Review Article

National Policy and the Role of Pharmacist in Averting Antibiotic Resistance in India

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ABSTRACT

The emerging problem of antibiotic resistance is a serious threat to global public health. The situation is aggravated by a substantial decline in the research and development of antibacterial agents. Resistance has emerged even to newer, more potent antimicrobial agents like carbapenems. Development and spread of antimicrobial resistance (AMR) is commonly due to overuse, misuse, and indiscriminate use of antimicrobials by doctors, nurses and pharmacists, non-compliance and self-medication by patients and use in animal husbandry and agriculture. Broad use has created a strong selective pressure, which consistently has resulted in the survival and spread of resistant bacteria, providing an excellent example of Darwinian evolution. Both the volume and the way antibiotics are applied contribute to the development of resistant strains. There are definite policies / guidelines for appropriate use of antimicrobials at national level in specific national health programmes being run in the country, viz., RNTCP, National AIDS control programme. To monitor antimicrobial resistance, it is necessary to enact regulations for use and misuse of antibiotics in the country, creation of national surveillance system for antibiotic resistance, regulatory provision for monitoring use of antibiotics in human, veterinary & industrial sectors and identification of specific intervention measures for rational use of antibiotics. Pharmacists are increasingly being involved in providing their expertise when AMR policies are being created, evaluated and implemented. Pharmacists are experts in medicines. In their advisory and clinical role, they ensure optimal management of antimicrobial treatment. Pharmacists ensure the quality of medicines and their safe disposal, and contribute to reduction of antimicrobials in the environment.

Keywords: AMR, RNTCP, Self-medication, Resistant strains, Carbapenems.

INTRODUCTION

Infections caused by microorganisms have threatened human life since time immemorial. During the pre-antibiotic era, they have been a major concern for the high morbidity and mortality in humans. Some of the virulent organisms with the potential to spread infection from one infected person to another at a very rapid rate may cause worldwide pandemics, epidemics or outbreaks. With the discovery of the first antibiotic, "the magic bullet" Penicillin in the year 1943, patients could be effectively cured of many life-threatening infections. This gave a huge relief to the medical practitioners. Next three decades saw the development and discovery of a wide variety of antimicrobial agents. Subsequently, the pace of discovery of newer molecules declined from 1970 to 1987. It has reached a "discovery void" level from 1987 onwards up till now. This is the post-antibiotic era in which the medical practitioners have to treat and manage all types of infections with equal or greater efficiency. The failure to develop innovative antibiotic molecules over the last few decades has made the task of combating resistant organisms more difficult.

The major cause of antimicrobial resistance (AMR) is the inappropriate use of antibiotics.[1] Poverty and inadequate access to antibiotics constitute a major factor in the development of resistance.[1] Another common cause of developing resistance is improper diagnosis.[1] In many instances death of an adequately equipped diagnostic laboratory in the vicinity compels the physician to prescribe antibiotics empirically, thus, increasing the likelihood of the patient receiving a wrong antibiotic. Furthermore, ready availability of antibiotics over-the-counter and sales promotion schemes by the pharmaceutical manufacturers also leads to the promotion of indiscriminate use, thus, increasing the likelihood of development of resistance.[1] Counterfeit drugs are also a problem contributing to development of resistance. These contain either the wrong ingredient, or lesser amount of the active ingredient. In some instances, the medication poisons are capable of causing disability or even death.[1] Over 40% of prescriptions for antibiotics were more or less inappropriate.[2] This was found to be directly related to the tendency towards self-medication and the unnecessary use of antibiotics for common sore throats and colds that most frequently are caused by viral infections on which antibiotics have no effect.[2]

Antibiotic resistance has increased dramatically in the last 20 years, and very few new products have been discovered, with almost no drug with any new mechanisms of action. Morbidity and mortality from bacterial infections resistant to antibiotics is already very high and make impressive reading.

Resistance affects both Gram-positive and Gram-negative bacteria. The antibiotic resistances of Gram-negative

bacteria has increased dramatically in the last two decades and pose a serious challenge as almost no new antibiotics active against them has been made available in the last few years, representing a dramatic public health threat. Potent antibiotics lost their efficacy over time, rendering them useless for conditions they could once successfully treat.

