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Antibiotic resistance –Asystematic review

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Abstract

Antibiotics play a vital role in increasing the life expectancy of patients with infectious diseases. Antibiotic resistance is development of tolerance to the effects of antibiotics and is a major global health problem.CDC identified the top 18 antibiotic resistance threats in the United States. They classified resistance threats as urgent, serious, and concerning. The adverse outcomes of antibiotic use may be clinical or economic outcomes and increase the morbidity and mortality. The burden of bacterial disease is high in India increasing their use resulting in the antibiotic resistance.WHO has initiated global action plan consisting 5 objectives for prevention and control of antibiotic resistance. Reducing consumption of antibiotics and Implementation of steward ship programs are tobe initiated to control antibiotic resistance.

Key words:infectious diseases, antibiotic resistance, morbidity, mortality, resistance.

Introduction

Antibiotics are the drugs thatdestroy or inhibitthe growth of bacteria that cause infections in humans by various mechanisms. They play a vital role in treatment and prevention of severe infectious diseases[1].Use of antibiotics improved the quality of life of patients in severe disease conditions by reducing the morbidity and mortality rates[2,3].

Antibiotic resistance:

Antimicrobial resistance is the ability of microorganisms to resist antimicrobial drug[3] effects where as antibiotic resistance occurs when the bacteria survive and replicate in the presence of the ability of a bacterium or other microorganisms to survive and replicate in the presence of antibiotics that are active against them. In simple terms, they develop tolerance to antibiotic effects leading to rapid replication of bacteria[1]. Bacteria resistance to multiple drugs are termed as superbugs[4,5].

Antibiotic resistance is a global health problem across the world mainly in developing countries. Effectiveness of antibiotics is reduced due to development of resistance. Imbalance between the development of resistance by microbes and limited availability of drugs to treat these infections is increasing the risk[5].

Resistant Bacteria especially, Enterococcus species, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species collectively known as ESKAPE develop resistance to multiple drugs to a greater extent and limit the therapeutic options

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and increase morbidity and mortality which is the is the unique characteristic of these bacteria[6]. The most common cause of antibiotic resistance is self medication.Indiscriminate use of antibiotics such as consumption of antibiotics for common flu, inappropriate prescribing, incorrect dose intervals are the other causes of resistance. Exposureto multiple antibiotics also increase the risk of infections with the resistant microorganisms. Overuse of antibiotics also destroy the useful bacteria in the gutthat help in the digestive process[2,7].

WHO's report—Antimicrobial Resistance, Global Report on Surveillance—provides a global review of antibiotic resistance including surveillance. WHO has classified seven bacteria of International concern; their identification and resistance is given below:

- E. coli: resistant to third-generation cephalosporins, Extended Spectrum Beta-Lactamases (ESBLs), and fluoroquinolones;
- K. pneumoniae: resistanttothird-generationcephalosporins, including ESBLs, and carbapenems;
- S. aureus: resistant to β-lactam antibacterialdrugs (methicillin, Methicillin Resistant Staphylococcus aureus);
- Staphylococcus pneumoniae: resistantornon-susceptible to penicillin (orboth);
- Non-typhoid Salmonella resistantto fluoroquinolones;
- Shigella species: resistantto fluoroquinolones; and
- Neisseria gonorrhoeae: decreased susceptibilitytothird- generation cephalosporins[8]

CDC Assessment of Antibacterial Resistance Threats

CDC identified the top 18 antibiotic resistance bacteria species in the United States. They classified resistance threats as urgent, serious, and concerning. Monitoring and prevention is required in urgent and serious threats whereas concerning threats require monitoring and management.

