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# The mechanisms, impacts, and stewardship approaches for antibiotic resistance in the current context: A review

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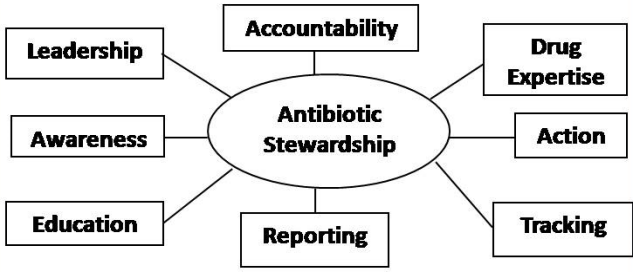
**ABSTRACT**




Since their discovery, antibiotics have played a revolutionary role in the prevention of casualties caused by pathogenic microbes. However, the defensive strategies applied by microbes coupled with their genomic plasticity have resulted in a grave threat to the living world in the form of antibiotic resistance. In this review, we recapitulate the basics about antibiotic action, the emergence of resistance and the potential remedial measures to prevent the spread of antibiotic resistance through the case study Enterococci. Overexploitation, improper disposal, and mismanagement of antibiotics have led to various degrees of resistance in harmful microbes which have eventually led to adverse impacts on the health and economic infrastructure. Here we discuss the role of antibiotic stewardship in controlling and tackling the imminent impacts of antibiotic resistance.

*Keywords:Antibiotic resistance, CDC, AMR, antibiotic stewardship, enterococcus, MDR, XDR,antibiotic targets.*

## INTRODUCTION

With theadvent of sulfonamides in the 1930s and β-lactam antibiotics and aminoglycosides in the 1940s, scientists believed that infectious diseases could be tamed by man. However, the reality is to the contrary due to the emergence of antibiotic resistance in microorganisms. WHO reports suggest that antimicrobial resistance is a grave threat to the sustainability of an effective, global public health response to the threat posed by various infectious diseases. Some prominent examples are *Staphylococci*, *Mycobacterium* species, *Enterococci*, *Candida* and many more. In 2014 the CDC (Center for Disease Control) cited antimicrobial resistance as the second-most significant health threat to humans.[1]

In 2013, CDC published a report which highlighted the danger of antibiotic resistance. It stated that in the U.S., at least 2 million people get an antibiotic-resistant infection, and at least 23,000 people die each year. The report identified and ranked 18 microbial threats (bacteria and fungi) into three main categories—urgent, serious, and concerning, based on their impact on human health.[2]

Antibiotic resistance is a result of immense genetic plasticity of bacterial pathogens that result in mutational adaptations,

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acquisition of genetic material or alteration of genetic expression producing resistance to virtually all antibiotics currently present in the current clinical practice. The resistance to antibiotics acquired by pathogens is basically biochemical and genetic. Magiorakos et al, a report in their research article that there is no consensus on the definitionand use of the terms 'multidrug-resistant', 'extremedrug-resistant', and 'pandrug-resistant' (PDR)which are used to basically characterize drug resistance in drug-resistant organisms.[3]

**Multiple Drug Resistance (MDR) -** Literally, MDR means 'resistant to more than one antimicrobial agent', more appropriately by some researchers as *in vitro* resistance to more than one antimicrobial agent. MDR is also described as 'resistant to three or more antimicrobial classes'.[3]

**Extensive Drug Resistance (XDR) -** It is the known susceptibility to at least one agent in all but two or fewer antimicrobial categories. These are likely to be resistant to all, or almost all approved antimicrobial agents. (i.e. bacterial isolates remain susceptible to only one or two categories).[3, 4]

**Pan Drug Resistance (PDR) -** It is definedas non-susceptibility to all agents in all antimicrobial categoriesor 'resistant to all antimicrobial agents'.(i.e. no agents tested as susceptible for that organism).[3,4]

## ANTIBIOTICS AND THEIR ACTIONS

Antibiotics, as the name suggests, are substances that inhibit or kill microorganisms, specifically bacteria. Some bacteria and fungi are able to naturally produce many of the commonly employed antibiotics as shown in Table 1.

**Table 1** Some antibiotics and their source micro organisms. (Modified from Prescott, Harley and Klein's Microbiology, 7th Edition

| Source Microorganism | Antibiotics | Microorganism Type |
|---|---|---|
| Streptomyces spp. | Amphotericin B<br>Chloramphenicol<br>Kanamycin<br>Neomycin<br>Rifampin<br>Streptomycin<br>Tetracyclines<br>Vancomycin | **Bacteria** |
| Micromonospora spp. | Gentamicin | |
| Bacillius spp. | Bacitracin<br>Polymyxins | |
| Penicillium spp. | Griseofulvin<br>Penicillin | **Fungi** |
| Cephalosporium spp. | Cephalosporins | |

Alternatively, several chemotherapeutic agents, such as sulfonamides, trimethoprim, chloramphenicol, ciprofloxacin, isoniazid, and dapsone, are synthetically manufactured by chemical procedures in a laboratory or industrial setup. The third class of antibiotics is semisynthetic i.e. they are natural antibiotics that have been structurally modified by chemical procedures. Semisynthetic antibiotics have certain advantages such as less susceptibility to inactivation by pathogens (e.g., ampicillin, carbenicillin, and methicillin), a broader spectrum of antibiotic activity than the parent molecule (e.g. semisynthetic penicillins - ampicillin, amoxicillin versus the naturally produced penicillin G and penicillin V). Antibiotics are indispensable for the treatment or prevention of infections in animals and humans.[5,6,7]

The antimicrobial function of antibiotics is achieved by specifically targeting a particular structure or component or metabolic pathway of the target microbe or by adopting a multipronged approach. Combinatorial therapy has been found to be quite effective in cases where drug resistance has emerged to a particular class of antibiotics. The major classification of antibiotics based on the mode of action is given below in Table 2. The major pathways targeted are:

(i) **Cell Wall Synthesis**. Drugs like penicillins, cephalosporins, vancomycin, and bacitracin have a high therapeutic index because they target cell wall, a structure not found in eukaryotic cells.

