A Review on Steps to Improve Antimicrobial Prescribing Practices in India

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Abstract

Although antimicrobial resistance is an anticipated threat to the globe, measures taken by developing countries to combat this problem are insufficient. If neglected, many surgical procedures and treatments that exist today could come to a standstill, because all of those carry a sizeable risk of infection. An enormous majority of the global population could die from incurable diseases. This review emphasises the significance of an antimicrobial stewardship team in the hospitals of developing countries as well as the steps to be taken to drive it forward. The pace at which antimicrobial resistance develops will multiply if hospitals fail to impose restrictions on antimicrobial prescribing. The nonchalant attitude of hospital administrations, infection control committees and pharmaceutical companies have a significant impact on this situation. To delay the accelerated progression of AR there should be further developments made in the field of diagnostic testing and alternatives to antimicrobial treatments. There should also be more trials conducted, to determine the effectiveness of antimicrobial stewardship, and the same should be implemented if possible, in every clinical setting. Clinical Pharmacists are undoubtedly the key to propel this movement towards Antimicrobial Stewardship.

KEYWORDS: Antimicrobial Stewardship; Antibiotic Resistance; developing countries; low and middle-income countries; resource-limited settings.

BACKGROUND

Antibiotic resistance (AR) is a high-priority cause for apprehensions about future medical treatments and patient care worldwide. According to the review of 2016 on AR, ten million people around the world could die, from AR-related infections. The progress of this forthcoming reality can be slowed down only if there is a halt to the pressure imposed on medical practitioners to prescribe antibiotics when it's veritably unnecessary and by hindering the food industry from fattening poultry with antibiotics.[1] It has been three billion years since the existence of bacteria and ten-thousand years since the first report of bacterial resistance. When Alexander Fleming serendipitously discovered penicillin in 1928, humanity foresaw a disease-free world. However, in 1945 he made premonitory statements on the potential for AR development. Major revolutions in the field of surgery such as organ transplant, joint replacement, stent placement and dialysis that have taken place over the past few decades, will come to a halt if antibiotic resistance develops; as these procedures carry a substantial risk of infection.

Antibiotic resistance develops when the bacteria intended to be killed upgrades itself to thrive even in the presence of the antibiotic. There are three categories of antibiotic-resistant organisms: multi-drug resistant organisms which are non-susceptible to at least one antibiotic in three or more classes; extensively drug-resistant organisms which are non-susceptible to at least one antibiotic from almost all classes of

antibiotics, excluding one or two classes; pan drug-resistant organisms which are non-susceptible to at least one antibiotic from all antibiotic classes.[2]

Modes by which antibiotic-resistant bacteria can spread are through contaminated surfaces, water, air, and close contact with infected persons, animals, and sexual contact. As per the 2019 AR Threats Report by CDC: carbapenem-resistant *Acinetobacter*, carbapenem-resistant *Enterobacteriaceae*, drug-resistant *Candida*, ESBL producing *Enterobacteriaceae*, vancomycin-resistant *Enterococcus*, methicillin-resistant *Staphylococcus aureus* and multi-drug resistant *Pseudomonas aeruginosa* were deemed as health threats requiring urgent and serious action.[3]

With reference to an article by Yong *et al.*, an incident of Urinary Tract Infection caused by Carbapenem-resistant *Klebsiella pneumoniae* strain (also known as NDM-1) was observed in a resident of Sweden that had travelled to India.[4] This bacterium conferred resistance to almost all antibiotics including the highest resort ones like Carbapenem. Further studies revealed the presence of NDM-1 in hospitalized patients of India and Pakistan.[5] NDM-1 was also detected in the environmental samples collected from New Delhi.[6] Although, NDM-1 is infamous in India, there are documentations of significantly increased rates of resistance in more bacteria like *Pseudomonas*, *Acinetobacter*, *E. coli*, *Klebsiella* and *N. gonorrhoeae*.[7]

An inappropriate choice of antibiotics or infelicitous determination of dose, frequency and duration of antimicrobial therapy could lead to the emergence of resistant organisms, unnecessary expenses, adverse drug reactions and wastage of healthcare resources. This dire strait calls for a topflight remedy to limit antibiotic misuse and overuse.