Urgent Threats

- Clostridium difficile
- Carbapenem-resistant Enterobacteriaceae
- Drug-resistant Neisseria gonorrhoeae

Serious Threats

- Multidrug-resistant Acinetobacter
- Drug-resistant Campylobacter
- Fluconazole-resistant Candida (a fungus)
- Extended Spectrum Beta-Lactamase-producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant Enterococci
- Multidrug-resistant Pseudomonas aeruginosa
- Drug-resistant non-typhoidal Salmonella

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Concerning Threats

- Vancomycin-resistant Staphylococcus aureus
- Erythromycin-resistant Group A Streptococcus
- Clindamycin-resistant Group B Streptococcus [2,9]

Table 1: Mechanisms of antibiotic resistance [10, 11]

Type of resistance	Resistance mechanism	Antibiotic class	Example
Target modification	Altered Penicillin binding proteins	Betalactam antibiotics	Mec A gene in S. aureus
	Methylation of ribosomal subunits causing resistance	Macrolides	Erm encoded methylases in S.aureus, S. pneumonia
	Glycopeptides	altered cell-wall precursors	Vancomycin resistance in E. faecium, E. faecalis (D-alanyl alanine is transferred to D-alanyl-D- lactate)
	Quinolones	mutations leading to reduced binding to active site	Mutations in gyr A gene and par C gene in S. pneumoniae
	Tetracyclines	production of proteins that bind to ribosome and alter the conformation of active site	Tet (M) and tet (O) in gram positive and Gram negative species
Detoxifying enzymes	AGE's acetyltransferase (enzyme modification) Betalactamases (enzyme degradation) Chloramphenicol	Amino glycosides Betalactams Acetyl transferase	Gram negative bacteria Mec A gene in S. aureus S.pneumonia
Decreased drug uptake	Changes in the outer membrane Active efflux	Aminiglycosides Macrolides Quinolones Tetracyclines	P. aeruginosa S. pneumonia Mutations in gyr A gene in S. aureus tet genes efflux proteins in Gram positive and Gram negative bacteria

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Impact of antibiotic resistance

Recent studies have shown that there is an interlink between antibiotic resistance, adverse outcomes and increased morbidity, mortality and economic burden on patients almost two times compared to the susceptible infections [12]. The adverse outcomes may be clinical (treatment failure or death) or economic (costs of health care, length of stay in the hospital). Effects of antibiotic resistance include

1. Morbidity and mortality
2. Increased resource utilization and cost
3. Guideline alterations
4. Reduced hospital activity

The outcomes of resistance are measured in terms of disease severity or virulence of bacterial strain.One of the factor responsible for negative impact of antibiotic resistance is the cost of the treatment delay and failurein health care system.For example, in Enterobacteriaceae, the production of Extended Spectrum Beta-Lactamase(ESBL) is associated with higher rates of treatment failure and mortalityin patients with bacteraemiarather thanbacteraemia caused by non-ESBL producers.

Due to failure of fluoroquinolone prophylaxis for trans-rectal ultrasound-guided prostate biopsy there is an increase in the rates of bacteraemia. Several factors are involved in the failure of the treatments for infections caused by bacteria resistant to antibiotics. Bacterial fitness, greater disease severity, delays in initiation of therapy and lack of effective therapy are some of the reasons for treatment failure [13].

Antibiotic Resistance in India

The burden of bacterial disease is high in India. Hence the use of antibiotics is more to limit the morbidity and mortality rates. Mortality rate in India is 416.75 per 100,000 persons due to infectious diseases and is twice the rate prevailing in the United States when antibiotics were introduced (roughly 200 per 100,000 persons).

Antibiotic use is more than doubled in India between 2000 and 2015, making it difficult totreat the common infections pneumonia, tuberculosis due to increased antibiotic resistance. Antibiotic use in India went up from 3.2 billion defined daily doses (DDD) to 6.5 billion in 2015, which implies rise in economic growth and more access to antibiotics in both the public and private sectors. The effect of Antibiotic resistance is mainly concentrated on neonates and elderly as they are easily prone to infections due to low immunity. Approximately, 58,000 neonatal deaths are due to sepsis caused bybacterial resistance to first-line antibiotics each year.

In 2010, India was the world's largest consumer of antibiotics at 12.9 x 10^9 units (10.7 units per person) followed by China at 10.0 x10^9 units (7.5 units per person) and the US at 6.8 x10^9 units (22.0 units per person). There is an overall increase of seventy-six percent in global antibiotic consumption between 2000 and 2010.

