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Antibiotic-Resistant Infections: Understanding the Dynamics

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Abstract

Background: Antibiotic-Resistant (ABR) infections pose a serious challenge worldwide. The medical profession is in doldrum on account of its failure to successfully treat a large proportion of cases suffering from serious infections, resulting in considerable morbidity and mortality. The uncontrolled pandemic of COVID-19 has contributed to escalation of such infections, thereby adding fuel to fire.

Objective: To provide a state-of-the-art detail about the dynamics underlying the ABR infections.

Design: Review of the English medical literature concerning dynamics of ABR infections.

Salient Features: ABR may be natural or acquired and its transmission vertical or horizontal. It may be mono, poly, multi, extensive or even pan drug resistance. The mechanisms involved are resistance to entry of the antibiotic at cell membrane level, modification of target, activation of destructive enzymes against antibiotic and rapid exit of the antibiotic. Though there is a long list of World Health Organization prioritized bacterial pathogens, the acronym, ESCAPE, highlights the most important causative pathogens. Research is needed to explore additional mechanism(s) if any.

Conclusion: A good understanding of the dynamics of antibiotic resistant infections is mandatory to carry forward further work in the field and for intensifying strategies to prevent and control infectious diseases and antibiotic resistance, developing novel antibiotics and alternative and complementary pharmacotherapeutic strategies.

Keywords: Antibiotic misuse; Antibiotic resistance; COVID-19; Multidrug resistance; Novel antibiotics

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Introduction

Antibiotic-resistant infections are the bacterial infections whose causative pathogens have developed resistance to antibiotics that were earlier effective against them [1,2]. This problem started overtly following the increasing use of antibiotics. Today the huge burden of the resistant bacterial infections is responsible for considerable morbidity and mortality globally [3]. Recent hike in such infections during the ongoing pandemic of COVID-19 [4] has further added to the concerns of the medical profession in particular and policy-makers and executers in general.

A good understanding of the dynamics, especially mechanisms of development of antibiotic resistance, should contribute endeavors aimed at its prevention and control, better treatment options and development of novel antibiotics that are empowered to withstand the attempts of the bacterial pathogens to develop resistance.

This review aims at providing a brief though comprehensive update on the important dynamics of antibiotic-resistant infections with special reference to the resource-limited countries such as India, Nepal, Bangladesh, Sri Lanka and Pakistan.

Relevant Definitions

Antibiotics: These are the molecules that have the inherent capacity to kill the bacterial pathogens or by inhibiting their growth and multiplication. Their use must be restricted to treating or, sometime, preventing bacterial infections only. Their irrational use contributes to development of tolerance or resistance. Recently the WHO has classified antibiotics into three categories, namely "Access", "Watch" and "Reserve", to emphasize the importance of their optimal uses and potential for antimicrobial resistance [5].

Figure 1: Is an infographic (a clipped compound of information and graphics) representation of etiology of ABR.a

Antibiotic resistance: Antibiotic resistant is defined as the peculiar ability of the bacterial pathogen to render antibiotic(s) ineffective in killing it though it was earlier effective against it. Infections caused by resistant bacteria are tough to treat. In a proportion of cases, none of the antibiotics may be effective, resulting in absolute treatment failure.

Antimicrobial resistance: AMR is defined as the peculiar ability of the bacterial, viral, fungal and parasitic pathogen to render antimicrobials (antibiotics, antivirals, fungicides, antiparasitic drugs) ineffective in killing the etiologic pathogen though these were earlier effective against it.

Mechanisms of Development of ABR

Understanding the mode of development of ABR is important for determining solutions to issues related to this silent pandemic that is eating the world's health and economy inside out and upside down [2,6].

Until now, the main known mechanisms of resistance are:

1. Limiting uptake of antibiotic: Glycopeptides

2. Modification of antibiotic target: β-lactams, glycopeptides, lipopeptides, aminoglycosides, tetracyclines, macrolides, lincosamides, oxizoladines, fluoroquinolones, metabolic pathway inhibitors

3. Inactivation of antibiotic: Beta lactams, chloraplhenicol,

4. Active efflux of drug: Fluoroquinolones, tetracyclines,

These mechanisms may be natural (native to the bacteria), or acquired from other bacteria.

Natural resistance evolves by genetic mutation. It is beyond our control. Acquired resistance is gained by previously vulnerable pathogens through mutation or horizontally from other bacteria already having such resistance *via* transformation, transduction, or conjugation. It is the major pathway of spreading single or multiple antibiotics.

In vertical transmission, bacteria may acquire resistance vertically through mutation and selection. In horizontal transmission, resistance develops horizontally through transduction, transformation or conjugation.

Most bacterial pathogenic have the capability to develop resistance to at least some antibiotics.