THE SOLUTION: ANTIMICROBIAL STEWARDSHIP

To move through the right trajectory, the Global Action Plan on Antimicrobial Resistance (2017) listed 'antimicrobial stewardship' as one among its objectives. The importance of commencing this at a global, national, hospital and community level has been emphasised. With proper AMS practices implemented, antimicrobial products will be under strict vigilance; right from the inception of the drug molecule to its ultimate consumer.[8]

The Infectious Diseases Society of America (IDSA) has defined antimicrobial stewardship as "coordinated interventions designed to improve and measure the appropriate use of [anti-infectious] agents by promoting the selection of the optimal [anti-infectious] drug regimen including dosing, duration of therapy, and route of administration." Evidence-based guidelines form the backbone of these programs.[9] As per the strategies stated in the Global Action Plan of 2017: educating and instilling an awareness of AR; boosting research; introducing measures for effective hygienic practices; judicious utilisation of antimicrobial drugs; and economic investment in novel drugs, diagnostic tools and interventions will result in quality assured and safe practice of medicine.[10, 11] AMS programs have proven to yield better patient outcomes, reduction in the rates of nosocomial infections, improved antibiotic susceptibility rates and optimization of health care resource utilisation.[12] However, there are certain barriers confronted by low and middle income countries: insufficient information technology, lack of investments or funding and prescriber objection.[13, 14]

During the last five years, there has been a steady rise in the publications on AMS. As per a systematic review on the extent of implementation of AMS and its reported outcomes in African countries conducted by Akpan *et al.*, the insufficiency of data on AMS studies in African countries posed as a roadblock to its implementation. However, the studies they included showed improved outcome measures following AMS intervention.[15, 16] This review aims to achieve the objective of evaluating and broadly summarizing the steps that could be taken to kickstart AMS in developing countries and the significance of clinical pharmacists in it

DISCUSSION

Steps to enforce Antimicrobial Stewardship in the Developing Countries

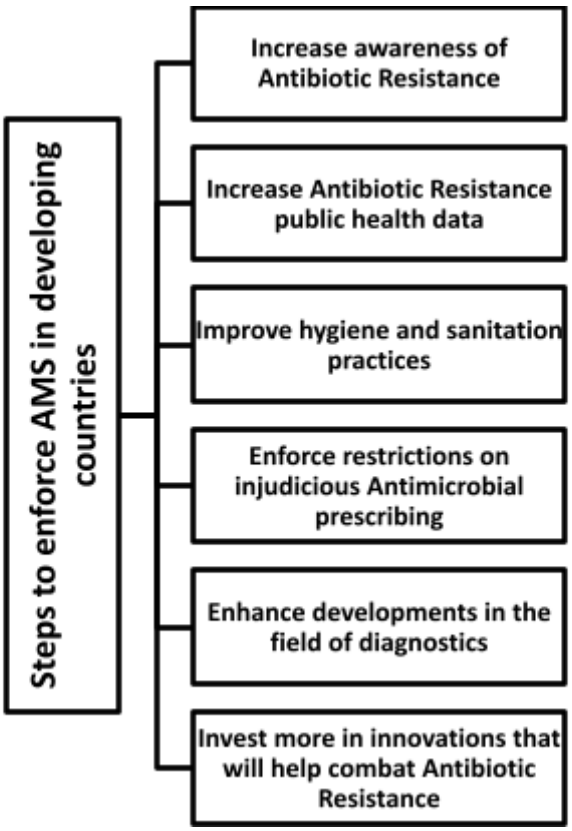

Figure 1: Steps to improve AMS in Developing Countries

Overuse of antibiotics can be toned down by implementing AMS programs under non-specialised health care providers like clinical pharmacists and clinical microbiologists, guided by infectious disease specialists.[17] (Figure 1)

1. **Increase the awareness of AR**

   The first and foremost measure to be exercised is to increase the awareness of AR rigorously from square one: starting from drug developers to the health care providers and patient population. It is only through enough knowledge and perception of this predicament in general, that the right decision can be made. To achieve this, there should be more emphasis on national awareness via social media and public platforms. In a study conducted by the Ministry of Health in China, a notable reduction in the intake of antibiotics after implementing the AMS program policies was observed. The policies incorporated were strict restrictions on prescribing various antibiotics and fixing goals for antimicrobial prophylaxis and prescription for inpatients.[18]