Development of various levels of resistance has been inevitable after the introduction of new antibiotic class, some with clinical implications becoming evident only shortly after being brought to market.[3] The objective of this article is to provide an insight about the role of national policy and pharmacist in averting the antibiotic resistance in India.

DISCUSSION

Resistant determinants were present prior to the introduction of antibiotics, but were mostly found in natural antibiotic producing organisms. Bacterial resistance has evolved with the increased number, volume and diversity of antimicrobial applications. Many of these resistant bacteria are not obligate pathogens, being part of indigenous microflora.[4]

Through a Darwinian selection process, microorganisms have developed robust mechanisms to evade destruction from many toxic substances. Most antimicrobial drugs are naturally produced by microorganisms, including environmental fungi and saprophytic bacteria, or are synthetic modifications of them, with only a few drugs (sulphonamides and fluoroquinolones) being wholly synthetic.[3] The protective mechanisms that have evolved include preventing entry of or exporting the drug, producing enzymes that destroy or modify the antimicrobial, or making changes to the antimicrobial target.[3] One example where a naturally occurring resistance mechanism has had an effect on human health is the resistance developed against β-lactam antimicrobial drugs, in which the enzymes (β-lactamases) that inactivate these antimicrobial molecules have existed for millions of years. The production of antimicrobial molecules by saprophytic organisms were originally thought to inhibit the growth of neighbouring organisms, providing a competitive advantage in the local environment; however, some studies suggest a more complex interaction.[3] First, the concentration of antimicrobial molecules in the soil seems to be too low to inhibit growth of other bacteria. Second, evidence suggests that even sublethal concentrations of antimicrobials have substantial effects on bacterial physiology, increasing the rate of microbial adaptive evolution and possibly acting as signalling molecules influencing microbial and host gene expression. Of particular note are some saprophytic bacteria that produce carbapenems (an important class of broad-spectrum antimicrobials in clinical use) in which the genes implicated in the synthesis of carbapenems might also have a role in the quorum-sensing apparatus (the mechanism through which a colony of microorganisms coordinates growth and gene expression) or formation of biofilms. This process leads to further questions about the unintended effects of antimicrobial drugs, with our understanding of their potential effect on microorganisms, beyond their inhibitory action, remaining incomplete. Emergence of resistance to synthetic antimicrobials also occurs. This resistance has unfortunately been widely exemplified in the case of fluoroquinolones, for which in Escherichia coli isolated. Fluoroquinolone resistance is now at 10–40% .[3]

Established Mechanisms of Antimicrobial Resistance

For an antibiotic to be effective, it must reach the target site in an active form, bind to the target, and interfere with its function. Thus, bacterial resistance to an antimicrobial agent can occur due to three general mechanisms.[1]

The drug does not reach its target

In Gram negative bacteria, many antibiotics enter the cell through protein channels called Porins. Mutations or loss of these channels can prevent/slow the rate of antibiotic entry into a cell, effectively reducing drug concentration at the target site. If the drug target is intracellular and the drug requires active transport across the cell membrane, a mutation that interferes with the transport mechanism can confer resistance (aminoglycosides). Bacteria can also transport antimicrobial drugs out of the cell through efflux pumps. Resistance to numerous drugs, including fluoroquinolones, macrolides, tetracyclines and beta lactam antibiotics, is mediated by this mechanism.[1]

The drug is inactivated

Bacterial resistance to aminoglycosides can be due to a plasmid encoded aminoglycoside-modifying enzymes. Similarly, β-lactamase production is the most common mechanism of resistance to penicillins and other β-lactam drugs. Many hundreds of different β-lactamases have now been identified. A variation of this mechanism is failure of the bacterial cell to activate a prodrug (loss of ability of M. tuberculosis to activate isoniazid).[1]

The target site is altered

This may be due to mutations in drug binding region of target enzyme (fluoroquinolones), target modification where ribosomal protection type of resistance to macrolides and acquirement of a resistant form of the susceptible target (methicillin resistance in Staphylococcus Spp.) due to production of a low-affinity penicillin-binding protein (PBP).[1]

Both the amount of antibiotics used and the manner in which they are used contribute to the development of resistance. The use of broad spectrum antibiotics rather than narrow spectrum drugs is known to favour the emergence of resistance by broadly eliminating competing susceptible flora.