(ii) **Protein Synthesis Inhibitors.** These inhibit protein synthesis by binding with the prokaryotic ribosome. Since these compounds discriminate between procaryotic and eucaryotic ribosomes, their therapeutic index is fairly high but not as high as that of cell wall inhibitors. Various targets of these drugs are 30S (small) ribosomal subunit, the 50S (large) subunit, aminoacyl-tRNA binding, peptide bond formation, mRNA reading, and translocation.[8, 9, 10]

(iii) **Metabolic Antagonists -** These compounds block or antagonize the functioning of target metabolic pathways by competitive inhibition mechanism.

(iv) **Nucleic Acid Synthesis Inhibition -** These act byinhibiting DNA polymerase and DNA helicase or RNA polymerase, thus blocking replication or transcription, respectively. Since procaryotes and eucaryotes do not differgreatly with respect to nucleic acid synthesis, these drugs have higher toxicity and comparatively lower therapeutic index.[11,12,13]

**Table 2** Antibiotics and the trageted pathway

| Mode of Action | Antibiotcs |
|---|---|
| Inhibitors of cell wall synthesis | Cephalosporins, Penicillin, Vancomycin, and Bacitracin |
| Protein synthesis inhibitors | Aminoglycosides (Streptomycin, Kanamycin, Neomycin, Tobramycin, and Gentamicin);<br>Tetracyclines (Oxytetracycline and Chlortetracycline);<br>Macrolides (Erythromycin, Azithromycin);<br>Chloramphenicol |
| Metabolic Antagonists | Sulfonamides or Sulfa Durgs;<br>Trimethoprim |
| Nucleic acid synthesis inhibition | Quinolones |

## HOW ANTIBIOTIC RESISTANCE EMERGES

It has been found that microbes possess remarkable genetic plasticity which allows them to respond to a range of environmental threats that threaten their survival, including the presence of antibiotic molecules.

Antimicrobial resistance is expected to be a result of the interaction of many organisms with their environment as most antimicrobial compounds are naturallyproduced by certain organisms against others (Table 1).

In order to survive the presence of these antimicrobial compounds in their microenvironment, various co-resident microbes have evolved mechanisms to overcome their detrimental effects. Thus, some organisms in nature are "intrinsically" resistant to one or more antimicrobials. Microbial cells may accumulate certain genetic errors in their genetic material leading to antibiotic resistance and may transfer the altered genetic material to progeny cells. This transmission of genetic traits from parents to progeny through reproduction is called vertical gene transfer (VGT).[11]

What is of significance is that antimicrobial resistance may also be an "acquired" feature in a microbial population which originally was susceptible to the antimicrobial compound(s). This acquisition of resistance may be due to mutations in certain regions of genetic material or due to the uptake of external genetic determinants of resistance, which is most probably obtained from the intrinsically resistant organisms present in the environment. From an evolutionary perspective, microbes (particularly bacteria) have the following genetic basis of microbial resistance to antibiotics:

***i***) mutations in genomic regions that are often associated with the mechanism of action of the antibiotic, and

***ii)*** uptake or entry of foreign DNA encoding the antibiotic resistance determinants through horizontal gene transfer (HGT).

HGT may be affected by any of the three well-known pathways namely transformation (uptake of naked DNA from the environment), transduction (a bacteriophage acts as vector and inserts DNA into recipient cell) and conjugation (physical contact between two bacterial strains for exchange of genetic material popularly known as bacterial "sex"). Hence, antimicrobial resistance is a phenomenon that has much complexity.[11,12,13]

## MECHANISMS OF ANTIBIOTIC RESISTANCE

It is quite often that microbes have multiple mechanisms operating simultaneously to ensure complete protection from the antibiotics. There are various mechanisms by which the microorganisms get resistant to antibiotics are shown in Figure 1.

1. **By preventing/restricting the entry of antibiotics into the cell:** In the Gram-negative bacteria, the outer membrane acts as the firstline of defense against the penetration of several antimicrobial agents. Vancomycin, a glycopeptide antibiotic, is not active against gram-negative organisms due to a lack of penetration through the outer membrane.[14, 15]

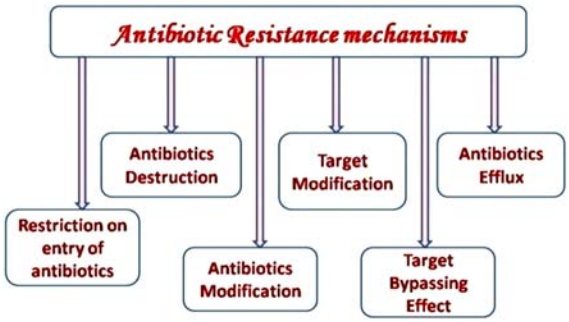


**Figure 1.** The major biochemical mechanisms of self-defense.

2. **Destruction of the antibiotic molecule:** The classical example of this type is β-lactam resistance which relies on the destruction of antibiotics by the action of enzymes called β-lactamases. Many different β-lactamases have been described to date.[16,17]

