ECRONICON OPEN ACCESS

EC PHARMACOLOGY AND TOXICOLOGY
Review Article

Challenges in Antimicrobial Resistance: An Update

Zenis Baluja, Nusrat Nabi and Arunabha Ray*

Department of Pharmacology, Hamdard Institute of Medical Sciences and Research (HIMSR), Jamia Hamdard, New Delhi, India

***Corresponding Author**: Arunabha Ray, Professor, Department of Pharmacology, Hamdard Institute of Medical Sciences and Research (HIMSR), Jamia Hamdard, New Delhi, India.

Received: June 05, 2018; **Published:** August 28, 2018

Abstract

Antimicrobials are by far one of the common group of drugs used in a health care facility and accounts for a major part of health care budget. Inappropriate prescription, dispensing and use has led to development of antimicrobial resistance which is rapidly emerging as a menace for effective medical care. Examples of misuse include taking antibiotics for viral infections such as colds and flu (in human sector), and using them as animal growth promoters on farms or in aquaculture (non-human sector). Antimicrobial resistance is threatening the effective treatment of even common infections like pneumonia, tuberculosis, STDs, septicemia etc. This has been accelerated by the misuse and overuse of antibiotics, as well as poor infection prevention and control. Antimicrobials target not the actual patient, but instead the growth and ecology of invading pathogens. As resistant microorganisms spread from one host to the next, the greatest burden falls on public health instead of the consumer of the drug. Rational use of antimicrobials must also be considered an issue of patient safety, as antibiotic use can have direct negative side effects on the individual consumer, including serious adverse drug reactions. Steps should be taken by all stake holders in healthcare to reduce the impact and limit the spread of antimicrobial resistance. At the same time, a large proportion of the world's population lack access to effective antibiotics, hence access to antibiotics is also mandatory within the framework of rational use. The implementation of antibiotic stewardship programs aims to maintain their effectiveness by a rational use of the available antimicrobials. It must be remembered that the essential target of therapy with antimicrobials is successful treatment of individual patients with microbial infections. With this background the current paper was planned with the primary objective to review and highlight the major domains pertaining to antimicrobial resistance.

Keywords: *Antimicrobials; Resistance; Irrational Use; Mutation; National Policy*

Introduction

Emergence and spread of antibiotic resistance is the biggest menace of 21st century. We are not only facing it in India but also globally entire human population is getting affected by it. Community acquired infections such as *Streptococcus, Enterococcus, Neisseria* etc. are getting difficult to treat due to increase in antibiotic resistance amongst pathogenic bacteria. This resistance to treatment is not only adding to the treatment cost of the patient but also poses a potential threat towards epidemic spread of non-responding infections. In the last few decades, not many new antibiotics have been introduced [1]. Thus there is an urgent need to conserve our present pool of antibiotics. There is widespread irrational use of various groups of antibiotics by health service providers in our country [2]. Environmental factors also directly or indirectly plays some part in development of resistance against an antibiotic in a particular geographical area. In hospitals [3], there is rise in number of both drug resistant gram-positive infections caused by *Staphylococcus aureus*, coagulase-negative staphylococci etc. as well as those caused due to drug resistance in gram-negative organisms like *Pseudomonas, Serratia* etc [4]. Resistant and virulent strains of *Mycobacterium tuberculosis* in recent times has called for rapid measures in the wake of potential reoccurrence of this disease. One of the examples of new antibiotic resistant genes is New Delhi metallo-ß-lactamase (NDM-1) in Gram-negative organisms

[5] which can hydrolyze all beta lactams except monobactams. The problem of antibiotic resistance is further aggravated as bacteria and their resistance genes are spreading far at a faster rate. Due to wide range of transportation option available, affected individuals travel across the world thus spreading the resistant bacteria. The exchange of eatables across the globe also contribute to taking the resistant bacteria across the boundaries. Poor hygiene in hospitals as well as community promote spread of infection. As per WHO report about 490 000 people developed multi-drug resistant TB globally in 2016. Drug resistance is also complicating the treatment outcome of HIV and malaria. With this background the current paper was planned with the primary objective to review and highlight the major domains pertaining to antimicrobial resistance.

Genetic basis of antimicrobial resistance [6]

Bacteria use two major genetic strategies to adapt to the antibiotic attack:

1. Mutations in gene(s) associated with the mechanism of action of the compound.
2. Acquisition of foreign DNA coding for resistance determinants through horizontal gene transfer (HGT).

Mutational Resistance

Antibiotic action is altered by mutation via one of the following mechanisms:

a) Modifications of the antimicrobial target.

b) Decrease in the drug uptake.

c) Activation of efflux mechanisms to extrude the harmful molecule

d) Global changes in important metabolic pathways via modulation of regulatory networks.