Antibiotics are frequently prescribed in the treatment of viral infections or at wrong doses for incorrect periods of

time. Antibiotic prescription practice can be more closely related to the emergence of resistance than the volume used.

The More You Use Them, the More You Lose Them [5]

The 7 key areas of action to address the problem of AMR

- Strengthen inter sectoral coordination.
- Strengthen surveillance of antibiotic resistance.
- Promote rational use and strengthen surveillance of antibiotic consumption.
- Strengthen infection control and surveillance in health – care settings.
- Prevent emerging resistance in the veterinary and food sectors.
- Promote innovation and research on new drugs.
- Improve awareness, patient safety and partnership.[(2)]

Role of Pharmacist in Averting Antibiotic Resistance In India

The spread of AMR cannot be combated at the national level alone. It is a global problem that requires a coordinated effort. The overall goal must be to preserve our ability to treat serious infections. In some contexts, preserving the effectiveness of antimicrobial medicines means to use them less.[6]

Although, multidrug-resistant strains of pathogens are increasing in hospital settings, an overall reduction of AMR can only be obtained by addressing the outpatient use of antibiotics. Thus, the role of the community pharmacist is key in reducing the threat of AMR. It is the pharmacist who has the last contact with the patient before he or she receives an antibiotic medicine and, thus, the pharmacist acts as the gatekeeper.[6]

Community pharmacists are often the first point of contact for the public and they have a pivotal role in advising patients on minor ailments and referring them to their physician when required. They are often the entry gate to the health system on account of their easy accessibility.[7]

That accessibility has been evaluated, where a recent study indicates that, between July 2011 and July 2012, 94% of people aged 18 years and over reported visiting a community pharmacy. This proportion increases to 99% for people aged 65 years and over. This situation gives pharmacists the unique opportunity to offer an effective medication therapy management and counselling on consumption of medicines and also engage patients in their appropriate, efficacious, safe and responsible use, as well as consulting and collaborating with physicians to ensure optimal and responsible use of antibiotics.[7]

Due to their special position in the community, pharmacists can educate and lead the general public in their (antimicrobial) medication-related needs. Roles played by community pharmacists include health promotion and infection minimisation or control, triage and optimal treatment management.

It is clear that a number of issues need to be addressed in the context of the pharmacist's role in combating AMR. These include:

- ✓ Dispensing antimicrobials without a prescription;
- ✓ Enforcing rules relevant to unauthorized dispensing;
- ✓ Developing appropriate regulations, where necessary;
- ✓ Using repeat prescriptions for antimicrobials;
- ✓ Adjusting quantity dispensed v/s quantity prescribed;
- ✓ Managing waste (used antibiotics);
- ✓ Using pharmacies in campaigns to promote and conduct awareness on the use of antimicrobials;
- ✓ Providing information (pharmacist to patient) on antimicrobials, AMR and AMR-related issues
- ✓ Training pharmacy students and pharmacists in AMR and AMR-related issues
- ✓ Cooperating with prescribing physicians
- ✓ Providing antibiotic stewardship in primary-care settings.[(7)]

Hospital Pharmacists fighting AMR

As well as dispensing medicines, in some countries hospital pharmacists are also responsible for their purchase, manufacture and quality testing. Pharmacists work closely with medical and nursing staff to ensure that patients receive the best treatment, advising on the selection, dose and administration route. They also provide help and advice to patients in all aspects of their medicines. These activities make pharmacists strong supporters in the fight against the threat of AMR in hospitals. Their work in multidisciplinary teams puts them in a good position to coordinate strategies for better antimicrobial stewardship and develop processes with regard to such activities as sterilization and hygiene.[7]

Pharmacist led stewardship programmes

Antimicrobial stewardship programmes in hospitals seek to optimise antimicrobial prescribing in order to improve individual patient care and slow the spread of antimicrobial resistance.

