A REVIEW ROLE OF PHARMACISTS: ANTIMICROBIAL STEWARDSHIP AND IN THE BATTLE AGAINST ANTIMICROBIAL RESISTANCE IN INDIA

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ABSTRACT

A common threat jeopardizing the globe is antimicrobial resistance (AMR). Being largest consumer of Antimicrobials, the problem of irrational use of Antimicrobials and Antimicrobial resistance (AMR) is deep and multifactorial in India. Hence, the present review made with the objectives of, identifying the seriousness of irrational antimicrobial use and AMR status in India and find out the actions taken national wide to combat the problem in the country. In addition, discover the position of the Indian Pharmacist in this battle. From the deliberate literature search, we found that, in the recent years, India has advanced in the making of antimicrobial treatment guidelines, stewardship programs, action plans in order to achieve rational Antimicrobial use, but found with obstacles in their practice, due to multiple factors. However, the implementation of such policies and guidelines is possible only by a coordinated teamwork of all health care professionals. Pharmacist, being a responsible team member in the health care setting and the last contacts to the patient, before taking antibiotics, can make best judicious Antimicrobial use in the nation. There is a paramount need of the Pharmacist for his active role in the health care team in the country, where several other countries with the pharmacist collaboration are achieving success over AMR and irrational Antimicrobial use. Pharmacist led research on Antimicrobial use and stewardship (ASH) programs can be best solutions. In this regard, the present manuscript attempted to notify the roles and responsibilities of the Indian pharmacist towards AMR and rational antimicrobial use.

Key words: Pharmacist, Antimicrobial resistance, Antimicrobial stewardship, India.

INTRODUCTION

The health is fundamental to happiness and welfare of the nation. Antimicrobials play a significant role in the health care system. More than 50% of the prescriptions contain antimicrobial agents, without which many treatments may fall impossible. Rational use of such medicines is a crucial element for better health outcomes and for providing better patient medical care. With regard to this, WHO has defined the rational use of antimicrobials as ‘the cost-effective use of antibiotics which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance (AMR)’ 1. It has been estimated that, around one quarter (25%) of total ADRs can be attributed to antimicrobial use 2.

The journey of Antimicrobial discovery to Antimicrobial resistance

The discovery of antibiotics over 70 years ago dramatically changed the situation to treat once deadly infections more effectively, and have taken a central role in modern medicine. They saved many lives from infectious diseases, and extended their role into many developments like surgery, transplantation, chemotherapy etc.; hence, they have become the foundation for modern treatment strategies. Presently the golden era of antibiotics is under threat called, Antimicrobial resistance (AMR), which says bacteria no longer killed effectively by Antimicrobials. Moreover, the clinical pipeline for new antibiotics discovery is extremely weak in the past decade, and the present existing drugs are not in a condition to save the life from every infections. The seriousness of the present condition, witnessed by the report of 2,50,000 deaths by the drug resistant tuberculosis. In addition to this, 12 other pathogens causing common infections like pneumonia, urinary tract infections now reporting resistant to presently available antibiotics 3.

This is an alarming period, to preserve the effectiveness of presently available antimicrobials. In the present condition, all the countries are focusing on research for the discovery of pathways to preserve the effectiveness of existing antimicrobials rather than on the discovery of new antimicrobials.

The best solution for the current problem is antimicrobial stewardship, which is the responsible use of antimicrobials. In connection with this situation, the WHO maps the key role of pharmacists. The definition of a pharmacist “A pharmacist is a scientifically trained graduate healthcare professional who is an expert in all aspects of the supply and use of medicines. Pharmacists assure access to safe, cost-effective and quality medicines and their responsible use by individual patients and healthcare systems” 4. From the definition, pharmacist has a responsibility in addressing problems related to drugs and its uses. Pharmacists, being the last contact to the patient, before taking antimicrobials, and thus can contribute largely in control of irrational use of antimicrobials 5.