Horizontal Gene Transfer

Bacteria acquire external genetic material through three main strategies:

- Transformation
- Transduction
- Conjugation

Antibiotic resistance mechanism can be classified according to the biochemical route involved in resistance as follows:

1. Modifications of the antimicrobial molecule
2. Prevention to reach the antibiotic target by decreasing penetration or actively extruding the antimicrobial compound
3. Changes and/or bypass of target sites
4. Resistance due to global cell adaptive processes.

Modifications of the Antibiotic Molecule

Chemical alterations of the antibiotic

One of the best examples of resistance via modification of the drug is the presence of aminoglycoside modifying enzymes (AMEs) that covalently modify the hydroxyl or amino groups of the aminoglycoside molecule. Worldwide many AMEs have been described and they have become the important mechanism of aminoglycoside resistance [7].

- APH(3) family is widely distributed in gram-positive and gram-negative bacteria and alters kanamycin and streptomycin, but spares gentamicin and tobramycin.
- AAC(6′)-I is mainly found in gram-negative clinical isolates and affects most aminoglycosides including amikacin and gentamicin.

Destruction of the antibiotic molecule

- The main mechanism of β-lactam resistance relies the action of β- lactamases which destroys the compound. Genes encoding for β-lactamases are generally termed *bla*, followed by the name of the specific enzyme e.g. bla_{KPC}. They have been found in the chromosome or localized in MGEs as part of the accessory genome.
- ESBLs (such as CTX-M) to carbapenemases like KPC (*Klebsiella pneumoniae* carbapenemase), an enzyme that is found in several gram-negative species [8,9].
- In 2008, a new carbapenemase was identified in a *K. pneumoniae* isolate recovered from a Swedish patient who had been previously admitted to a hospital in New Delhi, India. The enzyme was designated NDM-1, in reference to its origin (New Delhi Metallo β-lactamase) [10].

Decreased Antibiotic Penetration and Efflux

Decreased permeability

One classic example of porin-mediated resistance is the aberrant production of OprD in *P. aeruginosa*, which is normally used for the uptake of basic amino acids and antibiotics. Mutations in the *oprD* gene have been demonstrated in clinical isolates of *P. aeruginosa* during therapy [11].

Efflux Pumps

Tetracycline resistance is one of the classic examples of efflux-mediated resistance, where the Tet efflux pumps (belonging to the MFS family) extrude tetracyclines using proton exchange as the source of energy.

More than 20 different *tet* genes have been described, most of which are harboured in MGEs. The majority of these genes are found in gram-negatives, with Tet(K) and Tet(L) being among the few exceptions that predominate in gram-positive organisms [12,13].

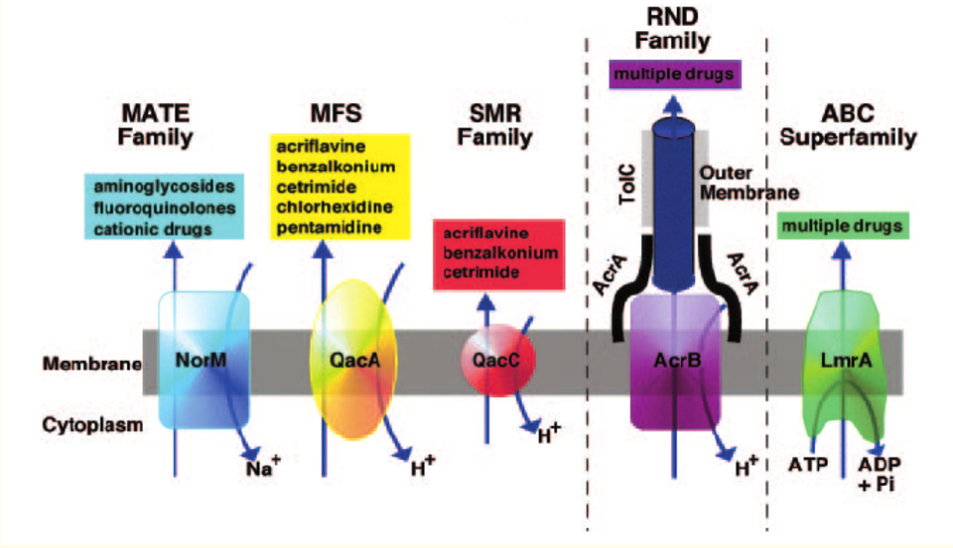

Figure 1: *Five families of efflux pumps as targets of antimicrobial resistance [14].*

Changes in Target Sites

Target protection

Examples of drugs affected by this mechanism include tetracycline (Tet[M] and Tet[O]), fluoroquinolones (Qnr) and fusidic acid (FusB and FusC).