Administering enough information regarding AR in schools also carry a huge impact because what better place to sow seeds of prosperity than inside young minds. Moreover, healthcare professional training organisations must establish stringent coaching on antimicrobial stewardship practices with particular focus on general principles of good AMS, decision-making on rational antimicrobial therapy for select indications, apprehension and application of antibiograms, use of institutional guidelines and audit of antimicrobial prescribing. They should also provide certification courses to build their competency towards this problem. To bring out maximum benefits, the AMS team should occasionally conduct educational sessions at physician and other healthcare staff meetings. McNulty *et al.* conducted a study to determine whether interactive antibiotic workshops would improve antibiotic prescription among general practitioners. Results revealed a considerable improvement in antimicrobial prescription.[19] Concealed under a pile of responsibilities, yet extremely crucial to project the best in any AMS team is the role of nurses. They are often in the frontline when attending to calls or primarily using invasive medical devices like IV tubing sets. Hence, paramount importance has to be given towards educating nurses and instilling awareness in them.

2. **Increase AR public health data in developing countries**

To gather sufficient public health data on food-borne antimicrobial-resistant organisms, an integrated antimicrobial surveillance programme is necessary. To stop the spread of resistant bacteria, developing countries should implement wide vaccine coverage. With the help of the AMS team who holds expertise in the latest standard guidelines; regional and global drifts in the occurrence of AR among the human population will be updated to prescribing physicians.[20] Further studies to accumulate public health data on antimicrobial-resistant organisms in developing countries should be promoted with the aid of global health fund donors.

3. **Improve hygiene and sanitation practices**

A huge amount of exhausting-to-treat antimicrobial-resistant infections occur inside hospitals. The lack of proper hygiene and sanitation measures is the constituents to blame. There has to be easy availability of alcohol-based rubs to physicians, healthcare workers and patients within hospitals.

Awareness of why it is essential to wash and sanitize hands thoroughly should be taught. A study on adherence to hand hygiene by nurses after proper training was conducted by Graveto *et al.* in Portugal.[21] Additional studies such as these will benefit the population of developing countries. Moreover, people should be conversant of infectious diseases transmitted through sex, abuse of needles, food and water.

4. **Enforce restrictions on injudicious antimicrobial prescribing**

Stringent control measures have to be laid to control inappropriate antimicrobial prescribing as well as dispensing. One of the most effective methods, to put reins on the prescribing of antimicrobials, is antimicrobial restriction via formulary limitations or by demanding justification for the particular choice of antimicrobial, and prospective audit with feedback. LOS or length of stay in the hospital is a significant parameter to measure AMS outcome. With decreased LOS, there is a substantial decrease in healthcare costs involved and the risk of adverse event occurrence.[22] The AMS team must prepare an antibiotic formulary which is frequently revised and updated to direct the apt utilisation of empirical antibiotics, dose reduction, intravenous to oral therapy conversion based on cost, length of stay and adverse drug event occurrence risks. To devise this, national guidelines can be extrapolated and adjusted to suit the local settings requirement. The WHO in association with the Global Antimicrobial Resistance Partnership (GAP) and policymakers have laid down a road map to combat AR.[8] With such technical guidelines and regular clinical audits, responsible utilisation and evidence-based selection of antimicrobials are possible.

5. **Enhance developments in the field of diagnostics**

Suitable antimicrobial selection cannot take place without a timely diagnosis of the causative pathogen and a laboratory that stays in a constant vigil of hospital AR. Despite advancements in the field of diagnostics, it fails to reach the clinical care ground. Rapid diagnosis helps tailor therapy to appropriate antimicrobial agents and result in improved patient outcomes.[23] Diagnostic procedures guide us from nascency by helping us identify the cause of illness and the treatment plan preferred. Starting right from the invention of the microscope and gram-staining techniques up to the novel

