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Antibiotic resistance: An emerging threat to public health

M Ranga Priya[1*], Jessly Chacko[2], Theertha CK[3], M Usha[4]
[1-4] Swamy Vivekanandha College of Pharmacy, Tiruchengode, Namakkal, Tamil Nadu, India

Abstract
Antibiotics have been significantly used in the management of many diseases caused by various infections. The issue of antibiotic resistance is becoming a major public health concern, as most of the bacteria are developing resistance to antibiotics commonly used to treat them. Antibiotic resistance may lead to treatment failure, added burden to healthcare cost, spreading of resistant bacteria in community and also it increases mortality. These problems may eventually become a threat which may force us to return to a pre-antibiotic era. Necessary actions such as infection control measures, preventing inappropriate prescriptions, ensuring that full course is prescribed with adequate doses, new discovery of antibiotics. Unnecessary use of antibiotics in horticulture and animal husbandry has to be avoided to combat the resistance. India is a major contributor to overall antibiotic consumption of the world. Excessive use of antibiotics as over-the-counter drugs without proper prescription and diagnosis may ultimately lead to development of powerful multidrug-resistant strains of bacteria. Rational and appropriate use of antibiotics, antibiotic stewardship programs and new discovery of antibiotics may reduce the problems of antibiotic resistance to a greater extend. There is indeed a growing need to reverse the public health issues associated with antibiotic-resistant infections. This article briefly describes various strategies and approaches to overcome antibiotic resistance.

Keywords: antibiotics, inappropriate, antibiotic resistance, infections, multidrug-resistant

Introduction

Antibiotics are frequently used in the ambulatory care environment in either clinics or hospital outpatient department. This excessive and inappropriate use leads to suboptimal clinical and economic outcomes and is believed to be a major contributing factor to the emergence and spread of antibiotic-resistant bacteria in the community [1]. Antimicrobial resistance is one among the most important public health issues particularly in developing countries wherever comparatively simple accessibility and better consumption of medicines have contributed to a disproportionately higher incidence of inappropriate use of antibiotics and higher levels of resistance compared to developed countries [2].

Antibiotic resistance develops when the bacteria change in a way that decreases or eliminates the effectiveness of drugs in curing or preventing the infection. Therefore, the widespread use of antibiotics promotes development of antibiotic resistance. Bacterial susceptibility to antibacterial agents is achieved by determining the minimum inhibitory concentration that inhibits the growth of bacteria. Moreover, the multiple drug resistance is outlined as the resistance to two or more drugs or drug categories [3].

Drug resistance happens for almost every antimicrobial drug, not just antibiotics, and in almost all pathogens and parasites, not just bacteria [4]. Antibiotic-resistant infections are becoming more frequent culprits in treatment failures and are escalating health care costs [5].

According to the World Health Organization (WHO)'s "First Global Report on Antibiotic Resistance" and the U.S. Centre for Disease Control & Prevention (CDC&P), the spread of "superbugs" (the bacteria that have changed such that the antibiotics are rendered ineffective against them) is a serious and growing threat around the world. Unfortunately, antibiotics have also been used in situations where they are not really needed and in animal husbandry for commercial purposes. Such a massive use of antibiotics around the world has imposed a large selective pressure on bacterial resistance which has become a serious global problem. Further, resistance has developed to several drugs, including those used for the treatment of tuberculosis, malaria, agricultural pests, which might render the treatments ineffective [6].

Most of the bacteria related to epidemics of human disease have emerged into multi-drug resistant (MDR) forms following antibiotic use. Tuberculosis causing bacteria is a dominant pathogen found in both developing and industrialized nations. Other serious infections include nosocomial (hospital-linked) infections with Acinetobacter baumannii, Burkholderiacepacia, Campylobacter jejuni, Citrobacterfreundii, Clostridium difficile, Enterobacter spp., Enterococcus faecium, Enterococcus faecalis, Escherichia coli, Haemophilusinfluenzae, Klebsiellapneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella spp., Serratia spp., Staphylococcus aureus, Staphylococcus epidermidis, Stenotrophomonasmaltophilia, and Streptococcus pneumoniae [7].