One of the best-studied examples of the target protection mechanism is the tetracycline resistance determinants Tet(M) and Tet(O). Tet(M) was initially described in *Streptococcus* spp. and Tet(O) in *Campylobacter jejuni*, but they are now both widely distributed among different bacterial species, likely because they have been found in several plasmids and in broad-range conjugative transposons [15].

Modification of the target site

Mutations of the target site

Example of mutational resistance is the development of rifampin (RIF) resistance. RIF is a rifamycin that blocks bacterial transcription by inhibiting the DNA-dependent RNA polymerase, which is a complex enzyme with a α2ββ'σ subunit structure. RIF binding pocket is a highly conserved structure located in the β subunit of the RNA polymerase (encoded by *rpoB*), and after binding, the antibiotic molecule interrupts transcription by directly blocking the path of the nascent RNA [16].

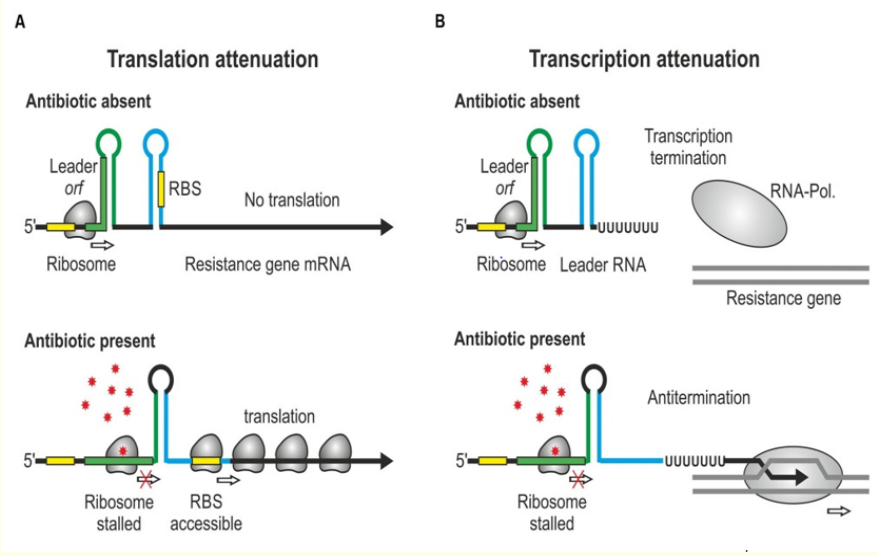

Figure 2: *Antimicrobial resistance involving regulatory RNA [17].*

Enzymatic alteration of the target site

Methylation of the ribosome catalyzed by an enzyme encoded by the erm genes (erythromycin ribosomal methylation), which results in macrolide resistance is one of the examples of resistance through this mechanism. These enzymes are capable of mono- or dimethylating an adenine residue in position A2058 of the domain V of the 23rRNA of the 50S ribosomal subunit. Due to this biochemical change, the binding of the antimicrobial molecule to its target is impaired [18,19].

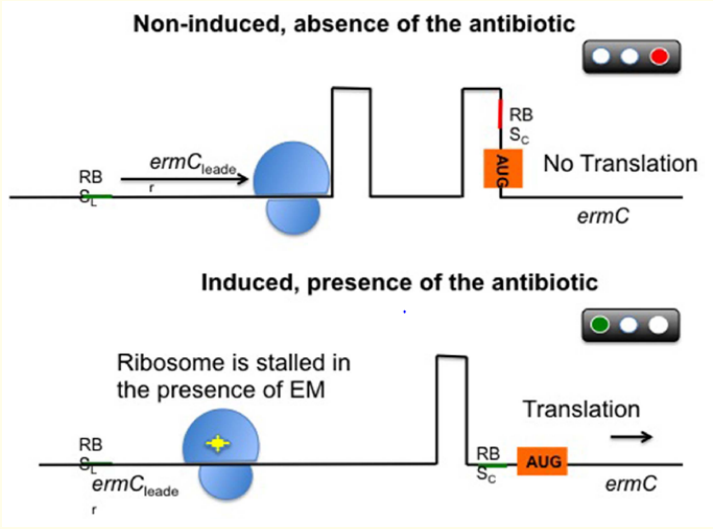

Figure 3: *Post transcriptional control of erm C gene [6].*

Complete replacement or by pass of the target site

Examples include methicillin resistance in *S. aureus* due to the acquisition of an exogenous PBP (PBP2a) and vancomycin resistance in enterococci through modifications of the peptidoglycan structure mediated by the *van* gene clusters.