In connection to this, the present review aims with the objectives of identifying the seriousness of irrational antimicrobial use and AMR status in India and find out the actions taken national wide to combat the problem in the country. In addition, discover the position of the Pharmacist in this battle. We also attempted to notify the roles and responsibilities of the Indian pharmacist towards AMR and rational antimicrobial use in accordance with
the WHO standards and few standard pharmaceutical organizations from developed countries.

**Risks with irrational use of antimicrobials**

In accordance with the Center for disease control and prevention (CDC) in 2017, like all other drugs, antimicrobials also have risks on their irrational use. More than 40% prescriptions are found containing antimicrobials, hence have a more chance of presenting risks, such as disruption of naturally occurring microbiome, in the human gut. Antibiotic taken to kill infection-causing “bad” bacteria also kill “good” bacteria that protect against infection, followed by allergic reactions and drug interactions. Another serious issue mainly faced in the hospital settings, is infections caused by resistant organisms to patients already on antibiotics, eg, *C. difficile* bacteria and Candida fungi infection chance is high in people taking antibiotics. Above all risks antimicrobial resistance considered as the global emergency condition, which needs an immediate action.

**ANTIMICROBIAL RESISTANCE**

Antimicrobial resistance (AMR), the result of irrational Antimicrobial use, has become a global health challenge jeopardizing the health of humans. The march of AMR is very silent capturing the highest cause of mortality. People using antimicrobials, as on their own, without therapy realization, is one of the major cause particularly in developing countries, affect not only the individual but also the entire society. The condition of AMR is due to, microorganisms developing resistance by mutating in the battle of survival when the antimicrobial is misused or acquire genetic information of resistance from previous generation of microbes. From the estimates of the Centers for Disease Control and Prevention (CDC), more than two million people infected with antibiotic-resistant organisms, resulting in approximately 23000 deaths annually.

AMR is not a modern phenomenon; it existed ten thousand years before modern man discovery of medicines. Recently, 1000 year-old mummies from the Inca Empire, discovered to contain bacteria in their gut, which is resistant to many of our modern antibiotics. While DNA found in 30,000-year-old permafrost sediments from Bering have found to contain genes that encode resistance to a wide range of antibiotics. Alexander Fleming, awarded for discovery of penicillin, in his Nobel Prize lecture, in 1945, with his foresight warned the threat of Antimicrobial resistance.

There is another factor contributing to spread of AMR and infections in many countries, wastewater from hospitals is poorly filtered, allowing the antibiotic-resistant bacteria escape in to local water bodies and flourish. People drinking this contaminated water or practicing poor hygiene are infected by this resistant bacteria. A part from hospital sewage, residues produced from pharmaceutical industries containing antimicrobials also contributed for the development of resistance in microbes present in environment. India and Bangladesh, being major contributors to global pharmaceutical production, antibiotics usage is also high in South East Asia. The rate of antimicrobial residues that contaminate the environment is also high.

**Factors contributing to antimicrobial resistance in India**

The picture of AMR in India runs deep and multifactorial with a question of tomorrow’s health. Based on World Bank data and the Global Burden of Disease, in 2010, India was the world’s largest consumer of antibiotics for human health at a rate of 12.9 x109 units (10.7 units per person). Antibiotics use in India as well as the prevalence of resistance is also very high, estimated by the Center for Disease Dynamics, Economics & Policy, Resistance reported to newer, broad-spectrum drugs such as Carbapenems, which are the last treatment options, is highly worrying situation.