Antibiotic-resistant bacteria

The World Health Organization (WHO) has identified the priority groups of bacteria concerning development of resistance [7] as shown in (Table 1).

Some important examples of MDR-resistant bacteria pathogens that cause serious disease are:

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multi-drug-resistant *Mycobacterium tuberculosis* (MDR-TB)
- Carbapenem-resistant *Enterobacteriaceae* (CRE) gut bacteria

Table 1: WHO suggested priority groups of bacteria regarding ABR [7].

Priority 1: Critical
• *Acinetobacter baumannii*, carbapenem-resistant
• *Pseudomonas aeruginosa*, carbapenem-resistant
• *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing
Priority 2: High
• *Enterococcus faecium*, vancomycin-resistant
• *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
• *Helicobacter pylori*, clarithromycin-resistant
• *Campylobacter* spp., fluoroquinolone-resistant
• *Salmonellae*, fluoroquinolone-resistant
• *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant
Priority 3: Medium
• *Streptococcus pneumoniae*, penicillin-non-susceptible
• *Haemophilus influenzae*, ampicillin-resistant
• *Shigella* spp, fluoroquinolone-resistant

Table 2: Five types of antibiotic resistance.

1. Mono resistance: Resistance to a single first line antibiotic only as in case of antituberculosis drugs.
2. Poly resistance: Resistance to two antibiotics
3. Multidrug resistance (MDR): Resistance to more than two antibiotics
4. Extensively drug resistance (XDR): Resistance to most standard antibiotics to virtually all antibiotics.
5. Pandrug resistance: The pathogens that are specifically resistant to seven antibiotics (cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam, ciprofloxacin, and levofloxacin)

The acronym, ESKAPE denotes the group of bacteria of both Gram-positive and Gram-negative species. It is made up of

1. *Enterococcus faecium*,
2. *Staphylococcus aureus*,
3. *Klebsiella pneumoniae*,
4. *Acinetobacter baumannii*,
5. *Pseudomonas aeruginosa*, and
6. *Enterobacter* species.

The ESCAPE pathogens are a common cause of life-threatening bacterial infections, especially in pediatric, immunocompromised and elderly patients [8].

Types of antibiotic resistance

Five types of resistance are usually recognized (Table 2) though there is variation in their definitions among the experts.

Etiologic Aspects

Bacterial microbes (infect all microbes) are known for their primary function of reproducing, thriving and spreading quickly and efficiently [10]. To achieve this, they adapt to given environments, ensure their survival. If something stops their ability to grow, such as an antimicrobial, Face to face with adverse attacks such as an antibiotic, they undergo genetic changes for survival.

Implications and impacts

Undoubtedly, an increasing prevalence of ABR pathogens world over is a hard reality. However, its health and economic impact has not been studied in depth, especially in the low and middle-income countries.

Health Impacts

An escalating number of bacterial infections have become difficult to treat [12] as the antibiotics used to treat them have now become either less effective or absolutely ineffective. Neonatal sepsis, pneumonia, tuberculosis, gonorrhoea, *Clostridium difficile* associated diarrhea, and salmonellosis are examples of such bacterial infections.

Furthermore, antibiotic resistance leads to higher medical expenditure, prolonged hospital stays, treatment failure and higher morbidity and mortality.

Economic impact

ABR has a considerable impact on economy [13]. According to conservative estimates, on an average, cost of treating a resistant infection revolves around 700 US dollar in USA. t the cost of antimicrobial resistance is $55 billion every year in the United States, $20 billion for health care and about $35 billion for loss of productivity. An estimated 750,000 people die annually from drug-resistant infections (link is external) and by 2050 this number could reach ten million and cost more than USD 100 trillion without collective action.

The way forward

The outlook for control and prevention of antibiotic resistance infections is not very promising. So far, despite endeavor by the WHO and its allied agencies and organizations, prevention and control of antibiotic resistant infections has not evinced a significant success. The following approaches warrant an urgent consideration"

• In addition to the four known mechanisms, here are probably more resistance mechanisms that need further exploration.

• Ensuring rational use of antibiotics through various concrete approaches [14,15].

• Intensification of work for developing novel antibiotics from classes other than those already in the midst of resistance [16,17].

• Intensification of research for alternative, complementary and adjuvant strategies [18].

Summary and Conclusion

ABR is a growing public health issue globally warranting urgent attention. Mechanisms involved in its development are resistance to action of the antibiotic at cell membrane level, modification of target, activation of destructive enzymes against antibiotic and rapid exit of the antibiotic. Though there is a long list of WHO-prioritized bacterial pathogens, the acronym ESKAPE highlights the important ones both from Gram positive and Grams negative bacteria. Research is needed to explore additional mechanisms if any, developing novel antibiotics and identifying alternative, complementary and adjuvant strategies.

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