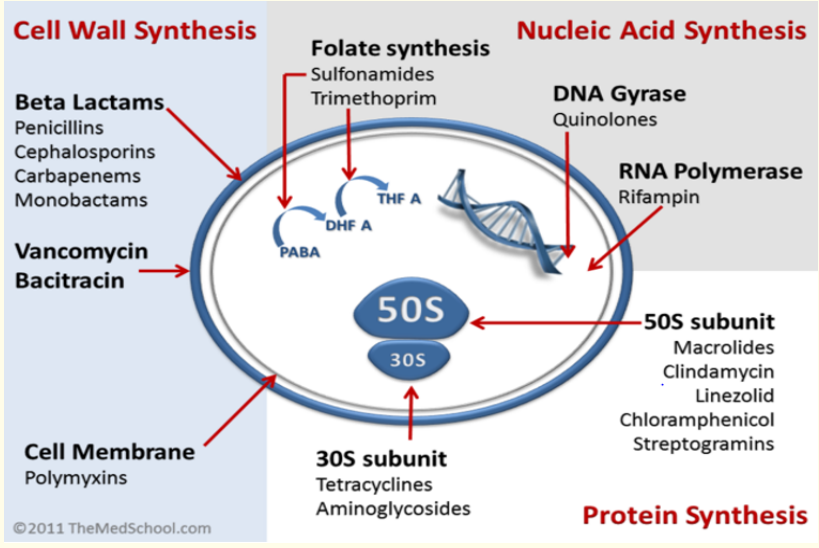

Figure 4: *Mechanisms of antimicrobial action and resistance by alteration of target site [20].*

Resistance due to Global Cell Adaptations

Development of resistance to daptomycin (DAP) and vancomycin are the most clinically relevant examples of resistance phenotypes to be the result of sequential and ordered genetic changes that usually involve genes forming part of regulatory systems controlling cell envelope homeostasis and result in global cell adaptive response to the antibacterial attack [21,22].

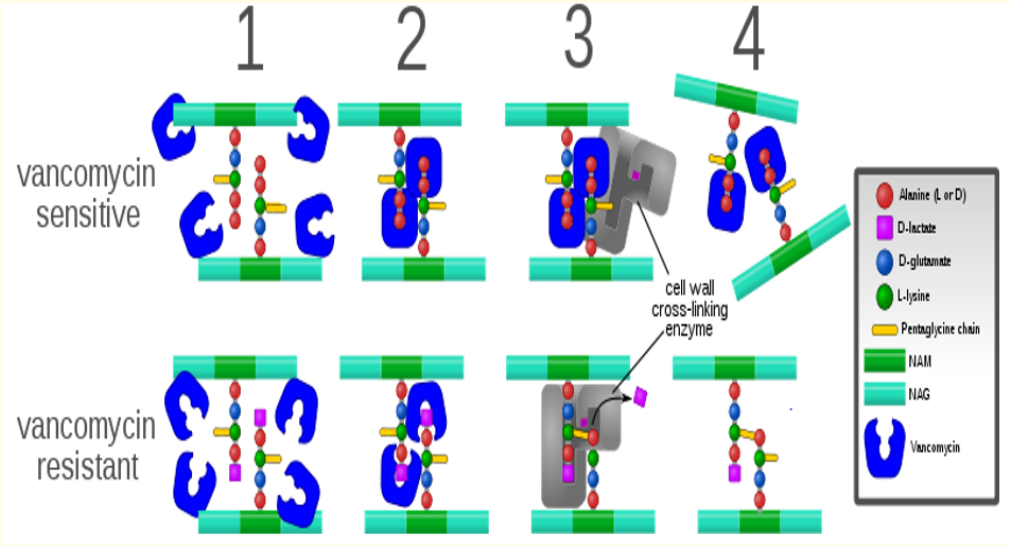

Figure 5: *Mechanism of vancomycin resistance [23].*

Antibiotic	Mode of resistance
β-Lactams	Hydrolysis, efflux, altered target
Aminoglycosides	Phosphorylation, acetylation, nucleotidylation, efflux, altered target
Glycopeptides	Reprogramming peptidoglycan biosynthesis
Tetracyclines	Monooxygenation, efflux, altered target
Macolides	Hydrolysis, glycosylation, phosphorylation, efflux, altered target
Lincosamides	Nucleotidylation, efflux, altered target
Streptogramins	C-O lyase , acetylation , efflux, altered target
Oxazolidinones	Efflux, altered target
Phenicols	Acetylation, efflux, altered target
Quinolones	Acetylation, efflux, altered target
Pyrimidines	Efflux, altered target
Sulfonamides	Efflux, altered target
Rifamycins	ADP-ribosylation, efflux, altered target
Lipopeptide	Altered target
Cationic peptides	Altered target, efflux

Table 1: *Modes of resistance of commonly used antibiotics [24].*

Factors responsible for rise of resistance in hospital [25]

