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Popular Article

Antibiotic resistance: A global threat to mankind

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Many bacterial species are evolving with the ability to tolerate antibiotics long before humans start to mass-produce them to prevent and treat infectious diseases (Sengupta et al., 2013). WHO has declared antibiotic resistance as one of the top 10 global public health threats facing humanity.

Antibiotic resistance in pathogenic bacteria can be categorized microbiologically or clinically. In microbiological resistance, there is presence of genetically determined resistance mechanism, either acquired or mutated, categorizing the pathogen as resistant. Whereas, in clinical resistance, there is a level of antimicrobial activity correlated with therapeutic failure.

Antibiotic resistance can be intrinsic or acquired. Acquired resistance occurs when naturally susceptible bacteria gain the genes encoding a resistance mechanism via mutation or the transfer of genetic material from other bacteria, of the same or a different species. For examples, all Gram-positive organisms are resistant to colistin. Similarly, the Enterobacteriaceae group is resistant to glycopeptides and linezolid. In case of intrinsic antimicrobial resistance, it is the innate ability of a bacterium to resist a class of antimicrobial agents (AMA), due to their inherent structural and functional characteristics, E.g. GNB resistant to vancomycin and *Pseudomonas aeruginosa* to a wide range of antibiotic (Costelloe et al. 2010). The infections caused by resistant microorganisms fail to respond to standard treatments. The single most important cause of development of acquired AMR is overuse and misuse of AMAs.

The antimicrobial resistance genes are carried on mobile genetic elements either via plasmids or transposons (‘jumping genes’). The transfer of antibiotic resistant genes can occur by several methods:

Conjugation: Direct cell-to-cell contact with plasmid transfer.

Transduction: Transfer of bacterial DNA by a bacteriophage, a bacterial virus that replicates in the bacterial cell and can incorporate a piece of bacterial DNA in the assembled viral particle, which is then transferred to the next bacterial cell that the virus infects.

Transformation: uptake of naked DNA from the environment.

Mechanisms of antibiotic resistance:

Bacteria develop antibiotic resistance by several mechanisms such as:

- Decreased permeability across the cell wall
- Efflux pumps
- Enzymatic inactivation
- Modifying target sites

Decreased permeability across the cell wall: Bacteria modify their cell membrane porin channels, either in frequency size or selectivity, thus preventing AMA from entering inside the cell. For examples, *Pseudomonas*, *Klebsiella* and *Enterobacter* against imipenem, Aminoglycosides and quinolones.

Efflux pumps: Bacteria possess efflux pumps which mediate expulsion of drug from the cell, soon after entry, preventing its intracellular accumulation. For example, *E coli* against tetracyclines and chloramphenicol, *Staphylococci* against macrolides and streptogramins, *S aureus* and *S pneumoniae* against fluoroquinolones

Enzymatic inactivation:

β-Lactamases: Hydrolysis of the β-lactam ring by these enzymes renders β-lactams inactive. There are many different types of β-lactamases that differ in their affinity for the particular β-lactam agents and classes, their structure and their response to β-lactamase inhibitors, such as clavulanic acid. The extended spectrum β-lactamases (ESBLs) produced by Enterobacteriaceae (e.g. *E. coli*, *Klebsiella* spp., *Enterobacter* spp.) makes infections even harder to treat as they confer resistance to penicillin and cephalosporins (first, second and third generation).

Carbapenemases: Carbapenems were stable to ESBL enzymes, but the rise in carbapenemase -producing Enterobacteriaceae (CPEs) have spread globally and has become endemic in many countries.

Modifying target sites:

Methicillin resistant *Staphylococcus aureus* (MRSA) and Pneumococci:

Target site of penicillin (PBP) gets altered to PBP-2a, which does not sufficiently bind to beta lactam antibiotics preventing inhibition of cell wall synthesis.

Vancomycin resistant enterococci (VRE)- mediated by *van gene (Van A/Van B), D-alanyl-D-*

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alanine side chain of peptidoglycan layer altered to D-alanyl-D serine or D-alanyl-D-lactate.

Concern of Antibiotic resistance

Increasing antibiotic resistance with little successful newer antibiotic development has now become a major global concern. In the past, when resistance to one antibiotic developed, another one could be used instead. Now, pan-resistant organisms, without new drugs to overcome them, are increasingly common. The species, which has become a major concern are the 'ESKAPE pathogens' (*Enterococcus faecium*, *Staphylococcus aureus*, *K. pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa* and *Enterobacter* spp.) especially relevant to nosocomial infections, as well as other *Enterobacteriaceae* (e.g. *E. coli*), *Mycobacterium tuberculosis* and *N. gonorrhoeae.*

Consequences of antibiotic resistance

Antimicrobial resistance has significant consequences for the health of the population as well as economic implications. It is estimated that around 25,000 people in Europe die each year from hospital-acquired infections caused by resistant bacteria (EARS-Net 2017). The increased population of people aged >65 years, along with their higher co-morbidity rates, require more antimicrobials for their complicated medical procedures. The growing number of untreatable infections and decreased effectiveness of empirical antibiotic regimens leads to increased morbidity and mortality with increased length of hospital stay causing a negative impact on the outcomes of many surgical and immunosuppressive treatments.

How can antibiotic resistance be overcome?

In recent years multiple strategies and campaigns are being taken up to combat antimicrobial resistance, which is being recognized as a significant threat at the highest political levels as well (MacGowan and Macnaughton 2017)

5 Strategies encompass the following.

- **Antimicrobial stewardship:** Judicious use of antibiotics needs to be improved on a global scale, including developing countries. Stopping the supply of over-the-counter antibiotic drugs and education of prescribers about antimicrobial resistance, may help to bring the antibiotic use under control.
- Increased global public awareness is also the need of the hour to reduce inappropriate demand.
- Veterinary use of antibiotic should be limited to treat infected animals and not applied for growth promotion.
- Surveillance of antibiotic use and resistance needs significant improvement to enable effective antimicrobial stewardship.
- Dosing strategies should follow pharmacokinetics and pharmacodynamics principles

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- Dosing regimens should follow Mutant prevention concentration (MPC) rather than just Minimum inhibitory concentration (MIC).
- MPC is 10-20fold higher than MIC for many classes of antibiotics
- Short courses of adequate doses of AMA

Decreased transmission of resistant strains and antibiotic resistance genes through effective infection control in healthcare settings: involving hand hygiene, isolation, screening and decolonization wherever effective.

Research and development: The identification and production of new antibiotics, especially with novel mechanisms of action, is needed to avert untreatable infections.

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