drug hydroxychloroquine, despite having no proper clinical evidence for their effectiveness. The huge shift towards telehealth consultations during the pandemic could also exacerbate antibiotic overprescribing. Many experts now fear the global effort to keep AMR in check could face a setback during the pandemic ³⁶.

Rational Use of Antibiotics

Prescribing the right drug(s), in adequate dose for the sufficient duration that is appropriate for the clinical needs of the patient at lowest cost is the rational use of drug. The goal of rational use of antibiotics is to ensure that the use is appropriate but not to reduce their use ³⁷.

Antibiotics are of finite resource and precious to tackle many serious infectious diseases but the benefit of their use must be evaluated against the risks for society and the patient. Importantly, rational use of antibiotics also means that it should be accessed but not exceeded as both the aspect are the integral parts of an effective response to ensure justifiable access to antibiotics for their effectiveness which is applicable for both human and animal use. Moreover, the matter of their access should not be seen as being at odds with rational use, as there is a positive correlation between antibiotics resistance and their consumption ³⁸.

The ATC (Anatomical Therapeutic Chemical) Classification

According to this classification drugs are divided into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics. Each drug is assigned at least one ATC code, which are classified into groups at five different levels ³⁹.



Table 5: Classification of Few Antibiotics Based on ATC Classification System

S. No.	ATC classification	ATC category	Description	References
1.	J	General anti-infectives for systemic use	1 st level, anatomical main group	39
2.	J01	Antibacterials for systemic use	2 nd level, therapeutic main group	
3.	J01C	Beta-lactam antibacterials, penicillins	3 rd level, therapeutic/pharmacological subgroup	
4.	J01C	A Penicillins with extended spectrum	4 th level, chemical/therapeutic/pharmacological subgroup	
5.	J01C A04	Amoxicillin	5 th level, subgroup for chemical substance	

Table 6: Examples of Some Antibiotics with their Defined Daily Doses

S. No.	ATC classification	ATC drugs	Defined Daily Dose	References
1.	J01C A04	Amoxicillin	1 g (oral or parenteral)	39
2.	J01M A06	Norfloxacin	0.8 g (oral)	
3.	J01M A02	Ciprofloxacin	1 g (oral) 0.5 g (parenteral)	
4.	J01F F01	Clindamycin	1.2 g (oral) 1.8 g (parenteral)	
5.	J01C A12	Piperacillin	14 g (parenteral)	

WHO Response to Antibiotic Resistance

WHO constituted a global action plan (GAP) on antimicrobial resistance, which was adopted at the World Health Assembly (WHA) in 2015. The goal of the GAP is to ensure the successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way and accessible to all who need them ⁴⁰.

The Objective of Global Action Plan for Antibiotic Resistance

- To spread awareness and understanding of Antibiotic Resistance.
- To gather more knowledge about AMR via surveillance and research.
- To minimise the incidences of infection.
- To optimize the use of antimicrobial agents.
- To develop the economic case for sustainable investment that takes account of the needs of all countries, and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

WHO's AWaRe Tool

WHO has developed a new tool, called AWaRe (Access, Watch, and Reserve), formed by the WHO essential medicines list, to -

- reduce the spread of antimicrobial resistance (AMR).
- limit the use of drugs which are at the highest risk of resistance.
- antibiotic-related adverse events.
- monitor the drug costs.
- increase the use of antibiotics in the countries where supply and availability is low ⁴¹.

Drugs falling under this list includes –

- Aware list includes - amoxicillin and cloxacillin these drugs should be promoted for increased use in several low-income countries, emphasizing that the under use of life-saving antibiotics is as dangerous as AMR.
- Watch list includes - fluoroquinolones that is still able to fight multi- (MDR) or extensively drug-resistant (XDR) bacteria.
- Reserve list includes - ceftazidime-avibactam and polymyxins, which should be only used when all other options fail ⁴¹.

WHO also directs all the nations to adopt this tool to strike a balance between accessing the life-saving antibiotics and drug resistance by reserving the use of some antibiotics for the hardest-to-treat infection.