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Some other factors driving antibiotic resistance in India include, use of high range broad-spectrum antibiotics, rather than narrow spectrum antibiotics. From the fig: 1, the use of cephalosporin and broad-spectrum penicillin consumption increase raised drastically from 2000-2015, whereas narrow spectrum penicillin consumption decreased. Another contributing factor for AMR is availability of high range of antibiotic fixed dose combinations in the market without a proven advantage over single therapeutic effect, safety and compliance. In India, approximately 118 fixed dose combination antibiotics are available. Other contributing factors are self-medication by patients without knowledge, and drug prescribed by health care providers with lack of updated knowledge.
India advances in the fight against AMR

Over all AMR emergence rate is very high all over the world, both in Gram positive and Gram-negative microbes, mainly taking a note on *Escherichia coli*, reporting high rate of resistance, over 80% of antibiotics in India. Likewise, methicillin-resistant *Staphylococcus aureus* (MRSA), causing 54.8% surgical infections, was documented in India. It was reported that, 1 in 7 infections related to catheter and surgery are suspected to be caused by antibiotic resistant bacteria including Carbapenem-resistant Enterobacteriaceae. Hospitals in India are making policies to improve the situation of antimicrobial use, but the time is running out and need urgent actions. Indian government has come up with many national policies, action plans against AMR since 2010. The National Task Force on AMR also established in 2011. The country advanced by passing the Chennai Declaration, a 5-year plan to address antimicrobial resistance in 2012. In spite of all the activities, the country has not gained success on AMR. However, in the very recent years there was a tremendous awareness in the health care team with the publication of ICMR treatment guidelines for antimicrobial use. Like many developed countries, now India also have their own treatment guidelines for antimicrobial use. On the other hand, among all the actions, the Schedule H1, red Line Campaign on Antibiotics, the treatment guidelines for antimicrobial use and national action plan are the most concerned areas for the pharmacist to involve for contribution in the battle against AMR.

**Schedule H1**

With the alarming rise in the rate of AMR, judicious use of currently available antimicrobials is utmost important, recognized by the Indian government and passed as an amendment to the Drugs and Cosmetics Rules of 1945, to included certain antibiotics in Schedule H1 category to avoid nonprescription sales of antibiotics. Schedule H1 notification passed from Government of India on Aug 30, 2013 and came into force from Mar 1, 2014. The primary intention is to control rampant use of antibiotics in India. Under this schedule, 46 antibiotics are placed under restricted category. In this point, there is a need of surveillance on what extent the pharmacies are educated in Schedule H1 and AMR.

**Red Line Campaign on Antibiotics**

To counter the superbug, AMR, India in 2016 stepped forward and launched a red line campaign on antibiotics packing. A vertical red line on the antibiotic packing indicates the dispensing pharmacist as well as patients that, these medicines dispensed only on prescription. Development of awareness in the society is required, that the red line antibiotics are no more over the counterdrugs.

**ICMR Treatment guidelines for antimicrobial use**

In a step forward, Indian Council of Medical Research Department of Health Research New Delhi has developed Treatment Guidelines for Antimicrobial Use in Common Syndromes in 2017. From the denying fact that India lacks proper Anti-microbial Guidelines (AMGL) for empiric management of infections, ICMR has developed evidence based antimicrobial treatment guidelines for often symptoms of infections.

2. Antibiotics use in Diarrhea.
3. Infections in bone marrow transplant settings as prophylaxis and treatment of Infections
4. Infections associated with devices.
5. Immune-compromised hosts and solid organ transplant recipient
7. Principles of Initial Empirical Antimicrobial Therapy in Patients with Severe Sepsis and Septic Shock in The Intensive Care Units
8. Prophylaxis and treatment of Surgical Site Infections.

**National Action Plan-2017**

WHO developed an action plan to combat AMR in May 2015 with emphasize for “one health” of all nations. In regard, to this Government of India Ministry of Health and Family Welfare, in April 2017, have prepared an action plan with the alignment of global action plan to combat AMR in India.
Table 1 Strategies of national and global action plan against AMR

