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Antimicrobial Resistance: A simplistic overview

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ABSTRACT *Recent years have witnessed sudden upsurge in not only various kinds of infections, but also, resistance to antimicrobials. National and international health organizations have already started acting to fight the menace. There are five types of biological mechanisms of development of resistance, of which 'enzymatic degradation of drug' is the most common. Antimicrobial resistance spreads in the community via vertical evolution or horizontal gene transfer. Indiscriminate and irrational use of antibiotics, both in office and intensive care practice has been sighted as one of the most common causes of development of antimicrobial resistance. All people, including, patients, health care providers and healthcare facility owners should act in conjunction to fight this emerging global health problem.*

INTRODUCTION

Recent years have shown an upsurge in the number and severity of infections, both in the office and the intensive care practice. A major reason cited for the same is the increasing antimicrobial resistance. This review article aims to present the very basics of 'antimicrobial reisistance' in a very simplified manner which shall specially be useful for the beginners.

MAGNITUDE OF PROBLEM

In 2014, the World Health Organization published its first global report[1] on surveillance of antimicrobial resistance, with data provided by 114 countries and concluded that antibiotic resistance is a currently ongoing problem, occurring throughout the world, and jeopardizing the clinician's ability to treat even common infections.

The problem has been attaining such a significant magnitude that the Indian Academy of Pediatrics has launched a nationwide campaign 'Avoid Antibiotic Abuse' against it for the year 2014-2015.

GLOSSARY OF COMMON TERMINOLOGIES

MICROBES/BUGS – These are microscopic living organisms which multiply and spread rapidly. They include bacteria, fungi and parasites. They can cause disease in human beings/animals/plants or may simply be commensals.

ANTIMICROBIALS – These are natural or artificially developed drugs which are effective against microbes either by inhibiting their potential to grow (static) or by causing their death (cidal).

ANTIMICROBIAL RESISTANCE - Antimicrobial resistance (AMR) is resistance of a microbe to an antimicrobial drug that was originally effective for treatment of infections caused by it.

MULTI DRUG RESISTANT (MDR)/ SUPERBUGS–Pathogens resistant to multiple antimicrobials.

HISTORICAL PERSPECTIVES

Antimicrobial resistance has persisted even prior to the antimicrobials having been known to us. Penicillin was discovered by Alexander Fleming in 1928. In1940, several years before the introduction of penicillin as atherapeutic agent, a bacterial penicillinaseenzyme was identified by twomembers of the penicillin discovery team itself[2]. Once the antibioticwas used widely, resistant strains, capable of inactivatingthe drug became widespread. Later, penicillin was modified chemically to prevent cleavage and consequent drug inactivation by bacterial penicillinases (β-lactamases), as an effort to prevent resistance against it.

MECHANISMS OF RESISTANCE

The main mechanisms[2, 5] of antimicrobial resistance are;

(1)Alteration in cell membrane permeability to antibiotics (decreased influx or increased efflux of antibiotics) – eg. Macrolides, Quinolones, Tetracyclines

(2)Chemical modification of the target binding site(Phosphorylation, Acetylation,

Nucleotidation, Mono-oxygenation, ADP Ribosylation) -Glycopeptides, Quinolones, Rifamycins, Tetracyclines, and

(3)Enzymatic degradation of antibacterial drugs- Glycopeptides. Recently, resistance to carbapenems has been a seriously developing problem. The cause is the spread of genes that encode enzymes that destroy these antibiotics, in particular KPC[3, 4] (Klebsiellapneumoniaecarbapenemase) and NDM[4] (New Delhi metallo-beta-lactamase).

Resistance to the two most commonly used classes of antibiotics viz. Aminoglycosides and beta lactams, is mediated via all the above mechanisms. Besides, the other two mechanisms of antimicrobial resistance are;

(4)Target amplification- Trimethoprim and Sulfonamides

(5)Alteration of metabolic pathways– Sulfonamideseg. Some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), for the synthesis of folic acid and nucleic acid. Instead, like mammalian cells, they begin using preformed folic acid.

COMMON EXAMPLES

The most common class of antibiotics against which resistance has been demonstrated are the beta lactam group of antibiotics (including the Penicillin group, sulphonamides and even carbapenems off late) and the anti-tubercular drugs.

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Accordingly, the most common resistant pathogens[2, 6, 7] have been named colloquially after the class of antibiotics they are resistant to. **MRSA** (Methicillin – resistant S.aureus) and **MDR – TB** (Multi Drug resistant M. tuberculosis) are probably the most well-known, but others are **VISA** (Vancomycin-intermediate S. aureus), **VRSA** (Vancomycin-resistant S. aureus), **ESBL** (Extended spectrum beta-lactamases), **VRE** (Vancomycin-resistant Enterococcus), **XDR – TB** (Extremely Drug resistant M. tuberculosis), **TDR – TB** (Totally Drug resistant M. tuberculosis) and **MRAB** (Multidrug-resistant Acinetobacterbaumannii).