To retain the efficacy of antibiotics, it is important to monitor the benefits of these drugs. Several new initiatives are being taken to halt the alarming trend of antibiotics resistance and to deal with the ever-increasing number of infections caused by resistant bacteria. The emergence of antibiotics resistance could be the result of the use and misuse of antibiotics. As a

result, it may lead to increased mortality, morbidity and costs of treatment. Even though there were various indications on the misuse of antibiotics by health care providers, unskilled practitioners and drug consumers, there is still inadequate awareness as well as surveillance on the control and prevention of antibiotic resistance [8]. There are suggestions that as resistant bacteria increase and the available antibiotics decrease transmission from inpatients to the larger population will increase and become a problem to the general public [9].

Table 1: The Top Drug-Resistant Threats

Bacteria	Effect	Priority
Clostridium difficile	Diarrhoea, colitis	Urgent
Carbapenem-resistant Enterobacteriaceae	Multiple enteric problems	Urgent
Neisseria gonorrhoeae	Gonorrhoea	Urgent
Multidrug-resistant Acinetobacter	Hospital–acquired pneumonia	Serious
Drug-resistant Campylobacter	Diarrhoea, dysentery	Serious
Extended-spectrum Enterobacteriaceae	Multiple enteric problems	Serious
Vancomycin-resistant Enterococcus	Urinary tract infection, meningitis	Serious
Multidrug-resistant Pseudomonas aeruginosa	Sepsis	Serious
Drug-resistant non-typhoidal Salmonella	Food poisoning	Serious
Drug-resistant Salmonella serotype Typhi	Typhoid fever	Serious
Drug-resistant Shigella	Dysentery	Serious
Methicillin-resistant Staphylococcus aureus (MRSA)	Bacteremia (blood poisoning), sepsis	Serious
Drug-resistant Streptococcus pneumoniae	Bacteremia, meningitis, pneumonia, sepsis	Serious
Drug-resistant Mycobacterium tuberculosis (MDR & XDR)	Tuberculosis	Serious
Vancomycin-resistant Staphylococcus aureus	Bacteremia, sepsis	Concerning
Erythromycin-resistant Group A Streptococcus	Bacteremia, pneumonia, sepsis	Concerning
Clindamycin-resistant Group B Streptococcus	Neonatal infections	Concerning

Emergence and causes of resistance

The development of resistance by previously sensitive organisms has been a problem ever since to the introduction of the sulphonamides in the 1930s. A number of factors are in this phenomenon, with the resistance of organisms responsible for nosocomial (hospital-acquired) infections playing a central role [10]. Unfortunately, the development of antibacterial drugs has been accompanied by the emergence of drug-resistant organisms. The phenomenon of resistance imposes serious constraints on the options available for the medical treatment of many bacterial infections. Antibiotic resistance in bacteria spreads in three ways:

- By transfer of bacteria between people
- By transfer of resistance genes between bacteria(usually on plasmids)
- By transfer of resistance genes between genetic elements between bacteria, on transposons [11].

A number of factors, individually or in combination, have led to the enhanced resistance now seen in some circumstances:

- Irrelevant prescription for non-specific febrile illness or common viral infections
- Inadequate dosage of treatment length to achieve eradication of infection.
- Poor compliance/ adherence to regimens by patients.
- Use of 'broad-spectrum' antimicrobials for specific infections, exposing non-pathogenic commensals to antibiotic pressure
- 'Over the counter' availability of antibiotics [12].

Mechanism of Antibiotic Resistance

Understanding the mechanisms involved in antibiotic resistance is crucial for the sensible clinical use of existing medicines and in the design of new antibacterial drugs [11].