All hospitals should have an antimicrobial lead pharmacist who promotes antimicrobial stewardship. This is a perfect scenario where pharmacists can manage the correct use of antimicrobials, and have a remarkable and positive impact on AMR prevention.[7]

National Policy

Antimicrobial resistance in pathogens causing important communicable diseases has become a matter of great public health concern globally including our country. There are definite policies / guidelines for appropriate use of antimicrobials at national level in specific national health programmes being run in the country e.g. RNTCP, National AIDS control programme.[8]

In this regard a task force has been constituted with following terms of reference:

- To review the current situation regarding manufacture, use and misuse of antibiotics in the country.
- To recommend the design for creation of a national Surveillance System for Antibiotic Resistance.
- To initiate studies documenting prescriptions patterns & establish a Monitoring system for the same.
- To enforce and enhance regulatory provisions for use of antibiotics in human & veterinary and industrial use.
- To recommend specific intervention measures such as rational use of antibiotics and antibiotic policies in hospitals.
- Diagnostic Methods pertaining to antimicrobial Resistance Monitoring.[8]

Aims of the national antimicrobial policy

- Understanding emergence and spread of antimicrobial resistance and the factors influencing it.
- Establish a nationwide well-coordinated antimicrobial program with well-defined and interlinked responsibilities and functions of different arms of the program.
- Rationalizing the usage of available antimicrobials
- Reducing antibiotic selection pressures by appropriate control measures.
- Promotion of discovery of newer and effective antimicrobials based on current knowledge of resistance mechanisms.
- Rapid and accurate diagnosis of infections and infectious diseases.[8]

Action Plans

General

- Establish government commitment and support for nation-wide antimicrobial program and within it the policy & set up national focal point for collaborations & compilation.
- Establish a National Alliance for prevention and control of antimicrobial resistance.
- Institute a surveillance system that captures the emerging resistance, seeks and envisions trends in its spread and correlates with utilization of antimicrobial agents in community as health care set ups.
- Promote rational usage of antimicrobial agents.
- Strengthen infection prevention and control measures- healthcare associated and community based.
- Support research in developing newer antimicrobial agents and improving usage of available ones, based on pharmacological properties.
- Educate, train and motivate all stake holders in rational and appropriate usage of antimicrobials and its regulation.
- Establish a Quality System and a National registry for Antimicrobial resistance for bacteria, fungi and viruses at national focal point.
- Co-development of antimicrobial agents with pharmaceuticals and leaving the distribution, sales and promotion with the government.[8]

Implementation

Establishing a surveillance system

- Establish that all Hospital/ health care set up should have an Infection control officer with well-defined role and responsibilities
- Formation of a Local Infection control team
- Protocols on antimicrobial testing to be formulated and distributed in a categorized manner- primary/secondary tertiary health care set ups/standalone labs with/without automation
- Interpretive criteria- (CLSI/BSAC) to be standardized as per our needs and adopted nationwide
- Software generation for data feeding and analysis
- Collection of Data from Microbiology laboratory for both health care setups and community
- Collection of Data from Pharmacy for both health care setups and community
- Collection of Data from pharmaceuticals-sale by distributors and sale by retailers to be compared
- Quality Control programs to be promoted and adopted EQAS to be set up at well-established institutes.[8]

Promotion of Rational usage of Antimicrobials

Personnel Involved

Local hospital/health care setup Infection prevention and Control Officer and Infection Control professionals.[8]

Action points

- Local healthcare setup Antimicrobial policy to be drawn by each healthcare setup.
- Training modules on rational prescription to be created
- Training of Undergraduate and postgraduate medical, dental, nursing, veterinary and pharmacy
- Training and awareness of General Practitioners and Specialists
- CMEs and workshops for all concerned
- Banning non therapeutic usage in animals and farms
- Pharmacists involvement
- Ban over-the-counter (OTC) sale of antimicrobials - Schedule H1
- Adherence on all levels to be sent in annually to the State director who shall put this data to the central director.[8]

Infection prevention and control program

- Establish and Strengthen Infection Control Programs
- In both Health care set ups
- Infection Control Plan and policy for tertiary care hospital
- Infection control Committee to be set up in all health care institutions
- Infection Control Team
- Standard Operating Procedures (SOPs)
- Immunization and vaccination of vaccine preventable diseases[8]

Research in Antimicrobials

- Government sponsored, public-private partnership (PPP) model or pharmaceutical industry collaboration with govt. and private health care setups
- Budget allotment, grants to be set aside
- Community based research
- Health care setup based research
- Veterinary research
- Agriculture, fisheries, farms to be included
- Rapid diagnostics researched and promoted
- Regulatory mechanisms to be in place for prioritizing research
- National Commitment in the form of Antimicrobial Policy and later on legislation Formation of Advisory Body
- Formation of Steering Committee under the advisory body
- Targets for all involved to be set up for tertiary care hospitals Deadlines to be formulated and implemented
- Software to be generated & evaluated.[8]