3. **Chemical alterations/modifications of the antibiotic:** This is a commonly used strategy forrendering an antibiotic ineffective. Typical examples are aminoglycoside antibiotics (kanamycin, gentamycin, and streptomycin) and chloramphenicol. Numerous aminoglycoside modification enzymes (AMEs) such as N-acetyl transferases (AAC), O-phosphotransferases (APH), and O-adenyltransferases(ANT) are expressed in the microbes which acetylate, phosphorylate, or adenylylate the aminoglycoside antibiotic, respectively.[17]

**Table 3.** Some of the major factors across the globe that contribute to direct or indirect dissmination of ABR

| Factor | Example | Reference |
|---|---|---|
| Occupational risk | Farmers, veterinaries, animal farm labour, dairy handlers, and abattoir workers | (Marshall and Levy, 2011) |
| Air travel, Medical tourism | Dutch travelers to North America, South America, and Asia were colonized by colistinresistant E.Coil strains harbouring mic-1gene. | (Coetzee et al., 2016) (Chen ans Wilson, 2013) |
| Environment as reservoir for ABR microorganisms | Farm soils, manure, and wastewater as "hot spots" of ABR pollution | (Zhu et al., 2013)(Wu et al., 2014) (Thanner et al., 2016) |
| Globalization of trade in food, animals, and products | Many developing countries are substantive exporters of food animals and hence potentially a significant source of dissernination of ABR microorganisms | (Marshall and Levy, 2011) (Fernandes et al., 2016) |

4. **Changes in target sites:** Microbes have evolved this strategy to bring about modifications of the target site so as to achieve decreased affinity for the antibiotic molecule. The typical

example of this mechanism is the tetracycline resistance determinants Tet(M) and Tet(O). TetO and TetM interact with the ribosome and dislodge the tetracycline from its binding site in a GTP-dependent manner. TetO has also been shown to compete with tetracycline for the same ribosomal space and to alter the geometry of the binding site of the antibiotic, displacing the molecule from the ribosome and allowing protein synthesis to resume.[16,17]

5. **Target Bypass:** Using this strategy, bacteria evolve new targets which accomplish the biochemical functions of the original target and hence are not inhibited by the antimicrobial molecule. An example is th synthesis of the additional B subunit of DNA gyrase for novobiocin resistance.[18, 19]

6. **Efflux pumps:** Microbes, especially bacteria are capable of extruding the toxic metabolites of the cell by efflux pumps which can also result in antimicrobial resistance. Many classes of efflux pumps have been characterized in microbes. Tetracycline resistance is a classic example of efflux-mediated resistance, wherein the Tet efflux pumps extrude tetracyclines using proton exchange as the source of energy.[18]

## HOW ANTIBIOTIC RESISTANCE SPREAD

The spread of ABR in humans is possible through direct or indirect routes via the biotic and abiotic agents of transmission.[18]

(i) The direct route involves immediate human exposure to the infected animal or the contaminated biological substance such as urine, feces, blood, milk, saliva, and semen. The high-risk individuals in this group are occupationally exposed. Some such workers are farmers, veterinarians, animal farm labor, dairy handlers and abattoir workers.[12]

(ii) The indirect route involves contact with or consumption of contaminated food products like milk, eggs, meat, and other dairy products. Various reports have described the presence of ABR microorganisms in ready-to-eat meat, cooked meat and bulk milk from various animal sources and from different food production stages.[14] Table 3 summarizes some of the major factors that have accentuated the problem of the dissemination of ABR across the world.

Resistance develops and spreads through the misuse and overuse of antibiotics. Antibiotics are also widely used in healthy animals to prevent disease and also to promote growth through mass administration to animals. Antimicrobial compounds are also commonly used in commercial fish and seafood farming.[7]

Some other anthropogenic factors implicated in the widespread dissemination of antibiotic resistance areas follows:

1. Long-distance travel/ Medical Tourism
2. Easy access through over-the-counter sales.
3. Over-prescription by medical practitioners
4. Non- compliance with standard disposal procedures by animal farming industries and pharmaceuticals.
5. Globalization of the food trade and industry.
6. Occupational hazards of working with drug-resistant strains in hospitals as well as farms.

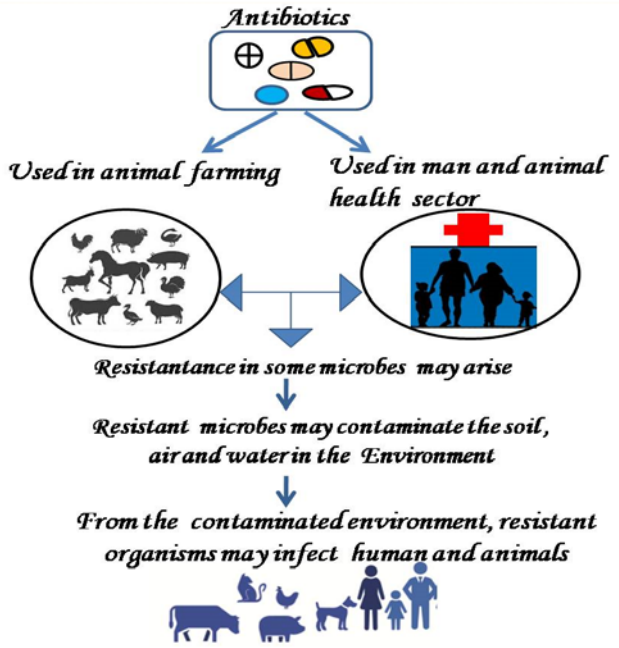


**Figure 2.** Spread of antibiotic resistance

Table 3 summarises the specific studies wherein the said anthropogenic factors have been found to be a major contributor to the spread of drug resistance globally.