Mechanisms of resistance act as follows

- **Naturally resistant strains:** Some bacteria are innately resistant to certain classes of antimicrobial agent, e.g. coliforms and many other gram-negative bacteria possess outer cell membranes which protect their cell walls from the action of certain penicillins and cephalosporins. Facultatively anaerobic bacteria such as Escherichia coli lose the ability to reduce the nitro group of metronidazole which therefore remains in an inactive form. In the course of therapy, naturally sensitive organisms are eliminated and those naturally resistant proliferate and occupy the biological space newly created by the drug.
- **Spontaneous mutation:** Brings about organisms with novel antibiotic resistance mechanisms if the cells are viable, in the presence of the antimicrobial agent selective multiplication of the resistant strain occurs so that it eventually dominates as above.
- **Transmission of genes:** Transfer from other organisms is the commonest and most important mechanism. Genetic material may be transferred,e.g.: In the form of plasmids which are circular strands of DNA that lie out with the chromosomes and contain genes capable of controlling various metabolic processes including formation of beta-lactamase (that destroy some penicilins and cephalosporins) and enzymes that inactivate aminoglycosides. Alternatively, genetic transfer may occur through bacteriophages, particularly in the case of staphylococci [13].

Mechanisms of resistance of common class of antiobiotics:

Beta-lactams

Altered gram-negative porin channels, modification of penicillin binding proteins (MRSA), production of hydrolysing β-lactamase enzymes (chromosomes or plasmid-mediated).

Glycopeptides

Large molecules; cannot penetrate Gram-negative porins, so Gram negative intrinsically resistant, chemical substitution to prevent binding to transpeptidase.

Aminoglycosides

Membrane impermeability, enzyme inactivation of active sites

(multiple enzymes now involved, specific for different aminoglycosides).

Macrolides, Lincosamides and Streptogramins
Modification of bacterial target (cross-resistance to all macrolides/lincosamides/streptogramins).

Tetracyclines: Active efflux of antibiotic from cells.

Chloramphenicol: Specific enzyme (acyltransferase) that inactivate the antibiotic often plasmid-mediated, reduced entry of drug through modified porins.

Quinolones: Mutation of topoisomerases, porin impermeability, active efflux.

Sulphonamides: Hyperproduction of PABA enzyme mutation[12].

Introduction of antibiotics in clinical practice and emergence of antimicrobial resistance
Penicillin, the first commercialized antibiotic, was discovered in 1928 by Alexander Fleming and it was developed for clinical use in 1943. After the discovery of penicillin, many other antibiotics were developed in the following years and resistance for some antibiotics developed subsequently.
1940-Penicillin resistant staphylococcus was identified.
1950-Tetracycline was introduced.
1953-Erythromycin was introduced.
1959-Tetracycline resistant shigella was identified.
1960-Methicllin was introduced.
1962-Methicllin resistant staphylococcus was identified.
1965-Penicillin resistant pneumococcus was identified.
1967- Gentamicin was introduced.
1968- Erythromycin resistant streptococcus was identified.
1972- Vancomycin was introduced.
1979- Gentamicin resistant enterococcus was identified.
1985- Imipenem and Ceftazidine was introduced.
1987- Ceftazidime resistant enterobacteriaceae was identified.
1988- Vancomycin resistant enterococcus was identified.
1996- Levofloxacin was introduced.
1996- Levofloxacin resistant pneumococcus was identified.
1998- Imipenem resistant enterobacteriaceae was identified.
2000- Linezolid was introduced.
2000- Extensively drug resistant Tuberculosis(XDR) was identified.
2001- Linezolid resistant staphylococcus was identified.
2002- Vancomycin resistant staphylococcus was identified.
2003- Daptomycin was introduced.
2004/2005- Pan-drug resistant acinetobacter and pseudomonas was identified.
2009- Ceftriaxone resistant neisseria gonorrhoeae was identified.
2010- Ceftaroline was introduced.
2011- Ceftaroline resistant staphylococcus was identified[14].