Nucleic Acid-based Amplification (NAAT) and Polymerase Chain Reaction (PCR) Technologies, innovations in the sphere of diagnostics have never failed to astound us. Recent progressions in molecular diagnostics assure us that there is a promising future to bacterial infection diagnosis.[24] One of the latest inventions, MALDI-TOF MS (Matrix Associated Laser Desorption Ionization - Time Of Flight Mass Spectroscopy) technique helps decrease pathogen identification time by 26 to 28 hours.[25] Another laboratory diagnostic parameter developed to guide antibacterial therapy: procalcitonin has been reported to reduce the number of DDD's and duration of antibacterial treatment in patients.[26] Yet, implementing these into the patient-caregiver level is the challenge at hand. A diagnostic test proves its benefit and worth only when clinicians can obtain results just in time to initiate the best and most effective treatment. This prompt delivery of results to physicians is at times hindered due to the lack of sufficient laboratory staff. A study carried out by Cairns et al proved that an AMS team improves the timeliness of active and appropriate therapy.[27]

6. **Invest more in innovations that will help combat AR**

   Extended time, research and financial investments in the innovation of new antimicrobials, diagnostic tools and interventions are inevitable. Research and development of antimicrobials are blackballed due to the swift development of resistance and hence limited return of invested effort and money. There is insufficient research, in the field of AR within developing countries. With a further focus on studies comparing clinical trial outcomes: LOS, decreased duration of antibiotic therapy (ABT)[28], and incorporation of primary care prescribing feedback; AMS programs can be strengthened.[29] Randomised Control trials on outcomes of rapid diagnostics utilization have to be brought into consideration.[30] Solutions to such problems have to be sought and urgent stratagems should be employed.

A good antimicrobial stewardship program is the result of exquisite teamwork among the antimicrobial stewardship committee and hospital infection control team along with the assiduous backup from the respective hospital administration. The results of a study conducted at the hospital of the University of

Pennsylvania by Gross *et al.* compared cases managed by the AMS team (comprising of a doctoral-level clinical pharmacist with post-graduate training in infectious diseases management and an infectious diseases physician) to infectious disease fellow residents to whom a handbook consisting of the guidelines for appropriate therapy were handed. The AMS team yielded better outcomes in terms of choosing the appropriate antimicrobial, a higher cure rate of infection and a lesser failure rate with the first regimen. The reason for this disparity was due to a more stringent adherence to the guidelines by the antimicrobial management team, who reasoned any antimicrobial choice inappropriate: if the cost of the chosen agent appeared higher than the equivalent regimen or route of administration was found unbefitting or if the spectrum of the favoured regimen was found to be broader or narrower than required for the patient's condition.[31] Antimicrobial stewardship teams are preferred over infectious disease physicians alone because it opens the door to person-to-person interaction. This kind of interaction is essential while making clinical decisions as this enhances treatment choice via teamwork and promotes the reliable transfer of information.

Employing clinical pharmacists; to scrutinise antimicrobial prescriptions, to educate health-care staff working in liaison with infectious diseases division regularly, and to ensure strict control of drug promotion activities carried out by medical representatives can take infectious disease control a long way.[32] Once a diagnosis is reached, the clinical pharmacist trained in infectious disease control along with the infectious disease physician takes charge. In a study conducted by Brink *et al.*, antimicrobial stewardship programmes were implemented across forty-seven hospitals in South Africa where they found that such programmes led by pharmacists could produce much better outcomes begetting a downward fall in the mean antibiotic defined daily doses per 100 patient-days.[33]

The Limitations conferred in Developing settings

Over the past two decades, there has been a significant rise in antibiotic consumption globally. Especially breeding serious concern is the use of last-resort antibiotics like Carbapenems and Polymyxins. According to the IMS Health MIDAS pharmaceutical sales data of 2017, antibiotic drugs usage increased by 36% (54,083,964,813 SU to 73,620,748,816 SU) just in one decade. Among these consumers: Russia, China, Brazil, India and South Africa were responsible for the rapid escalation.[34] As per the IQVIA MIDAS

pharmaceutical sales data of 2018, the total global antibiotic consumption in 2015 was 42.3 billion Defined Daily Doses (DDD) with 31.6 billion DDD's arising from Low and Middle-income countries.[35] This implies that the surge observed in the consumption of antibiotics is steeper in resource-limited countries.