- High severity of illness
- More immuno-compromised patients
- Increase transfer of resistant organisms from the community
- Inadequate infection control
- Ineffective isolation practice and compliance
- More empirical polymicrobial therapy
- Newer procedures and devices
- More usage of antimicrobials for a particular area per unit time

Factors responsible for global antimicrobial resistance [26]

- Human Antimicrobial mis-/over-use
- Animal Antimicrobial mis-/over-use
- Environmental contamination like sewage and heavy metals
- Healthcare transmission
- Sub-optimal rapid diagnostics
- Sub-optimal preventive medicine/vaccination
- Sub-optimal dosing
- Travel
- Mass drug administration

Other than the above cause, we are majorly lacking behind in national level policies which can monitor as well as set an accountability for irrational use of antibiotics. Also our surveillance system and regulatory bodies are not very active. Natural evolution of resistance cannot be halted but we can prevent or reduce this epidemic by appropriate and timely measures in our health care delivery system.

Evaluating the use of antibiotics [27]

The use of antibiotics is broadly divided into specific, empirical and prophylactic. Further the irrational use of antimicrobials was grouped as follows:

- No valid Indication
- Improper dosage/interval
- Improper/unnecessary combination
- Using Reserve or broad spectrum antibiotics
- Improper beginning time for prophylactic use or improper duration of treatment
- Incorrect choice of antibiotic
- More expensive and toxic drug
- Any combination of any of above

Economic burden of antimicrobial resistance

In a developing nation like India where we all already facing shortage of budgets in the health care field, the treatment cost is doubled by this resistant bacteria. In absence or unavailability of first and second line of antibiotics, physicians have no other options but to pre-

scribe expensive and more stronger agents [28,29]. Patient suffering from resistant infections take more time to recover, hence longer hospital stay, more visits by the consultant thereby adding to their total treatment cost. The average duration of hospital stay for a resistant case is said to increase by 6 - 12 days in comparison to a non-resistant case [30]. The treatment cost varying between $18,588 to $29,069 [31]. Not only the treatment cost add to the overall cost but also the time taken by the patient to recover from his illness and lost wages add to the overall health care cost [32].

Preventive and Regulatory Policies

Measures taken to check the spread of resistant bacteria include:

1. Improvement of hospital hygiene [33]
2. Vaccines [34]
3. Limit the antibiotic use [35]
4. Rotation of various antibiotics [36].

The ultimate goal is to preserve the present pool of antibiotics. Some models have been introduced in order to compare and evaluate the competition between sensitive and resistant bacteria [37] specially the community wide treatment success rate of tuberculosis [38].

There are two models suggested to analyze a series of mathematical models which are used to generate data related to the effects of drug treatment patterns at the population level. The first model deals with single drug treatment and resistance to that drug and analyze different usage patterns. The second model analyzes the population-level consequences of different usage patterns of the two drugs. The goal of analyzing such models is to understand how antibiotic usage patterns may be optimized to preserve or restore antibiotic effectiveness.

In the wake of widespread cases of antimicrobial resistance, many programmes are launched in order to curb this problem.

- India Clen: Indian Clinical Epidemiology Network is generating data on national level regarding Anti-microbial resistance in various pathogens like *Pneumococcus, H. influenzae* etc.
- IIMAR: Indian Initiative for Management of Antibiotic Resistance- It was started by the WHO in 2008 to promote rationale use of antibiotics with collaboration with several NGO's.
- INSAR: Indian Network for Surveillance of Antimicrobial Resistance- It also helps in generating data in anti-microbial resistance with about 20 labs associated with it in public as well as private sector.
- Indo-Swedish workshop was also held in 2010 to discuss a joint strategy to control the cases of AMR [39].
- The Indian Council of Medical Research (ICMR) have started a project to address the growing AMR threat in India
- Central Drugs Standard Control Organization (CDSCO) implemented Schedule H1 in the year 2014. This schedule consists of 24 antibiotics mainly third- and fourth-generation cephalosporins, carbapenems, anti-tuberculosis drugs, and also newer fluoroquinolones.

As per a community-based surveillance by the WHO, in Delhi, Mumbai, Vellore in India and Durban, Brits of South Africa, it was depicted that there were very high incidence of AMR rates to cotrimoxazole and amoxicillin. Also there were findings showing that usage of expensive and third generation drugs was more in private sector in comparison of government hospital which prescribed cheap and first line of anti-microbial drugs [40].

In India, a national antibiotic policy is implemented urging hospitals to get accredited with the National Accreditation Board for Hospitals and Health Care Providers thus promoting rationale use of antimicrobial agents [41]. Unfortunately very few studies in India are conducted to promote the quality use of antibiotics and for evaluation of its effectiveness.