Strategies and Approaches to overcome Antibiotic Resistance:
Clinical practice guidelines:
Good clinical practice has to be developed and promoted with the aid of local authorities. The guidelines may include the following:

- Peer (or small group) education: To recruit trained and educated personnel who may deliver and cater to the territorial and native desires.
- Feedback: The recruited personnel have to gather the feedback from native input and place them for comparison with the quality.
- Direct mailing of information and lectures: This would help in the flow of relevant information and various opinions of leaders and other professional groups.
- Education of patients and the public: This is of utmost importance. It helps to increase patient awareness and interest.[3]

Antibiotic Stewardship Program:
Antimicrobial agents have long been used to treat patients with infectious diseases. These medications have reduced the health problems and death from infectious diseases for many years. Unfortunately, antimicrobials are used so widely and for a longer period, that those infectious organisms have tailored over time to become resistant to some drugs. Because of the threatening impact of such resistance, Antibiotic Stewardship Programs (ASPs) have become a requirement for hospitals. Antibiotic stewardship refers to the careful and accountable management of anti-infective agents. The goals of ASPs are to limit inappropriate antimicrobial use, optimize antimicrobial selection and to limit unintended consequences [15].

Core Elements of Hospital Antibiotic Stewardship Programs

- Leadership Commitment: Providing necessary human, financial and information technology resources.
- Accountability: Appointing a responsible single leader who is effective in program outcomes.
- Drug Expertise: Appointing a responsible single pharmacist leader for working to improve antibiotic use.
- Action: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e. “antibiotic time out” after 48 hours).
- Tracking: Monitoring antibiotic prescribing and resistance patterns.
- Reporting: Regular reporting information on antibiotic resistance and use to doctors, nurses and relevant staff.
- Education: Educating clinicians about antibiotic resistance and optimal prescribing.

Leadership Commitment
Leadership support is essential to the success of antibiotic stewardship programs and can take a number of forms, including:

- Formal declarations to facility the support efforts to improve and monitor antibiotic use.
- Including stewardship-related duties in job descriptions and annual performance reviews.
- Ensuring staff from relevant departments are given adequate time to contribute to stewardship activities.
- Supporting training and education.

- Assure participation from the many groups that can support stewardship activities.

Policies that support Optimal Antibiotic Use

Appliance policies which are administered in all situations to support optimal antibiotic prescribing, for example:

- **Document dose, duration, and indication:** Specify the dose, duration and indication for all courses of antibiotics so that they are readily identifiable. Making this information helps to ensure that antibiotics are modified as needed and/or discontinued in a timely manner.
- **Develop and implement facility specific treatment recommendations:** Based on national guidelines, formulary options and local susceptibilities, facility-specific treatment recommendations can enhance antibiotic selection and duration, especially for common indications for antibiotic use like community-acquired pneumonia, urinary tract infection, skin and soft tissue infections and surgical prophylaxis [16].

The Search for New Antibiotic Agents:

The availability of new antibiotics would aid in combating the impact on the development of antibiotic resistance in the future[17]. Researchers are undergoing an investigation on novel antibiotics that are designed to demolish bacteria before they can even begin to develop resistance. Towards that effort, here are some of the next-generation antibiotics that are designed to withstand resistant microbes.

Teixobactin

It is a cyclic depsipeptide, as potential as a superbug killer. The compound will be the first in a new class of antibiotics that could eradicate resistant superbugs, such as methicillin-resistant Staphylococcus aureus (MRSA) and Mycobacterium tuberculosis, without detectable resistance. It was found that teixobactin analogues were highly potent against S. aureus, MRSA, and vancomycin-resistant enterococci. More than 99% of the bacteria was killed when administered topically into the eyes of mice with S. aureus keratitis and significantly decreased corneal edema compared with control mice. Teixobactin attaches itself to the outer surface of the bacterial cell and disrupts the foundations of the cell wall, leading to cell wall rupture during cell division and destroying the bacteria. The drug is under preclinical development and it is not ready for human trials.