The burgeoning population accompanied by rapid urbanization resulting in rapid transmission of infectious diseases could be the contributing means to this. With a hastily growing economy due to urbanization in developing countries, the spread of infectious diseases cannot be restricted. This ultimately compels us to find a resort in newer antimicrobial therapies which can be challenging because of the short time available to frame the drugs tolerant and effective. Socioeconomic conditions and cultural diversities are the biggest challenges encountered in developing countries. There is an alarmingly increasing rate in the dispensing of antibiotics within developing countries [36–39] owing to the dearth in the level of which consumers are aware of AR. The availability of irrational fixed-dose combination antimicrobials results in the consumption of extraneous antibiotics.[40] The risk of self-prescribing practices of antibiotics increases among groups which have a poor education background. The perception among the low and middle-income groups that visiting a physician involves huge costs and time investment constrains them to buy antibiotics without a prescription.[41] Despite strict regulations (like Schedule H & H1 in India) to curb antimicrobial dispensing without a physician's script, being enforced: sales of antimicrobials have not declined.

Apart from this, lack of electronic medical records, adequate infection prevention measures, dedicated staff and highly-equipped diagnostics are some restraining elements. Not infrequently, physicians fail to adhere to the standard antimicrobial prescribing guidelines by irrational use of antibiotics. This may be due to recklessness or the failure to make a proper clinical diagnosis, incautious prescribing of empiric antibiotic therapy, lack of awareness on the local resistance pattern based on institutional antibiogram, an inability to choose the appropriate antibiotic, the optimal duration of therapy and to optimize the pharmacokinetic and pharmacodynamic parameters.[42]

Besides, although clinical pharmacists bring significant influence to AMS teams, certain constraints in low and middle-income countries handicap them. This profession has to still dive much deeper to blend with the already existing healthcare environment. Due to the lack of availability of essential medicines, pharmacists

fail to deliver the best therapeutic suggestions despite evidence-based guidelines. Other factors causing handicap to this group of professionals are scarcity of trained and competent pharmacists, sporadic distribution of pharmacists to catch up with population needs, and unaffordable medicines.[43]

Measures to develop Clinical Pharmacy practice in Developing Countries

As an initiative to improve clinical pharmacy practice, the Doctor of Pharmacy degree has been introduced to many developing countries in recent years.[44] Having mastered almost every discipline in healthcare, they will be of benefit to industries, hospitals, nurses and healthcare staff, and even patients.[45] A study conducted by Waters at the Intermountain Healthcare's McKay-Dee Hospital employed only pharmacists without infectious disease physicians and achieved a considerable reduction in antimicrobial utilization.[46] Clinical Pharmacists are trained to participate in ward rounds, optimize drug therapy, provide drug toxicity and poison information, report adverse drug reactions or events, review medication history, provide patient counselling services and conduct clinical researches.

The key to unlocking AMS programs in developing settings lie largely in the hands of clinical pharmacists. Firstly, they are equipped to review drug charts of inpatients receiving antimicrobials and provide prospective audit and feedback for them. They can determine the right time to de-escalate the dose or switch from intravenous to oral therapy. As they hold a good rapport with hospital pharmacies, they can also suggest the most cost-effective antimicrobial for diseased patients. Secondly, they hold the necessary qualification to update infectious disease control physicians with antimicrobial prescribing guidelines and to make suggestions on a patient's therapy. Thirdly, being in good relationship with nurses and other healthcare staff, they will have a big impact on infectious disease control within hospitals by spreading awareness and monitoring hygiene practices. And finally, the role of clinical pharmacists in AMS cannot confine just to hospitals as AR spreads even through illicit and unregulated consumption of antibiotics. There should be more forums and public awareness programs in every developing country hosted by clinical pharmacists to curb self-prescribing of antibiotics. Apart from this, lack of recognition of clinical pharmacists from developing countries as effective antimicrobial stewards must not discourage or pull them back from active ward round participation.

CONCLUSION

Every country has its limitations and yet, to put them all aside and bring about transformation lies in the hands of healthcare professionals. With an increasing bulk of health-science professionals and paramedics emerging, there is no reason to restrain from eliminating the faults of the present healthcare system. Many hands make light work. Antibiotic resistance is quick to develop and there are organisms which have developed resistance to a particular antibiotic in the same year in which it was released. Conducting more randomised clinical trials to determine the impact of antimicrobial stewardship services is crucial. There should be more innovations in the field of diagnostic testing: to confirm the effectiveness of drug therapy; to sound the alarm on time in case of emerging resistant pathogens; to reduce the time taken to identify the causative pathogen. Despite the hurdles and limitations faced by resource-limited settings, standing up to fight on this barbaric microbial battleground is imperative.

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