<table>
<thead>
<tr>
<th>WHO action plan-2015</th>
<th>National action plan-2017</th>
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<tbody>
<tr>
<td>• To improve awareness and understanding of AMR;</td>
<td>• Enhancing awareness,</td>
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<td>• To strengthen knowledge through surveillance and research;</td>
<td>• Strengthening surveillance,</td>
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<tr>
<td>• To reduce the incidence of infection;</td>
<td>• Improving rational use of antibiotics,</td>
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<td>• To optimize the use of antimicrobial agents; and</td>
<td>• Reducing infections and promoting research,</td>
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<tr>
<td>• To ensure sustainable investment in countering antimicrobial resistance.</td>
<td>• Support neighboring countries in the collective fight against infectious diseases.</td>
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Role of pharmacist in the battle against AMR

Pharmacist is a profession, which dedicates entire life to drugs, from discovery to dispensing. Nearly 40% of prescriptions containing antibiotics are inappropriate. Pharmacist, being the last contacts to the patient, before taking antibiotics, and thus can control the irrational use of medicines. In the present situation, the main role of the clinical pharmacist in hospital settings is, cooperating with prescribing physicians and providing antibiotic stewardship in primary health-care settings. The pharmacist along with prescriber can best improve the situation by making appropriate use of antibiotics in their countries followed by professional associations and patient communities.  

Guidelines on Good Pharmacy Practice (GPP)

In accordance with, the guidelines by, International Pharmaceutical Federation (FIP), WHO Expert Committee, the pharmacists can help the situation, antimicrobial resistance in many ways by following guidelines on good pharmacy practice (GPP). “The mission of pharmacy practice is to contribute to health improvement and to help patients with health problems to make the best use of their medicines.”  

Objectives of mission of pharmacy practice-to make the best use of their antimicrobials:
1. Providing proper counseling to the patients, as well as their family members regarding antibiotic use, and adverse events.
2. Patients encouraged taking the full-prescribed antibiotic regimen.
3. Collaborative working of the pharmacist with the prescriber to order sufficient doses to complete or continue a course of therapy.
4. Recommending alternative therapies for minor diseases, other than antibiotics.
5. Providing updated information on antibiotics to prescribers.
6. Monitoring the supply of antibiotics and their use by patients.
7. In patient counseling, pharmacists can reassure patients and correct any misunderstandings.

International Pharmaceutical Federation (FIP)

The FIP, a global federation of national associations of Pharmacists and Pharmaceutical scientists, in support to fight against AMR, made a document on an overview of the different activities that community and hospital pharmacists should get involved in to prevent AMR and to reverse AMR rates. The responsibilities of pharmacists in AMR,

- Promoting Optimal Use of Antimicrobial Agents.
- Reducing the Transmission of Infections.
- Assured effectiveness of medicines.
- Education of health team on AMS.
- Education on proper immunization.
- Preventing possible drug related problems.

In development of policies against AMR, many countries involve Pharmacists, who are expertise with medicines. Given an advisory and clinical role in prescribing and/or antibiotics with regard to indication, selection, dose, duration and adjustment of dose, the pharmacist would not only assure optimal use of antimicrobials but also can reduce the incidence of drug interactions and adverse drug events. A well-trained pharmacist can tailor the regimes with knowledge of responsible use of antimicrobials knowing the situation. By the knowledge in quality of medicines and safe disposal, the pharmacist can contribute for the reduction of microbes in the environment.

ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship (AMS) is a blanket term, directing to appropriate use of antimicrobial agents while reducing collateral damage of emerging drug resistance. AMS is a design of an inter-professional workout, for an improved, optimal, antimicrobial use in the health care settings. The saying, “The right antibiotic for the right patient, at the right time, with the right dose, the right route, causing the least harm to the patient and future patients” is the motto of AMS. It is a supervisory program over appropriateness of the treatment, like drug selection, correct dosing, duration of therapy, administration interval, therapeutic drug monitoring for certain antimicrobial agents. AMS program assure best clinical outcome in the treatment of infection by not only halting antimicrobial resistance, but also minimizing toxic effects to the patients and by decreasing adverse events, and controls health care cost.