Monitoring and Evaluation

- QC checks
- Audits Feedbacks to Advisory body
- Review of Action Plan annually
- New actionable for implementation to be developed regularly & give feed back[8]

Situation in India

Data on the use of antimicrobial agents at the population level are lacking in India as we do not have any database for the consumption of antimicrobials (antibiotics) in the community. This is mainly because, in India (unlike many developed countries), prescriptions are kept by the patient and not with the pharmacist and antibiotics may be obtained with or without a prescription. Therefore, determining consumption of antibiotic or trends in antibiotic use is problematic, more so in private sector, since there are no prescription records. Hence, there was an utmost need to develop a methodology that can measure consumption and trends in antibiotic use in the community.

SUMMARY AND CONCLUSION

Pharmacists are the most accessible health care professionals, and are fully competent in all aspects of medicines. They possess scientific knowledge for the entire medicines- use, process, including procurement, preparation, storage, security, distribution, dispensing, administration and safe disposal

Pharmacists are on the front line of community health services, and are the entry point for patients to health care and the health system. This position gives them various opportunities. Pharmacists serve as communicators and educators on healthy behaviours and infection prevention. They increase the coverage of immunization in hard-to-reach groups, and they are in good position to explain the importance of using antimicrobials only when needed.

The pharmacy is a place where pharmacists evaluate the needs of patients and provide a sort of triage. In this process pharmacists assess whether they can successfully

treat the patient or whether the patient needs to be referred to another health care professional. Depending on the results of the assessment, there are three possible outcomes: the patient can be treated by the pharmacist without antibiotics, the patient can be treated by the pharmacist with antimicrobial treatments where this is legally allowed to happen, or the patient can be referred to another health care professional, usually a physician or a specialist.

Where pharmacists are legally allowed to prescribe antibiotics, fast and reliable diagnostic tests can support them in the proper diagnosis of common infections such as chlamydia or Lyme disease.

Pharmacists provide effective medication management for both short- and long-term treatments. They support adherence, minimise interactions and ensure quality of medicines. In hospitals, pharmacists lead stewardship programmes and are competent in hygiene and sterilisation. Pharmacists collect unused medicines, reducing the presence of antimicrobials in the environment.

Pharmacists are fully committed to support the development of programmes to combat AMR, through promotion, prevention and control of antimicrobial treatments, and providing access to high quality treatments in the community and at all levels or care. Pharmacists encourage the commitment of all health care professionals to fight the AMR threat via programmes developed in collaboration with stakeholders.

All of the above can help to prevent AMR in the community and in hospitals, and increases the likelihood of successful antimicrobial policies being implemented. This document clearly articulates the important role of pharmacists in addressing this public health issue and can provide a foundation for discussion among various stakeholders.

REFERENCES

1. Alison H Holmes et al; understanding the mechanisms and drivers of antimicrobial resistance, www.thelancet.com, November18, 2015.
2. The role of pharmacist in encouraging prudent use of antibiotics and averting antimicrobial resistance- a review of policy and experience, (http://www.euro.who.int/pubrequest).
3. Dr. R.K. Srivastava, Ministry of Health and Family Welfare, Government of India, National Policy for Containment of Antibiotic Resistance in India 2016.
4. Liselotte Diaz Högberg, The global need for effective antibiotics: challenges and recent advances, Trends in Pharmacological Sciences, vol.31, no 11, pp. 509-515.
5. D. Raghunath, Emerging Antibiotic resistance in bacteria with special reference to India, Journal of Biosciences, vol. 33 no 4, 2008, pp. 593-603.
6. Fighting antimicrobial resistance, the contribution of pharmacists, 2015.
7. Rationalizing antibiotic use to limit antibiotic resistance in India, Indian J Med Res 134, September 2011, pp. 281- 294.
8. Teresa M Barbosa et al; The impact of antibiotic use on resistant development and persistence, Drug resistance updates (2000), vol 3, pp. 303-311.

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