Also there is a need for urgent involvement by the medical institutions to evaluate antibiotic prescriptions and introduce education programs regarding the rational use of antibiotic for all health professionals stressing upon:

- Rational and valid antibiotics prescribing
- Hygiene improvement
- Better patient care
- Careful treatment selection
- Identification of pathogens as well as resistant pathogens

Medical institutions and hospitals should setup:

- Infection control committee
- Drug therapy committee
- Adequate guidelines for evidence based use of antibiotics
- Evaluate pharmacy reports
- Establish a list of essential drugs
- Educate staff about importance of rationale antibiotics use.

Along with this, there should also be strict monitoring of community pharmacies so they do not dispense antibiotic without a valid medical prescription [42]. There is transfer of resistant bacteria to humans by farm animals as antibiotic resistance were found in the intestinal flora of both farm animals and the man [31]. Thus antibiotic prescribing in animals and their use in soils must be put to control along with improvement in vaccination programs and farm hygiene.

Global Action Plan on Antimicrobial Resistance

In the year 2015, WHO introduced Global Action Plan on Antimicrobial Resistance (GAP-AMR). Whereas, in India the Ministry of Health and Family Welfare implemented the National Action Plan on Antimicrobial Resistance (NAP-AMR) on the similar lines of global action plan with one extra addition.

Objectives of NAP-AMR [43]

- To improve awareness and understanding of antimicrobial resistance.
- To strengthen surveillance and research.
- To reduce the incidence of infection.
- To optimize the use of antimicrobial medicines in health, animals and food
- To ensure sustainable investment in countering antimicrobial resistance.
- Strengthening India's leadership on AMR

Antibiotic policies and preventive strategies of Australia

The Department of Health and the Department of Agriculture began to develop a 'one health' approach to resistance management in the year 2013 and published the National Antimicrobial Resistance Strategy in June 2015 [44].

- The Australian Commission on Safety and Quality in Health Care initiated the Antimicrobial Use and Resistance in Australia (AURA) project which had all the data on antimicrobial use and resistance in human health captured by surveillance strategies and the first national AURA report was published in the year 2016 [45]. The National Antimicrobial Usage Surveillance Program (NAUSP) was responsible for data on antimicrobial use in hospitals.
- Pharmaceutical Benefits Scheme (PBS) collected information on antimicrobial prescriptions in the community.

- National Antimicrobial Prescribing Survey handled data on appropriate use and compliance as per hospitals guidelines.
- NPS Medicine Insight program was responsible for the data related to antibiotic use in general practice
- The Australian Group on Antimicrobial Use and Resistance collected resistance and outcome data of selected pathogen in hospitals and in the community.
- Queensland Health had a data cube of antimicrobial resistance data across Queensland public hospitals.
- Sullivan Nicolaides Pathology had antibiogram data across Queensland and northern New South Wales
- National *Neisseria* Network was responsible for resistance data for Neisseria gonorrhoeae and N. meningitidis.
- National Notifiable Diseases Surveillance System compiled data on Mycobacterium tuberculosis.

Antibiotic Policies and Strategies in USA

- In 1997, The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) issued Guidelines for the Prevention of Antimicrobial Resistance in Hospitals [25,46].
- In 2007, "Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship," were published by IDSA and SHEA to be implemented by all health care facilities [47].
- Combating Antimicrobial Resistance: Policy Recommendations to Save Lives" which is issued by IDSA [48] stresses upon strengthening and adopting antimicrobial stewardship programs in the US healthcare.

Recommendations and Suggestions

- Research to set up goals as well as content of antimicrobial stewardship programs
- Enhance educational activities on antimicrobial stewardship
- Prevention of the over prescription of newer antibiotics.
- To develop new antibiotics and vaccines
- Rapid diagnostic tests and not using antibiotics for viral infections.

CMS must monitor overall implementation of antimicrobial stewardship plans and programs by:

- Reporting of the Antimicrobial Use and Resistance to Centres for Disease Control and Prevention's (CDC's) National Healthcare Safety Network (NHSN).
- Surveillance and intervention to limit irrational use of antibiotics.
- National benchmarking of use of antibiotics at the institutional level.

Antibiotic policies of European Union

- The EU initiated Community strategy against AMR as early as in 2001. This policy was reintroduced as One Health approach by the commission action plan in 2011and it dealt antibiotic resistance problem in both humans and animals.
- A new EU action plan on AMR was conceptualised in 2016 based on principles on 2011 plan. This new One Health action plan against AMR will increase the efficiency of EU against its fight against AMR.