Consumption of antibiotics ampicillin and co-trimoxazole is declining in India, while quinolone consumption is high and increasing in India. Rate of use of carbapenemshad risen to over 10 million standard units.

Lack of public health measures, inappropriate and overuse of antibiotics, rising incomes, over-the-counter sale, a poorly regulated private hospital sector, high rates of hospital infection, inexpensive antibiotics and frequent infectious disease outbreaks are the factors responsible for increased antibiotic consumption in India.

Central Drugs Standard Control Organization (CDSCO) has implemented Schedule H1 in India to prevent over-the-counter (OTC) sales of important antibiotics which includes24 antibiotics, such as third- and fourth -generation cephalosporins, carbapenems, antituberculosis drugs, and newerfluoroquinolones [14].

Management of antibiotic resistance:

The Center for Disease Control and Prevention (CDC), recommends variousstеps to reduce antibioticresistance, such as adopting anantibioticstewardship program; improving diagnosis, trackingand prescribing practices; optimizing therapeutic regimens;and preventing infection transmissions.

A global action plan is undertaken to manage antimicrobial resistance, including antibiotic resistance, was endorsed at the World Health Assembly. The main aim of global action plan is to ensure prevention and treatment of infectious diseases with safe and effective medicines.

The "Global action plan on antimicrobial resistance" has 5 strategic objectives:

1. To improve awareness and understanding of antimicrobial resistance
2. To strengthen surveillance and research
3. To reduce the incidence of infection
4. To optimize the use of antimicrobial medicines
5. To ensure sustainable investment in countering antimicrobial resistance [8]

Risk assessment in target pathogens needs to consider

a. the pathogen itself, as there are different dosing strategies for different species
b. time of exposure—the duration of treatment should be kept for as short as possible
c. drug exposure related to risk in an inverse U relationship
d. patterns of drug exposure
e. inoculum size, with different dosing for high-load (pneumonia) and low-load infections (surgically treated complicated skin and soft tissue infection) and
f. combination therapy to suppress resistance

Implementation of antimicrobial stewardship programsis necessary to minimize the adverse effects of antibiotics. Antimicrobial stewardship should include the following:

1. educational measures such as antibiotic guidelines and educational sessions
2. active interventions such as clinical rounds, audits
3. restrictive measures to limit use of antibiotics, reporting of susceptibility by the microbiology laboratory, preauthorization and
4. supplemental measures like computer-assisted management programs, multidisciplinary stewardship teams [15]

Preventing Infection

Preventing infections reduces the need to use antibiotics and the chances that resistance will develop. Infections can be prevented through immunization, safe food handling, frequent and thorough hand washing, good disinfection practices in healthcare settings, and using antibiotics as prescribed to prevent infection.

Surveillance for emerging and existing antibiotic resistant bacteria is an important step in developing strategies to combat such bacteria. The CDC sponsors a number of surveillance programs to track resistant bacteria. For example, the National Healthcare Safety Network allows healthcare facilities to electronically report infections, antibiotic use, and resistance.These networks support local healthcare facilities, laboratories, and health departments so they can detect outbreaks of drug-resistant bacteria faster and respond to them before they can spread more widely[8].

Conclusion:

The resistance of bacterial species to the antibiotics is increasing rapidly challenging the treatment of infectious diseases.Decline in the effectiveness of antibiotics increases mortality and morbidity. Measures should be undertaken to regulate the use of antibiotics and monitor over the counter sale of antibiotics. Reducing the consumption of antibiotics, improving hygiene, sanitation, vaccination and diagnostic tools decrease overuse of antibiotics andburden of infectious disease.Implementation of guidelines for prevention and controlas well as antimicrobial stewardship programs to reduce morbidity, mortality and the costs associated with bacterial resistance is recommended.Clinical Pharmacist must conduct awareness programs to educate both public and physicians about the adverse effects of inappropriate use of antibiotics.

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