Role of Pharmacist in Antimicrobial stewardship

ASHP, statement recommends that, the pharmacist, due to their unique expertise over drugs, when given a prominent role in AMS program can play a responsible role and fulfill the objectives like, promotion of the optimal antimicrobial use, reduction in the transmission of infections, and education of other health professionals, patients, and the public. America provided first AMS practice guidelines in 2007, a foundation for buildup of today’s modern AMS programs. From the past to recent updated AMS guidelines, the vital components of the program are collaborative working relationships between a physician and pharmacist and a sound training in the AMS program.
stewardship and concurrently curbing hospital infections through feasible infection control practices.

One of an exemplary program reported in 2008, the Center for Antimicrobial Stewardship and Epidemiology (CASE) formed at St. Luke’s Episcopal Hospital (SLEH) to improve the quality of care for patients related to antimicrobial therapy. This program aimed at following factors,

- Optimize antibiotic therapy by ensuring the selection of the most appropriate agent, dose, and duration of therapy;
- Screening for significant adverse drug reactions and drug–drug interactions;
- Modifying initial therapy based on patients’ culture and sensitivity reports

The CASE team consists of at least two infectious diseases pharmacists and one physician (the medical director) who provide direct oversight for antimicrobial utilization within the hospital. The charter of CASE contained specific aims, for improving patient care, furthering clinical research, and training the next generation of clinical infectious diseases pharmacists. Another key innovative feature of CASE is its extensive involvement in training new infectious diseases pharmacists and conducting research. Trained pharmacists in antimicrobial stewardship along with the physicians (the medical director) could provide direct oversight for antimicrobial utilization within the hospital. Such trained pharmacist can contribute in research and development of policies on antimicrobial use.

**Pharmacist education in AMS**

Well-trained pharmacist, in the health care team and research areas can achieve success over AMR. This can be therefore possible when the fundamental principles of antibiotic stewardship made integrated into preclinical medical curricula. ASHP, also recognizes the current shortage of advanced trained pharmacists in infectious diseases and supports the need for an evolutionary change in pharmacy education and postgraduate residency training on infectious diseases in order to produce adequate and well-trained pharmacists who can deliver essential services.

In connection to this, in the America, there is a special training program available for pharmacist in Infectious disease control.

In a mini review on professional development, describes the importance and principle concepts for training clinical professionals in AMS practices. AMS education, included in Pharm D curricula is most suggested, where students introduced to patient care under the guidance of a preceptor, similar to an apprenticeship, in their final year of coursework. This will develop future training opportunities on infectious diseases, research scope and improves patient outcomes with appropriate use of antimicrobials.

Common barriers identified for the implementation of AMS in India include, lack of funding, human resources, lack of information technology, lack of awareness in the administration and healthcare team and prescribers option. A well-trained clinical pharmacist in infectious diseases working in hospital settings can fix all the barriers. Therefore, the country should also think in this way and make necessary expansions in the Pharm D curricula.

**Research opportunities for a pharmacist**

Possible ways for rational use of antimicrobials can be discovered with a sound research on antimicrobial use, resistance patterns, and drug related problems. Data from CDC’s National Healthcare Safety Network say, one-third of antibiotic prescriptions in hospitals involve potential prescribing problems. India, being world’s largest consumer of antibiotics, lack national surveillance data on resistant pathogens. Research, in India focused predominantly on, drug discovery and development, rather than on stewardship and drug related problems. Discovery of possible ways to control irrational Antimicrobial use is possible with a sound research on antimicrobial use, resistance, drug related problems. Assessment of percentage use of antimicrobials in the health care settings enables to suggest the actions to control the irrational use. The studies are more important because, one-third of antibiotic prescriptions in hospitals involve potential prescribing problems.

National Action Plan on AMR (NAP-AMR), launched by the government of India in 2017, to promote research investment in AMR research in India with main focus on,

- Epidemiology, which understands the incidence and burden of resistant pathogens upon the community settings.
- Research into the mechanism of AMR is the second most common type.
- Development of interventions to tackle AMR.