The main objectives of this new plan are:

1. Establishing EU a best practice region
2. Promoting research, development and innovation
3. Shaping the global agenda and protocols against AMR

Conclusion

Rapidly emerging resistant bacteria is a worldwide crisis depicting the global misuse and overuse of anti-microbial agents. The golden pipeline of antibiotic discovery dried up quickly as the manufacture of new antimicrobial agents became more challenging. Big Pharma companies have shifted their efforts on other more profitable fields, causing the wave of resistance grow intensely. In order to handle and sort this problem, a complete understanding of the mechanisms by which bacteria become resistant to antibiotics is of prime importance so we can design novel strategies to counter this urgent threat of resistance. There is a requirement for developing newer antibiotics with the acceptance of the fact that the microorganism will eventually develop resistance to them through their evolutionary mechanism. Therefore, all efforts related to developing antibiotics and studying the mechanisms of resistance must be a continuous, resilient and a steady procedure. On the other hand, rising incomes and the availability of cheap antibiotics over the counter without a valid prescription are all converging to create an ideal scenario for a large-scale selection and dissemination of resistance genes in India. India is not alone in this struggle and the experiences of other countries in dealing with antimicrobial resistance are described in State of the World's Antibiotics Report (2015) [49]. There are many lacunae in the structure and functioning of public health care delivery system with regards to quantification of the problem and various factors related to antimicrobial resistance. There is an urgent and desperate need to develop and strengthen antimicrobial policy, standardize the treatment guidelines and national plans for containment of AMR in each country. More focus should be on research related to public health aspects of AMR at community and hospital level. Also along with the monitoring of Information Education Communication activities there must be evaluation of the existing health care delivery system for both health care providers as well as consumers to improve drug use simultaneously.

There is an immediate need for coordinated efforts in order to implement these new preventive policies, to increase research projects and pursue adequate steps to manage the current crisis.

Bibliography

1. Wright GD. "The antibiotic resistome: the nexus of chemical and genetic diversity". *Nature Reviews Microbiology* 5.3 (2007): 175-186.
2. Raghunath D. "Emerging antibiotic resistance in bacteria with special reference to India". *Journal of Biosciences* 33.4 (2008): 593-603.
3. Parry MF. "Epidemiology and mechanisms of antimicrobial resistance". *American Journal of Infection Control* 17.5 (1989): 286-294.
4. Grayson ML and GM Eliopoulos. "Antimicrobial resistance in the intensive care unit". *Seminars in Respiratory Infections* 5.3 (1990): 204-214.
5. Yong D., *et al*. "Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India". *Antimicrobial Agents and Chemotherapy* 53.12 (2009): 5046-5054.
6. Jose M Munita and Cesar A Arias. "Mechanisms of Antibiotic Resistance". *Microbiology Spectrum* 4.2 (2016): 10.
7. Ramirez MS and Tolmasky ME. "Aminoglycoside modifying enzymes". *Drug Resistance Updates* 13.6 (2010): 151-171.
8. Bush K. "The ABCD's of β-lactamase nomenclature". *Journal of Infection and Chemotherapy* 19.4 (2013): 549-559.
9. Bush K and Jacoby GA. "Updated functional classification of β-Lactamases". *Antimicrobial Agents and Chemotherapy* 54.3 (2010): 969-976.
10. Kumarasamy KK., *et al*. "Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study". *Lancet Infectious Diseases* 10.9 (2010): 597-602.

11. Quinn JP., *et al*. "Emergence of resistance to imipenem during therapy for Pseudomonas aeruginosa infections". *Journal of Infectious Diseases* 154.2 (1986): 289-294.

12. Poole K. "Efflux-mediated antimicrobial resistance". *Journal of Antimicrobial Chemotherapy* 56.1 (2005): 20-51.

13. Laura J V Piddock. "Clinically Relevant Chromosomally Encoded Multidrug Resistance Efflux Pumps in Bacteria". *Clinical Microbiology Reviews* 19.2 (2006): 382-402.

14. Roberts MC. "Update on acquired tetracycline resistance genes". *FEMS Microbiology Letters* 245.2 (2005): 195-203.

15. Connell SR., *et al*. "Ribosomal protection proteins and their mechanism of tetracycline resistance". *Antimicrobial Agents and Chemotherapy* 47.12 (2003): 3675-3681.

16. Campbell EA., *et al*. "Structural mechanism for rifampicin inhibition of bacterial rna polymerase". *Cell* 104.6 (2001): 901-912.

17. Dersch P., *et al*. "Roles of Regulatory RNAs for Antibiotic Resistance in Bacteria and Their Potential Value as Novel Drug Targets". *Frontiers in Microbiology* 8 (2017): 803.

18. Leclercq R. "Mechanisms of resistance to macrolides and lincosamides: nature of the resistance elements and their clinical implications". *Clinical Infectious Diseases* 34.4 (2002): 482-492.