## Impacts

The CDC reporttitled Antibiotic Resistance Threats in the United States, 2013 (AR Threats Report)ranked 18 threats (bacteria and fungi) into three categories based on the level of concern to human health and revealed the dangers of drug resistance to humankind. They are as follows:

(i) Urgent Threats :
- Clostridioides oifficile,
- Carbapenem-resistant Enterobacteriaceae (CRE),
- Drug-resistant Neisseria gonorrhoeae

(ii) Serious Threats:
- Multidrug-resistant Acinetobacter
- Drug-resistant Campylobacter
- Fluconazole-resistant Candida
- Extended-spectrum beta-lactamase-producing Enterobacteriaceae
- Vancomycin-resistant Enterococcus (VRE)
- Multidrug-resistant Pseudomonas aeruginosa
- Drug-resistant non-typhoidal Salmonella
- Drug-resistant Salmonella Serotype Typhi
- Drug-resistant Shigella
- Methicillin-resistant Staphylococcus aureus (MRSA)
- Drug-resistant Streptococcus pneumonia
- Drug-resistant Tuberculosis

(iii) Concerning Threats:
- Vancomycin-resistant Staphylococcus aureus (VRSA)
- Erythromycin-Resistant Group A Streptococcus
- Clindamycin-resistant Group B Streptococcus

The report helps in identifying the minimum estimates of morbidity and mortality from antibiotic-resistant infections, higher risk groups, gaps in knowledge about antibiotic resistance, prevention and control strategies.[22, 23]

The report further highlighted the key areas of further research to understand, combat and control the infections caused by the various threat group organisms. It necessitates the critical review of strategies in practice and suitable alterations in the global governing policies in every country.

## A Brief Case Study of Antibiotic Resistance by Enterococci

**Habitat** Enterococci is an inhabitant of the intestine of nearly all animals. Outdoor habitats are vegetation and surface water contaminated with animal excreta or untreated sewage. It can tolerate very harsh environments such as 10 to 45 °C temperature, very high to low salt concentrations, sodium azide, and concentrated bile salts.[21]

**Main resistant species of enterococcus** According to data collected by the TSN database between 1995 to 1997 the main species of enterococcus which are showing resistance are *E. faecalis* and *E. facium*.

Then there was SENTRY antimicrobial surveillance program 1997 to 2016. In this program also the most common enterococci species in four regions Asia Pacific, Europe, Latin America, and North America were *E .faecalis* and *E. faecium*.[24,25]

**Type of resistance in enterococci** It exhibits MDR type of resistance. *E. faecalis* and *E. facium* are resistant to multiple antibiotics vancomycin, macrolides, tetracycline, fluoroquinolones (ampicillin, doxycycline, piperacillin). A high-level gentamycin resistance was reported in enterococci in 1979. A number of nosocomial infections in the 1980s. Then *E. faecalis* and *E. facium* appeared with penicillin resistance due to beta-lactamase production. Finally, MDR enterococci lost susceptibility to vanomycin in the united states and Europe.[20,21]

**Mechanism of resistance** Intrinsic resistance is caused by chromosomal genes that are not transferred. Enterococci often acquire resistance by the exchange of resistance encoding genes carried on conjugative transposons. Inducible genes encoding these phenotypes alter cell wall synthesis and strains resistant to glycopeptides.[21]

The resistance mechanism of some of the antibiotics by *E. faecium* and *E. faecalis* is tabulated below:

| Antibiotic Class | Resistance Type | Resistance Mechanism |
|---|---|---|
| Glycopeptides | Altered target | D-alanyl-alanine is changed to D-alanyl-D-lactate |
| Oxazolidinones | Altered target | Mutation leading to reduced binding to the active site(anti resist prob sol) |
| Vanomycin | Genetic | By van gene |

**Problems**

In a survey from 2011 to 2014 conducted by National healthcare safety network at United State CDC the states of enterococci resistance problem was following[26]:

| Status of Enterococci Infection | Type of Infection |
|---|---|
| Second Rank | Healthcare-associated infections |
| First Rank | Bloodstream infections |
| Second Rank | Surgical site infections |
| Thrid Rank | Urinary tract infections |

The other cause of concern is the possibility of transfer of resistant genes from enterococcus to other gram-positive bacteria such as *staphylococci* and *streptococci*.

**Solutions** Resistance of *enterococcus* to glycopeptides and MDR needs attention and continuous monitoring.

- **Control of Enterococci MDR**
  - → Knowledge of interaction between *enterococcus*, hospitals, and humans.
  - → Careful use of antibiotics
  - → Better surveillance

## Preventive and Remedial Measures

Antibiotic stewardship programs are started by hospitals at the recommendation of centers for disease control. CDC also recommends that a pharmacistbe employed at the hospital that can especially focus on antibiotic use.[2] There is a time to analyze the old age techniques for disease control. Not to use harsh antibiotics for small infections. Developing immunity to diseases is a good solution also. Let the children involved in outdoor playing, vaccination at the time, etc.