AWaRe Five-Year Goal Outline

- All countries should report antibiotic use by 2023.
- To limit 60% of global antibiotic consumption to drugs from the "access" category.

Currently 65 countries track antibiotic use, and only 29 of the 65 meet the 60% access antibiotics goal. Out of those 29, Brazil is the largest ⁴¹.

The Global Antibiotic Research and Development Partnership (GARDP) initiative

Global Antibiotic Research and Development Partnership (GARDP) is a non-profitable public health research and development (R&D) organization established in 2016. Which is co-founded by Drugs for Neglected Disease initiative (DNDi) and the World Health Organization (WHO). It is a core element of the global action plan on Antimicrobial Resistance (AMR) ².

The main aim of the organisation is to bring together the private and the public sectors in order to develop new treatments against bacterial infection. Hence, they ensure responsible and sustainable access, addressing the public health impact of antibiotic resistance ².

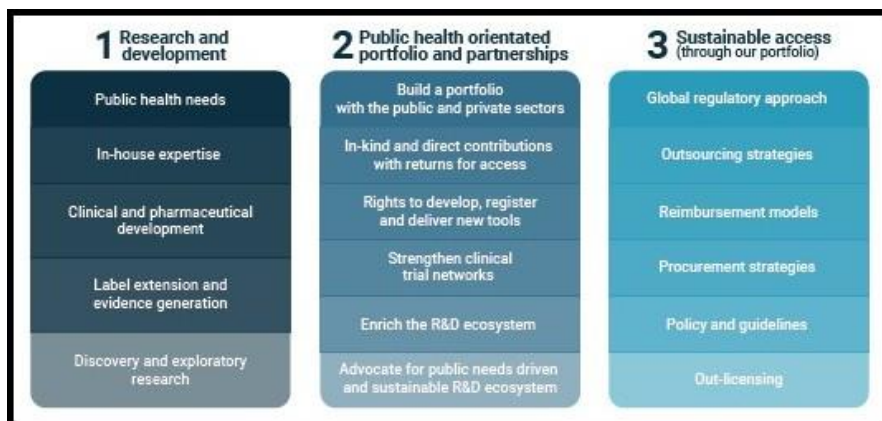


Figure 3: Strategic Pillars of GARDP²

Interagency Coordination Group (IACG) on Antimicrobial Resistance Recommendations

Interagency Coordination Group (IACG) on Antimicrobial Resistance Recommendations was set up by United

Nations Secretary-General in order to improve coordination between international organizations and to ensure effective global action against AMR ⁴².



Figure 4: Recommendations by IACG on Antibiotic resistance⁴²

CONCLUSION

Being thermostable and enrich with nutrient material bacteria loves human body to feed on as it provides all the favourable stuffs at a very single unit to rely upon for their growth and development. So does bacteria do, and as they feed some of them causes infection to their hosts too and to tackle this, we use antibiotics against which they slowly but progressively developed resistance.

Antibiotics are the global health arms race through which the medical professionals are battling against the

infectious community of the microorganisms to prevent the lethality among the human race. In fact, human body contain more bacterial cells than their own native cells but bacteria are continuously modifying themselves and also the rate of mutation and development of resistance against antibiotics is very rapid among the infectious community so as to increase the probability of winning this battle we consistently need to develop newer weapons (antibiotics) against them and also need to preserve those which are still non-resistance by practicing good antibiotics prescribing habit by accessing them when in need but not



in improper manner or quantity., and if we access them in excess them surely we will return back to pre-antibiotic era in which a mere infection would become pandemic very easily, example sore throat infection.

At present time the healthcare sector is facing a major threat of antibiotic resistant to which most of the antibiotic that we know has been now ineffective against many infection and infectious microorganisms have been developed/mutated themselves as superbugs. This threat will be borne by the masses to which mortality rate is elevating by each passing year and further upcoming years there may be delay in the development of any new class of antibiotic but to deal with the current situation several measure that have discussed in this review should be followed strictly to somehow slow down the further spread of resistance against those antibiotics which are still effective. Every medical professional should follow the good practices to access antibiotic and abide to the guidelines by WHO. Though in tough time several initiatives have been made between governmental, public and private sectors for the development of newer antibiotics.

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