In connection to this, is the first survey carried out under the AMSP program, in India 2013 in 20 hospitals from different parts of the country. The survey results came up with the suggestions.

Suggestions made from the first survey on AMSP practices in India.

1. Standardization of health care (including AMSP practices) is possible only when all hospitals in country get government accreditation.
2. ID trained clinical pharmacists and physicians should be provide in all hospitals for better control and use of therapeutics.
3. A comprehensive record, maintained and AMR data must be regularly analysed.
4. AMSP guidelines must be available easily to all practitioners and regular feedbacks and audits be conducted.
5. For the best results, continuous research in all aspects of AMSP is warranted.

The picture of AMR in India is worrying with a question of tomorrow’s health. The march of AMR is very silent capturing the highest cause of mortality. People using antibiotics as on their own, without therapy realization, will affect individual and the entire society. Resistance reported to newer, broad-spectrum drugs such as Carbapenems, which are the last option is highly worried situation. In April 2017, Indian council of medical research (ICMR) strictly advised 20 tertiary hospitals in south India for controlled use of Carbapenems and Polymyxins and labeled them as highly needed or end antibiotics.

ICMR in a meeting with WHO and Global antibiotic research and partnership, states that it is working closely with the Ministry of Health and WHO to implement an AMR stewardship program in hospitals. Dr Jagdish Prasad, in the meeting says, ‘We also need more standardization and harmonization of the ways that clinicians prescribe drugs; this is challenging because, in absence of standard treatment guidelines, individual clinicians may have very different ways of treating the same disease’. Dr Henk Bekedam, WHO representative to India, says, ‘Today, a simple infection can lead to a life-threatening situation due to resistance to antibiotics. However, there are huge encouraging research opportunities on AMR. There is a need to understand antibiotics globally in terms of usage, awareness, knowledge, and practice’.

In a recent publication ‘Scoping Report on Antimicrobial Resistance in
India’, made recommendations on future research, the author has said the need for the development and study of the impact of various antimicrobial stewardship activities and infection control measures. All the countries involve pharmacist in such stewardship programs is highly recommended in Indian healthcare. A pharmacist led AMSP was a good research with better outcomes reported in many literature.

CONCLUSION

In India being the largely populated country, it is difficult to control and educate the effects of irrational use of the antimicrobials. India is one of the countries reported by WHO for its high unjustifiable use of antimicrobial agents and high rates of drug resistance and poor surveillance. In the present condition, Pharmacist along with other health professionals should join in research and development of ways to make better use of antimicrobials and thereby reduce drug related problems like, adverse events and antimicrobial resistance. India mainly focuses on research and drug discovery, rather than on stewardship. As developed countries are moving towards development of stewardship and encouraging research in this area research. Definitely, there is a need for new antibiotic discovery, but the present very serious issue is AMR, which is the result of irrational antimicrobial use. We have to treat the problem rather than searching from anew solution for the future. India has forwarded in the fight against antimicrobial resistance by making antimicrobial guidelines, stewardship programs, action plans etc., in recent years. Implementation of them at all parts of the country is possible when there is a close collaboration among all health care team, including physician, pharmacist, nurse, microbiologist as well as patients. In a large populated country like India, it is difficult to bring all together. In this account, there is a need to address the need as well as responsibility of a pharmacist in the fight against AMR by review of different literature, which indicates the pharmacist responsibilities. This evil, AMR may avert through strong antimicrobial stewardship programs led by a pharmacist. As now, India has strengthened in the department of pharmacy practice, with the introduction of Pharm-D program in 2008, and the out coming students have a good knowledge in rational use of drugs. A known fact is that most of the doctors are busy with their hectic schedules and they have less time for research and development in drug utilization. Hence, the clinical pharmacist appointed in the hospitals can better control the situation of AMR by implementation of stewardship programs and by sound research. Its a best opportunity for the upcoming clinical pharmacist in India to participate in stewardship programs, provide safe and effective treatment with minimized side effects and adverse events, and hence actively take part in fight against AMR.

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