- **Role of society** Antibiotic resistance is increased by misuse or excessive use of antibiotics. All levels of society play an important role in tackling this problem:
- **Role of Patients:** Patients should not demand antibiotics from physicians for faster relief. They must understand the long term side effects of recurrent use of antibiotics. Patients should take antibiotics only under medical supervision.[4]
- **Role of Policy Makers:** Ensure political commitment to meet the threat of antibiotic resistance. The need for antibiotics is reduced through immunization by Improving coverage for existing vaccines.
- **Role of Health Professionals:** Hospital infection control and antibiotic stewardship have to be improved. Better hygiene, particularly handwashing is also a crucial thing. The health professionals, policymakers, and the public must be educated and informed about sustainable antibiotic use.
- **Role of Healthcare Industry:** The Development of new drugs, treatments, and diagnostics through better collaboration between research councils, academia, industry, and others; and by encouraging greater public-private investment in the discovery and development of a sustainable supply of effective new antimicrobials, rapid diagnostics, and

complementary tools for use in health, social care, and veterinary systems will also help. The updation of professional education, training, and public engagement to improve clinical practice and promote a wider understanding of the need for more sustainable use of antibiotics. Better identification and prioritization of AMR research needs to focus on the activity and understanding of AMR. This may identify alternative treatments to new drugs as well as new or improved rapid or point-of-care diagnostic tests.[29, 30]

- **Role of Agriculture Sector:** To prevent and control the spread of antibiotic resistance, the agriculture sector can:
  - ❖ Only give antibiotics to animals under veterinary supervision.
  - ❖ Not use antibiotics for growth promotion or to prevent diseases in healthy animals.
  - ❖ Vaccinate animals to reduce the need for antibiotics and use alternatives to antibiotics when available.
  - ❖ Promote and apply good practices at all steps of production and processing of foods from animal and plant sources.
  - ❖ Improve biosecurity on farms and prevent infections through improved hygiene and animal welfare.[7, 8]

## ANTIBIOTIC STEWARD SHIP

Antibiotic stewardship refers to interventions designed to promote the optimal use of antibiotic agents including drug choice, dose, route and duration of administration. To address antimicrobial are clinicians must become stewards of antimicrobials by prescribing them appropriately and educating their patients and colleagues on the proper use of scarce medical sources.[4]

Antibiotic stewardship programs are started by hospitals at the recommendation of centers for disease control. CDC also recommends that a pharmacist be employed at the hospital that can especially focus on antibiotic use.[2] There is a time to analyze the old age techniques for disease control. Not to use harsh antibiotics for small infections like cough & cold. Developing immunity to diseases is a good solution also. Let the children involved in outdoor playing, vaccination at the time, etc. Minor infections should be treated with natural techniques that most of the Indians know from their elders.[10,11]

Core elements of hospital antibiotic stewardship program are given below:

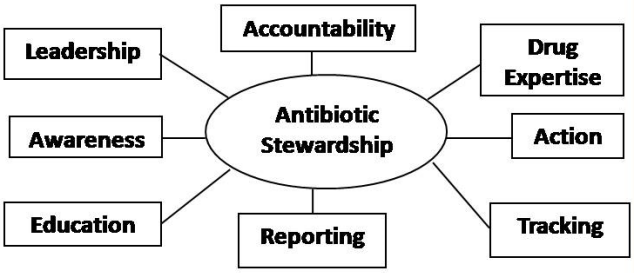


**Figure 3.** Core Elements of Antibiotic Stewardship

## DIGITAL AWARENESS

Digital education can help us a lot in tackling the problem of antibiotic resistance. Learning contents can be made available by different types of digital education such as online or offline to pre and post registered healthcare professionals. This will lead to an increase in knowledge of health professionals and it leads to behavioral changes in practicians. It will also help to improve cost-related outcomes. The digital education of health professionals could help to address the problem caused by overprescribing antibiotics. It will also help in tackling poor infection control in hospitals and clinics.[28]

The digital content in a set of fourteen modulesis available at the WHO site regarding antibiotic stewardship.[29]

## CONCLUSION

In this paper, various causes, problems, and solutions to antibiotic resistance are discussed. It is important for a health care worker to understand, how resistance develops, what are the problems caused by antimicrobial resistance, and what are the possible solutions to antibiotic-resistance.[30-82] The excess use of antibiotics causes serious issues such as longer illness, more casualty and the cost of treatment is also increased. Vancomycin which is called last resort drug is becoming less effective for the treatment. The public, researchers and the hospital personnel give a lot of attention to the issue of drug-resistant bacteria. In order to study and to control the spread of antibiotic stewardship programs have been started in the number of hospitals. Currently, the problem of antibiotic resistance needs a lot of research work to be done to have a convenient solution. Public awareness also plays an important role in tackling the problem. Digital awareness is also playing an important role in this field.

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## REFERENCES AND NOTES

1. Antibiotic Resistance Threats in the United States. Centers for Disease Control and Prevention. October **2013**.
2. CDC Year in review: Mission: Critical. In the Centers for Disease Control and Prevention. **2014.**
3. P. Magiorakos et al.Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin. Microbiol. Infect.* **2012**. 268–281.
4. M. Bassetti, D. R. Giacobbe, A.Vena, A. Brink. Challenges and research priorities to progress the impact of antimicrobial stewardship. *Drugs in Context.*. ***2019.*** DOI: 10.7573/dic.212600 ISSN: 1740-4398
5. C.Garzoni. Multiply Resistant Gram-Positive Bacteria Methicillin-Resistant, Vancomycin-Intermediate and Vancomycin-Resistant Staphylococcus aureus (MRSA, VISA, VRSA) in Solid Organ Transplant Recipients. *In Wiley Online Library,* December 16, **2009**.
6. E. Goldman. What to do when patients demand unnecessary antibiotics. *In Holistic: Primary Care*, November 23, **2014**.
7. CDDEP. Global Antibiotic Resistance Partnership. The State of the World's Antibiotic. **2015**.
8. B. M. Kyaw, L. T. Car. Health Professions Digital Education on Antibiotic Management: Systematic Review and Meta-Analysis by the Digital Health Education Collaboration. *J Med Internet Res.* **2019**. 21(9).
9. A. Tamrakar, A.K. Singh, M. Chodhrary, P. Kodgire. Fighting with Gram-negative enemy: Can outer membrane proteins aid in the rescue? *Chem. Biol. Lett.* **2017**, 4 (1), 9–19.