Lefamulin

Lefamulin comes under the class of pleuromutilin antibiotic, binding to an integral part of the bacterial ribosome, which inhibits peptide transfer and thus, prevents protein synthesis. This novel antibiotic is effective against gram-positive and other organisms associated with community-acquired bacterial pneumonia (CABP), including Streptococcus pneumoniae, Haemophilusinfluenzae, Mycoplasma pneumoniae, Legionella pneumophila, and Chlamydophilapneumoniae.

Both oral and intravenous forms of Lefamulin are undergoing trials. Lefamulin was as effective as a 7-day course of oral Moxifloxacin and has the advantage of little or no drug resistance at present. The disadvantage of Lefamulin was that significantly more patients experienced adverse effects of diarrhea and nausea than those on the fluoroquinolone. An investigation is also going on for their use against acute bacterial skin and skin structure infections.

Gepotidacin

Clinical trials on Gepotidacin for treating Neisseria gonorrhoeae infection (gonorrhea), including multidrug-resistant strains is going on. In recent years, N. gonorrhoeae has developed resistance to most antibiotics used for treatment, which point out that gonorrhea may one day become virtually untreatable. Gepotidacin is a topoisomerase inhibitor, blocking the enzyme topoisomerase from assisting in DNA replication in bacterial cells, stopping the infection in its tracks, which could prevent it from becoming resistant. Oral gepotidacin was at least 95% effective against N. gonorrhoeae and it may prove to be a therapeutic alternative for the treatment of uncomplicated gonorrhea [18].

Odilorhabdins

Odilorhabdins (OLDs) are processed by symbiotic bacteria found in soil-dwelling nematode worms that colonize insects for food. The major advantage is that the bacteria help to kill the insect and, importantly, secrete the antibiotic to keep competing bacteria away. ODLs work by targeting the ribosome, disrupts its ability to interpret and translate genetic code. When ODLs are introduced to the bacterial cells, they impact the reading ability of the ribosome and cause the ribosome to make mistakes when it creates new proteins. The bactericidal mechanism of ODLs and the fact that they bind to a site on the ribosome not exploited by any known antibiotic are the very strong features that ODLs have the capacity to treat infections that are unresponsive to other antibiotics.

The ODL compounds are active against bacterial pathogens, including many known to develop resistance and exhibited activity against both Gram-positive organisms, notably including carbapenem-resistant Enterobacteriacae and Gram-negative organisms [19].

Research and development (R&D) of new antibiotics

Due to the emerging negative impact of antibiotic resistance over society, WHO has presented its first ever list of antibiotic-resistant "priority pathogens" – a list of 12 families of bacteria that constitute the greatest threat to human health. The list was made in order to combat growing global resistance and to promote research and development (R&D) of new antibiotics. The list emphasize on the threat of gram-negative bacteria that are resistant to multiple antibiotics due to their built-in abilities to find new ways to resist treatment and can transfer genetic material that allows other bacteria to become drug-resistant as well.

According to the priority of need for new antibiotics, WHO has divided the list into three categories: critical, high and medium priority. Multidrug-resistant bacteria which is a major threat in hospitals, nursing homes and among patients who are on devices such as ventilators and blood catheters fall under the category of critical group. They can cause life-threatening infections such as bloodstream infections and pneumonia. Carbapenems and third generation cephalosporins – the best available antibiotics for treating multi-drug resistant bacteria

are facing the threat of resistance to these bacteria.Other increasingly drug-resistant bacteria that cause more common diseases such as gonorrhoea and food poisoning caused by salmonella comes under second and third categories – the high and medium priority categories.

WHO in association with the Division of Infectious Diseases at the University of Tubingen, Germany, developed this list using a multi-criteria decision analysis technique. The criteria for selecting pathogens on the list were: how deadly the infections they cause are; whether their treatment requires long hospital stays; how frequently they are resistant to existing antibiotics; how easily they spread between animals, from animals to humans, and from person to person; whether they can be prevented (e.g. through good hygiene and vaccination); how many treatment options remain; and whether new antibiotics to treat them are already in the Research &Development pipeline.