19. Weisblum B. "Erythromycin resistance by ribosome modification". *Antimicrobial Agents and Chemotherapy* 39.3 (1995): 577-585.

20. Kapoor G., *et al*. "Action and resistance mechanisms of antibiotics: A guide for clinicians". *Journal of Anaesthesiology Clinical Pharmacology* 33.3 (2017): 300-305.

21. Wolf D., *et al*. "In-depth profiling of the LiaR response of Bacillus subtilis". *Journal of Bacteriology* 192.18 (2010): 4680-4693.

22. Gardete S and Tomasz A. "Mechanisms of vancomycin resistance in Staphylococcus aureus". *Journal of Clinical Investigation* 124.7 (2014): 2836-2840.

23. https://goo.gl/images/bUPxy6

24. Davies J and Davies D. "Origins and Evolution of Antibiotic Resistance". *Microbiology and Molecular Biology Reviews* 74.3 (2010): 417-433.

25. Shales DM., *et al*. "Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the prevention of antimicrobial resistance: guidelines for the prevention of antimicrobial resistance in hospitals". *Infection Control and Hospital Epidemiology* 18.4 (1997): 275-291.

26. Holmes AH., *et al*. "Understanding the mechanisms and drivers of antimicrobial resistance". *Lancet* 387.10014 (2016): 176-187.

27. Gilbert DN., *et al*. "The Sanford Guide to Antimicrobial Therapy". 34 edition. Antimicrobial Therapy Inc. USA (2004): 1-128.

28. Lushniak BD. "Antibiotic resistance: a public health crisis". *Public Health Reports* 129.4 (2014): 314-316.

29. Centers for Disease Control and Prevention, Office of Infectious Disease Antibiotic resistance threats in the United States (2013).

30. Golkar Z., *et al*. "Bacteriophage therapy: a potential solution for the antibiotic resistance crisis". *Journal of Infection in Developing Countries* 8.2 (2014): 129-136.

31. Bartlett JG., *et al*. "Seven ways to preserve the miracle of antibiotics". *Clinical Infectious Diseases* 56.10 (2013): 1445-1450.

32. Michael CA., *et al*. "The antibiotic resistance crisis: causes, consequences, and management". *Frontiers in Public Health* 2 (2014): 145.

33. Murray BE. "Can Antibiotic Resistance be Controlled?". *New England Journal of Medicine* 330 (1994): 1229-1230.

34. Jernigan DB., *et al*. "Minimizing the impact of drug-resistant streptococcus pneumoniae (DRSP): A strategy from the DRSP working group". *Journal of the American Medical Association* 275 (1996): 206-209.

35. Anonymous. "Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC)". *American Journal of Infection Control* 23.2 (1995): 87-94.

36. Swartz MN. "Hospital-acquired infections: diseases with increasingly limited therapies". *Proceedings of the National Academy of Sciences of the United States of America* 91.7 (1994): 2420-2427.

37. Massad E., *et al*. "Modeling and simulating the evolution of resistance against antibiotics". *International Journal of Bio-Medical Computing* 33.1 (1993): 65-81.

38. Blower SM., *et al*. "Control strategies for tuberculosis epidemics: new models for old problems". *Science* 273.5274 (1996): 497-500.

39. World Health Organization. "Prevention and containment of antimicrobial resistance. Report of a regional meeting Chiang Mai, Thailand, 8th to 11th of June 2010" (2011).

40. Behera B and Mathur P. "High levels of antimicrobial resistance at a tertiary trauma care centre of India". *Indian Journal of Medical Research* 133.3 (2011): 143-145.

41. World Health Organization. "WHO Global Strategy for Containment of Antimicrobial Resistance" (2011).

42. Dreser A., *et al*. "Uso de antibióticosen México: revisión de problemas y políticas". *Salud Pública de México* 50.4 (2008): 480-487.

43. National Action Plan on Antimicrobial Resistance (NAP-AMR) 2017 - 2021. Ministry of Health and Family Welfare Government of India.

44. Department of Health and Department of Agriculture. National Antimicrobial Resistance Strategy 2015-2019. Canberra: Commonwealth of Australia (2015).

45. Australian Commission on Safety and Quality in Health Care. AURA 2016: first Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC (2016).

46. Shlaes DM., *et al*. "Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals". *Clinical Infectious Diseases* 25.3 (1997): 584-599.

47. Dellit TH., *et al*. "Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship". *Clinical Infectious Diseases* 44.2 (2007): 159-177.

48. Spellberg B., *et al*. "Combating antimicrobial resistance: policy recommendations to save lives". *Clinical Infectious Diseases* 52.5 (2011): S397-S428.

49. CDDEP. The State of the World's Antibiotics, 2015. Washington DC: Center for Disease Dynamics, Economics and Policy (2015).

Volume 6 Issue 9 September 2018