10. G. Pitari. Scientific research in Homeopathic Medicine: Validation, Methodology, and Perspectives. *Evidence-based Complementary and Alternative medicine. **2006.*** 4(2), 271-273.
11. L. L. Founou, R. C. Founou, and S. Y. Essack. Antibiotic Resistance in the food chain: A Developing Country-Perspective. *Front. Microbiol.,* **2016,** 23.| https://doi.org/10.3389/fmicb.2016.01881
12. J. M. Willey, L. M. Sherwood, and C. J.Woolverton. Prescott, Harley, and Klein's Microbiology Seventh Edition", a book published by McGraw Hill/Higher Education, Boston, Massachusetts, U.S.A., **2008**.
13. B. M. Marshall, and S. B. Levy. Food animals and antimicrobials: impacts on human health. *Clin. Microbiol. Rev.* **2011**, 24. 718–733.
14. L. B. Price, M. Stegger, H. Hasman, M. Aziz, J. Larsen, P. S. Andersen. *Staphylococcusaureus*CC398: Host adaptation and the emergence of methicillin resistance in livestock. M. *Bio **2012***. DOI: 10.1128/mBio. 00305.
15. P. M. Dacosta, L. Loureiro, and A. J. F. Matos. Transfer of multi-drug resistant bacteria between intermingled ecological niches: the interface between humans, animals and the environment. *Int. J. Environ. Res. Public Health. **2013***, 278–294.
16. L. Wang, G. C. Atkinson, N. S. Thakor, U. Allas U, C. C. Lu, K. Y. Chan, T. Tenson, K. Schulten, K. S. Wilson, V. Hauryliuk, J. Frank. Mechanism of tetracycline resistance by ribosomal protection protein Tet(O). *Nat Commun*. **2013**. 4, 1477.
17. E. Peterson, P. Kaur. Antibiotic Resistance Mechanisms in Bacteria: Relationships Between Resistance Determinants of Antibiotic Producers, Environmental Bacteria, and Clinical Pathogens. *Frontiers in Microbiology*. **2018.** 9, 1-21.
18. L.M. McMurry, R.E.J. Petrucci, S.B. Levy. Active efflux of tetracycline encoded by four genetically different tetracycline resistance determinants in Escherichia coli. *Proc Natl Acad Sci USA.* **1980.** 77, 3974–7.
19. M.G. Blanco, C. Hardison, J.A. Salas. Resistance in inhibitors of RNA polymerase in actinomycetes which produce them. *J. Gen. Microbiol.* 130, **2013.** 2883–2891.
20. M.M. Huycke, D.F. Sahm, M.S. Gilmore. Multiple-Drug Resistant Enterococci: The Nature of the Problem and an Agenda for the Future. *Emerging Infectious Diseases.* **1998.** 2, 239-249.
21. M.A. Pfaller, M. Cormican, R.K. Flamm, R.E. Mendes, R.N. Jones. Temporal and Geographic Variation in Antimicrobial Susceptibility and Resistance Patterns of Enterococci: Results From the SENTRY Antimicrobial Surveillance Program, 1997–2016. *Open Forum Infectious Diseases.* **2019.** 54-62.
22. L. H. Chen, and M. E. Wilson. The Globalization of healthcare: implications of medical tourism for the infectious disease clinician.*Clin. Infect. Dis.* **2013**. 57, 1752–1759.
23. Y.G. Zhu, T.A. Johnson, J.Q. Su, M. Qiao, G.X. Guo, R.D. Stedtfeld. Diverse and abundant antibiotic resistance genes in Chinese swine farms. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, 110, 3435–3440.
24. Wu,X.L., Xiang,L., Yan,Q.Y., Jiang,Y.N., Li,Y.W., Huang,X.P. Distribution and risk assessment of quinolone antibiotics in the oils from organic vegetable farms of a subtropical city, Southern China. *Sci. Total Environ.* **2014**. 487,399–406.
25. S. Thanner, D. Drissner, and F. Walsh. Antimicrobial resistance in agriculture. *M Bio* **2016**, 7, 02227–e02215.
26. L.H. Chen, M.E. Wilson. The Globalization of healthcare: implications of medical tourism for the infectious disease clinician. *Clin. Infect. Dis.* **2013**, 57, 1752–1759.
27. M.R. Fernandes, Q. Moura, L. Sartori, K.C. Silva, M.P. Cunba, F. Esposito. Silent dissemination of colistin-resistant *Escherichiacoli*in South America could contribute to the global spread of the MCR-1gene. *Euro.Surveill.* **2014**, 21.
28. S. G. Howard, R.C. Moellering. Antimicrobial-Drug Resistance. *The New England Journal of Medicine*, **1996,** 335, 1445-1453.
29. M.J. Zervos, C. A. Kauffman, P. M. Therasse, A. G. Bergman, T. S. Mikesell, D. R. Schaberg. Nosocomial infection by gentamicin-resistant Streptococcus faecalis an epidemiologic study. *Ann Intern Med* **1987.** 687-91.