WHO priority pathogens list for research & development of new antibiotics

Priority 1: Critical

- Acinetobacterbaumannii, 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
- Haemophilusinfluenzae, ampicillin-resistant
- Shigella spp., fluoroquinolone-resistant[20]

Role of Healthcare Professionals in managing Antibiotic Resistance:

Rational use of antibiotic in hospitals should ensure effective treatment of patients and reduce unnecessary prescriptions. Multidrug-resistant bacteria causes infection which may prolong hospital stay and death compared with infections caused by susceptible bacteria[21].The daily practices needed for responsible antimicrobial use within an institution are inherently multidisciplinary, with different healthcare workers capable of contributing in a variety of ways[22]. Antibiotic resistance is increased by the misuse and overuse of antibiotics, as well as poor infection prevention and control. Steps can be taken to reduce the impact and limit the spread of resistance at all levels of society[23].

Table 2: Activities of healthcare professional team, which contribute to responsible antibiotic management

Professional	Responsibilities
Medical Professionals & Prescribers	• Accurate diagnoses of infections • Appropriate antibiotic prescription • Patient education
Clinical Pharmacologist	• Development and monitoring of antibiotic policies • Monitoring for adverse effects • Patient education
Pharmacist	• Reviewing Prescription • Handling formularies and stocks • Patient education
Nurses	• Microbiology sample collection • Monitoring of patients and proper administration of drugs • Patient education
Hospital managers	• Resourcing antibiotic stewardship teams • Visibly prioritizing antibiotic stewardship within an institution • Encouraging antibiotic stewardship teams to support primary care
Emergency department	• Accurate diagnoses of infections • Collecting sample before starting therapy • Initiating timely and appropriate therapy
Laboratory staff & microbiologists	• Developing protocols for sample taking • Selective reporting of susceptibility testing

Limitation of resistance to antibiotics may be achieved by

- Avoidance of indiscriminate use by ensuring that the indication,thedoseanddurationoftreatmentare appropriate.
- Using antibiotic combinations in appropriate circumstances,e.g. tuberculosis
- Constant monitoring of resistance patters in a hospital of community (changing recommended antibiotics used for empirical treatment when the prevalence of resistance become high),and good infection control in hospitals (e.g. isolation of carriers, hand hygiene practices for ward staff) to prevent the spread of resistant bacteria.
- Restricting drug use, which involves agreement between clinicians and microbiologists, e.g. delaying the emergence of resistance by limiting the use of the newest member of a group of antimicrobials so long as the currently-used drugs are effective[5].

Conclusion

As the beneficial effects of antibiotics are considerable, there was a progressive misuse through different ways such as indiscriminate prescribing, inappropriate dosing and duration of treatment and over the counter availability of antibiotics to the public. Such issues have contributed to the increase of antibiotic resistance among various common human pathogens, alarming the core purpose for which antibiotics were developed.

The high incidence of bacterial resistance makes culture and sensitivity testing essential, especially in the hospital. The spread of resistance within hospitals is of prime concern and may be associated with a lack of adequate isolation facilities. Simple infection control procedures, e.g. hand washing, ward cleaning, mask-wearing and the sterilization of uniforms, should be strictly enforced.

Surveillance of antibiotic resistance levels will help us in realizing the levels of resistance, which have emerged greatly over recent years, and to identify particular problems of multi-resistant pathogens that are and able to spread. Such knowledge on a national and global range allows us to modify local antibiotic policy according to those antibiotics can be specifically used in different clinical situations. However, it cautions us to the significance of developing new antibiotics and antibiotic classes, possible approach to the management and prevention of infectious diseases and eventually control of antibiotic resistance.

Conflict of Interest

The authors declare no conflict of interest.

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