MECHANISMS FOR SPREAD OF ANTIMICROBIAL RESISTANCE

The two main mechanisms for spread of antimicrobial resistance are6;

VERTICAL EVOLUTION – It is the development of antimicrobial resistance by mutation of the existing genes.

HORIZONTAL GENE TRANSFER(HGT)– It is the acquisition of new resistance genes from other species by mobile genetic elements viz. plasmids, and transposons. Some new mobile genetic elements, including, integrons (integrative conjugative elements) and ISCR (Insertion Sequences with Common Regions) elements have also been discovered[7].

Modes of HGT may be transformation, transduction and conjugation. Transformation is the uptake of resistance genes naturally by certain bacteria. Transduction involves transfer of resistance genes from one bacterium to another via vectors ie,

bacteriophages. Conjugation involves transfer of resistance genes via sex pili from one bacterium to another.

CAUSES

(A) NATURAL (BIOLOGICAL)

Selective Pressure – Microbes carrying the resistance genes, escape the effect of antimicrobials and survive[8]. They replicate rapidly and their progeny quickly predominate the microbial population.

Mutations – Some mutations which arise offer a survival advantage to the microbes, which thus become resistant.

Gene transfer – Acquisition of resistance genes by horizontal gene transfer.

(B) ACQUIRED

Inappropriate use of antimicrobials – Inappropriate use of antimicrobials by healthcare providers for an undiagnosed condition or to pacify anxious and insistent patients and their relatives.

Inadequate diagnostics – Prescription of an antimicrobial 'just in case' or prolonged use of a broad spectrum antibiotic, empirically, promote 'selective pressure'.

Hospital use - The extensive use of antimicrobials, especially in intensive care settings, creates a fertile environment for the spread of antimicrobial resistance amongst the critically ill patients and their close contacts.

DIAGNOSIS OF ANTI-MICROBIAL RESISTANCE

Microbes isolated from the pathological specimens of patients, are cultured in presence of different antimicrobials to test the sensitivity and resistance patterns.

TREATMENT OF ANTI-MICROBIAL RESISTANCE

Treatment of antimicrobial drug resistance depends on the culture sensitivity results of the microbial growth and discretion of the treating physician.

INTERVENTIONS TO REDUCE ANTIMICROBIAL RESISTANCE

(A)ANTIBIOTIC PRESCRIPTION POLICIES

Antibiotic Cycling

Antibiotic cycling is the scheduled rotation of one class of antibiotics with one or more different classes with comparable spectra of activity[9, 10, 11]. This decreases resistance when an antibiotic is no longer used. This promotes antibiotic heterogeneity altering the selective pressure and preventing emergence of resistance to any particular antibiotic.

Restricted use

Antibiotic restriction is withholding a specific class of antibiotics[9] without the intent to reintroduce it at a later date. This decreases established resistance to the agent being restricted. It does not, however, create a mechanism to prevent the emergence of resistance to the antimicrobials that are not restricted.

Combination therapy

Combination therapy involves the use of more than one antimicrobial agents, with different mechanisms of action,to treat an active infection[9]. Combination therapy has been used successfully in treatment of tuberculosis and HIV (Human Immunodeficiency Virus) infection. However, toxicity may increase associated with combination therapy.

(B)ANTIMICROBIAL SREWARDSHIP

Antimicrobial stewardship is the ability to rationalize the use of antimicrobials by selecting the appropriate drugs, doses, duration and route of administration[12, 13]. Antimicrobial stewards seek to achieve optimal clinical outcomes alongwith minimizing drug toxicity, reducing the costs of health care for infections, and preventing emergence of antimicrobial resistance.

PREVENTION

All must work in co-ordination to prevent the growing menace of antimicrobial resistance. Certain simplistic measures to ensure the same are as follows;

Patientsshould:

- Take antibiotics without skipping the doses and complete the prescribed course of treatment.
- Not insist on or take antibiotics when the doctor does not think it to be necessary; for instance, for viral upper respiratory tract infection.
- Prevent infections by practising good hand hygiene.
- Getting vaccinated against potentially antimicrobial resistant bacteria (C. diphtheria, S pneumonia, N. meningitides, H influenza type B, C. tetani, S. typhi)[14].

Healthcare providers should:

- Prescribe antibiotics rationally – Make a microbiological diagnosis whenever possible, and optimize the drugs, doses and duration of therapy. Reassess the prescription as soon as the reports of culture sensitivity are available, de-

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pending on the clinical response of the patient.

- Stay aware of antibiotic resistance patterns in their facility.

- Follow hand hygiene and other infection control measures with every patient.

Healthcare Facility Administratorsand owners should;

- Adopt an antimicrobial stewardship program depending on the microbial flora and antimicrobial resistance patterns of their own health facility.

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