30. M. Piplani, A.C. Rana, P.C. Sharma. Synthesis, characterization and evaluation of prodrugs of ciprofloxacin clubbed with benzothiazoles through N-Mannich base approach. *Chem. Biol. Lett.* **2016**, 3 (2), 52–57.
31. D.K. Shay, S.A. Maloney, M. Montecalvo. Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infection. *J Infect Dis* **1995.** 993-1000.
32. R. C. J. Moellering. Antimicrobial susceptibility of enterococci: in vitro studies of the action of antibiotics alone and in combination. *In Bisno AL, ed. Treatment of infective endocarditis. New York: Grune& Stratton,* **1981.** 81-96.
33. H. Jafri, F.M. Husain, I. Ahmad. Antibacterial and antibiofilm activity of some essential oils and compounds against clinical strains of Staphylococcus aureus. *J. Biomed. Ther. Sci.* **2014**, 1 (1), 65–71.
34. J.E. McGowan, D.N. Gerding. Does antibiotic restriction prevent resistance? *New Horiz.* **1996**, 4(3), 370–376.
35. M Mendelson, M Balasegaram, T Jinks, C Pulcini, M Sharland. Antibiotic resistance has a language problem. *Nature*. **2017**; 545(7652): 23–25.
36. N. Gupta, C. Gupta, S. Sharma, R.K. Sharma, H.B. Bohidar. Comparative study of antibacterial activity of standard antibiotic with silver nanoparticles synthesized using ocimum tenuiflorum and garcinia mangostana leaves. *Chem. Biol. Lett.* **2015**, 2 (2), 41–44.
37. Monnier AA, Eisenstein BI, Hulscher ME, Gyssens IC, group D-AW. Towards a global definition of responsible antibiotic use:results of an international multidisciplinary consensus procedure. *J Antimicrob Chemother*. **2018**, 73(suppl_6), vi3–vi16.
38. B. Nand, K. Meena, S. Gupta, et al. Synthesis of novel 2-(3-aryl/alkylamino propoxy)-12-aryl xanthene derivatives as antifungal and antibacterial agents. *Chem. Biol. Lett.* **2017**, 4 (2), 81–90.
39. Dyar OJ, Huttner B, Schouten J, Pulcini C, ESGAP. What is antimicrobial stewardship? *Clin Microbiol Infect.* **2017**; 23(11), 793–798.
40. S. Dahiya, A. Kaushik, K. Pathak. Formulation optimization of multicomponent aqueous coground mixtures of Meloxicam for dissolution enhancement. *Chem. Biol. Lett.* **2019**, 6 (1), 1–7..
41. S. Dhanarani, S. Congeevaram, P. Piruthiviraj, J.H. Park, T. Kaliannan. Inhibitory effects of reserpine against efflux pump activity of antibiotic resistance bacteria. *Chem. Biol. Lett.* **2017**, 4 (2), 69–72.
42. Falcone M, Paul M, Yahav D, et al. Antimicrobial consumption and impact of antimicrobial stewardship programmes in long term care facilities. *Clin Microbiol Infect.* **2019**; 25(5):562–569.
43. P.C. Sharma, S. Padwal, A. Saini, K. Bansal. Synthesis, characterization and antimicrobial evaluation of benzimidazole clubbed benzothiazole derivatives. *Chem. Biol. Lett.* **2017**, 4 (2), 63–68..
44. K.G. Goud, N.K. Veldurthi, M. Vithal, G. Reddy. Characterization and evaluation of biological and photocatalytic activities of selenium nanoparticles synthesized using yeast fermented broth. *J. Mater. Nanosci.* **2016**, 3 (1), 33–40.
45. Pulcini C. Antibiotic stewardship: update and perspectives. *Clin Microbiol Infect*. **2017**;23(11):791–792.
46. Emberger J, Tassone D, Stevens MP, Markley JD. The current state of antimicrobial stewardship: challenges, successes, and future directions. *Curr Infect Dis Rep*. **2018**;20(9):31.
47. I. Singh. Antimicrobials in Higher Plants: classification, mode of action and bioactivities. *Chem. Biol. Lett.* **2017**, 4 (1), 48–62.
48. Van Santen KL, Edwards JR, Webb AK, et al. The standardized antimicrobial administration ratio: a new metric for measuring an comparing antibiotic use. *Clin Infect Dis.* **2018**;67(2):179–185.
49. B.S. Chhikara, B. Rathi, K. Parang. Critical evaluation of pharmaceutical rational design of Nano-Delivery systems for Doxorubicin in Cancer therapy. *J. Mater. Nanosci.* **2019**, 6 (2), 47–66..
50. Sharland M, Pulcini C, Harbarth S, et al. Classifying antibiotics in the who essential medicines list for optimal use-be aware. *Lancet Infect Dis*. **2018**;18(1):18–20.
51. Hsia Y, Sharland M, Jackson C, Wong ICK, Magrini N, Bielicki JA. Consumption of oral antibiotic formulations for young children according to the who access, watch, reserve (aware) antibiotic groups: an

analysis of sales data from 70 middle-income and high-income countries. *Lancet Infect Dis*. **2019**; 19(1): 67–75.
52. Moehring RW, Anderson DJ, Cochran RL, et al. Expert consensus on metrics to assess the impact of patient-level antimicrobial stewardship interventions in acute-care settings. *Clin Infect Dis*. **2017**; 64(3):377–383.
53. Lindsay PJ, Rohailla S, Taggart LR, et al. Antimicrobial stewardship and intensive care unit mortality: a systematic review. Clin Infect Dis. 2019;68(5):748–756.
54. Evans SR, Rubin D, Follmann D, et al. Desirability of outcome ranking (door) and response adjusted for duration of antibiotic risk (radar). *Clin Infect Dis*. **2015**;61(5):800–806.
55. Naylor NR, Zhu N, Hulscher M, Holmes A, Ahmad R, Robotham JV. Is antimicrobial stewardship cost-effective? A narrative review of the evidence. *Clin Microbiol Infect*. **2017**;23(11):806–811.
56. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis*. **2016**;16(7):819–827.
57. Nora D, Salluh J, Martin-Loeches I, Povoa P. Biomarker-guided antibiotic therapy-strengths and limitations. *Ann Transl Med*. **2017**;5(10):208.
58. Giacobbe DR, Signori A, Tumbarello M, et al. Desirability of outcome ranking (door) for comparing diagnostic tools and early therapeutic choices in patients with suspected candidemia. *Eur J Clin Microbiol Infect Dis*. **2019**;38(2):413–417.
59. Sime FB, Roberts MS, Roberts JA. Optimization of dosing regimens and dosing in special populations. *Clin Microbiol Infect*. **2015**;21(10):886–893.
60. Dulhunty JM, Roberts JA, Davis JS, et al. A multicenter randomized trial of continuous versus intermittent beta-lactam infusion in severe sepsis. *Am J Respir Crit Care Med*. **2015**;192(11):1298–1305.
61. N. Sharma, A. Verma, P. FNU, P. Kempaiah, B. Rathi. Chemical libraries targeting Liver Stage Malarial infection. *Chem. Biol. Lett*. **2019**, 6 (1), 14–22..
62. Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME. Prolonged versus short-term intravenous infusion of antipseudomonal beta-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. *Lancet Infect Dis*. **2018**;18(1):108–120.
63. R. Kumar, M. Sharma. Herbal nanomedicine interactions to enhance pharmacokinetics, pharmaco-dynamics, and therapeutic index for better bioavailability and biocompatibility of herbal formulations. *J. Mater. Nanosci*. **2018**, 5 (1), 35–58.
64. Wong G, Brinkman A, Benefield RJ, et al. An international, multicentre survey of beta-lactam antibiotic therapeutic drug monitoring practice in intensive care units. *J Antimicrob Chemother*. **2014**;69(5):1416–1423.
65. Bassetti M, Peghin M, Vena A, Giacobbe DR. Treatment of infections due to mdr gram-negative bacteria. *Front Med (Lausanne)*. **2019**;6:74.
66. Bassetti M, Giacobbe DR, Giamarellou H, et al. Management of kpc-producing klebsiella pneumoniae infections. *Clin Microbiol Infect*. **2018**, 24(2), 133–144.
67. Daikos GL, Tsaousi S, Tzouvelekis LS, et al. Carbapenemase-producing klebsiella pneumoniae bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. *Antimicrob Agents Chemother*. **2014**;58(4):2322–2328
68. Gonzalez-Padilla M, Torre-Cisneros J, Rivera-Espinar F, et al. Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant klebsiella pneumoniae. *J Antimicrob Chemother*. **2015**;70(3):905–913.
69. Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by klebsiella pneumoniae carbapenemase-producing k. Pneumoniae. *Clin Infect Dis*. **2019**;68(3):355–364.
70. Gutierrez-Gutierrez B, Salamanca E, de Cueto M, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing enterobacteriaceae (increment): a retrospective cohort study. *Lancet Infect Dis*. **2017**;17(7):726–734.
71. B.S. Chhikara. Current trends in nanomedicine and nanobiotechnology research. *J. Mater. Nanosci*. **2017**, 4 (1), 19–24..
72. Paul M, Carmeli Y, Durante-Mangoni E, et al. Combination therapy for carbapenem-resistant gram-negative bacteria. *J Antimicrob Chemother*. **2014**;69(9):2305–2309.
73. Bassetti M, Peghin M, Vena A, Giacobbe DR. Treatment of infections due to mdr gram-negative bacteria. *Frontiers in Medicine*. **2019**;6:74.
74. Giacobbe DR, Mikulska M, Viscoli C. Recent advances in the pharmacological management of infections due to multidrugresistant gram-negative bacteria. *Expert Rev Clin Pharmacol*. **2018**; 11(12): 1219–1236.
75. De Waele JJ, Akova M, Antonelli M, et al. Antimicrobial resistance and antibiotic stewardship programs in the ICU: insistence and persistence in the fight against resistance. A position statement from esicm/escmid/waaar round table on multi-drug resistance. *Intensive Care Med*. **2018**;44(2):189–196.
76. Martin-Loeches I, Diaz E, Valles J. Risks for multidrug-resistant pathogens in the icu. *Curr Opin Crit Care*. **2014**;20(5):516–524.
77. Miller BM, Johnson SW. Demographic and infection characteristics of patients with carbapenem-resistant enterobacteriaceae in a community hospital: development of a bedside clinical score for risk assessment. *Am J Infect Control*. **2016**;44(2):134–137.
78. S.S. Malapure, S. Bhushan, R. Kumar, S. Bharati. Radiolabelled nanoparticles in cancer management: current status and developments. *Chem. Biol. Lett*. **2018**, 5 (1), 25–34..
79. Bassetti M, Carnelutti A, Peghin M. Patient specific risk stratification for antimicrobial resistance and possible treatment strategies in gram-negative bacterial infections. *Expert Rev Anti Infect Ther*. **2017**;15(1):55–65.
80. Cano A, Gutierrez-Gutierrez B, Machuca I, et al. Risks of infection and mortality among patients colonized with klebsiella pneumoniae carbapenemase-producing k. Pneumoniae: validation of scores and proposal for management. *Clin Infect Dis*. **2018**;66(8):1204–1210.
81. Brink AJ, Van Wyk J, Moodley VM, et al. The role of appropriate diagnostic testing in acute respiratory tract infections: an antibiotic stewardship strategy to minimise diagnostic uncertainty in primary care. *S Afr Med J*. **2016**;106(6):30–37.
82. Giacobbe DR, Mikulska M, Tumbarello M, et al. Combined use of serum (1,3)-beta-d-glucan and procalcitonin for the early differential diagnosis between candidaemia and bacteraemia in intensive care units. *Crit Care*. **2017**;21(1):176.

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