

Antimicrobial Resistance and Antimicrobial Stewardship

Sayan Bhattacharyya

Abstract

Antimicrobial resistance (AMR) is a real problem across the world. In fact, it is fast emerging as a pandemic. Bacteria acquire resistance antibiotics by many mechanisms. However, AMR also exists in parasites and fungi. Strategic plans and concerted efforts are needed to counter the exceedingly high burden of AMR.

Keywords: Antibiotic; Antimicrobial; Stewardship.

Introduction

Antimicrobials are a boon to the medical world. Antimicrobial stewardship is the need of the hour, keeping in mind the mounting cases of AMR or Antimicrobial resistance across the world. The problem is especially acute in developing countries of South East Asia, Africa and South America. It is estimated that by 2050, the total number of deaths due to AMR will be higher than deaths due to cancer and road traffic accidents, combined. Only two new classes of antibiotics have come up in the last decade. The development of new antibiotics needs time and lot of money. Hence existing antibiotics should be used cautiously and judiciously.

Antimicrobial resistance due to antimicrobial misuse was predicted long ago by Alexander Fleming, the discoverer of the first natural antibiotic, Penicillin. Now, many bacteria causing infections are resistant to one or more classes

of antibiotics. The antibiotic resistance is more pronounced in Gram negative bacteria. However, it is also common in Gram positive bacteria like *Staphylococcus aureus* and *Enterococcus* spp. Often clinicians have to resort to last line antibiotics like Vancomycin and Colistin for treating drug-resistant bacteria. These pathogens which are notorious for antibiotic resistance are also termed by the acronym ESKAPE pathogens (*Enterococcus* spp., *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Escherichia coli*). They mostly cause nosocomial infections but can also lead to community acquired infections. Interestingly, AMR is a problem not only in the hospital set up but also in the community. According to our own experience, now about 30-46% of uropathogenic *Escherichia coli* from the community are resistant in vitro to Nitrofurantoin, a drug commonly used to treat UTI.

AUTHOR'S AFFILIATION:

Associate Professor, Department of Microbiology, All India Institute of Hygiene and Public Health, Kolkata, West Bengal 700098, India.

CORRESPONDENCE AND REPRINT REQUESTS:

Sayan Bhattacharyya, Associate Professor, Department of Microbiology, All India Institute of Hygiene and Public Health, Kolkata, West Bengal 700098, India.

E-mail: sayantheboss@yahoo.co.in

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The role played by environment in AMR

In India open air defecation is still very common in remote villages and this can disseminate drug resistant pathogens into the soil and water.¹ Use of antibiotics in crop production, as manure and in animal husbandry also compounds the problem and makes persistence of multi drug resistant bugs in the environment easier.² Poor sanitation, effluents from the pharmaceutical industry and healthcare facilities also renders persistence of antibiotic resistant bacteria easier.² In 2021, the WHO, World Organization for Animal Health, FAO and UNEP (United Nations Environmental Program) joined hands to form the One Health quadripartite to combat the health risks including AMR, at the human, animal and plant ecosystem interface.²

Key players for high burden of AMR

Several things go into attaining the high burden of AMR in clinical settings, like poor knowledge of antibiotics among the masses, improper implementation of the regulatory acts, improper drug - drug combinations and many other reasons. Other factors can be listed below:

- a. Consumption of antibiotics in inadequate doses.
- b. Consuming antibiotics when not at all necessary.
- c. Availability of antibiotics over the counter.
- d. Using antimicrobials as daily injection, thus reducing compliance.
- e. Using antibiotics empirically, without sufficient knowledge of susceptibility pattern of common pathogens in the given area.
- f. Improper escalation and de-escalation of antibiotics.
- g. Lack of knowledge of difference between in vivo and in vitro susceptibility of pathogens to antimicrobials.
- h. Budgetary constraints hampering proper surveillance of AMR.³
- i. Health systems in low income and middle-income countries often have less functional and infrastructural resources to cater to a large population, more so in rural areas, and there universal access to primary healthcare services and antibiotics becomes a major challenge.
- j. Prescribing of antibiotics by unqualified medical practitioners or quacks in many peripheral areas.

- k. Poor educational status and low awareness among people lead to many myths which can promote self-medication of antibiotics.
- l. Hospital acquired bacterial pathogens often possess biofilms comprising bacterial colonies and exopolymeric matrix (EPM), which impairs penetration of antibiotics to the bacterial cells.
- m. Use of antibiotics like Colistin and colistimethate rampantly in animal husbandry and also as growth promoters leads to dissemination of dangerous drug-resistant bugs in the community.

Animal husbandry and AMR

Antibiotics are often used inadvertently and sometime purposefully in animal husbandry. The use of the antibiotic Avoparcin in food of animal in Europe was primarily responsible for spread of VRE or Vancomycin resistant Enterococci across the world. Effluents from the abattoirs and animal facilities can contain high load of drug resistant bacteria which get mixed with soil and water and thus can spread AMR to man also.

The pathogens which top the table in AMR

Among bacteria, Methicillin resistant Staphylococcus aureus or MRSA tops the list of pathogens having high load of AMR, followed by multidrug resistant extensively drug resistant tuberculosis (MDR TB), third generation cephalosporin resistant *E-coli*, carbapenem resistant Acinetobacter baumannii, fluoroquinolone resistant *E-coli*, carbapenem resistant K pneumoniae, and third generation cephalosporin resistant K pneumoniae.⁴

Among the pathogenic fungi, non-albicans Candida, particularly Candida auris is notorious for exhibiting antifungal resistance to many antifungal classes of compounds. They are always resistant to Fluconazole. Among parasites, Plasmodium falciparum and Leishmania donovani are often resistant to the available antimicrobials. Among viruses, HIV is notorious for developing resistance to HAART in cases of poor compliance.

Mechanisms of Antimicrobial resistance in microbes

Many mechanisms are there for antibiotic resistance in microbes. In bacteria, the common mechanisms are thickening of cell wall (as in VISA or Vancomycin indeterminate Staphylococcus

aureus), altered antibiotic binding site in cell wall or ribosomes (as in MRSA or aminoglycoside or macrolide resistant bacteria). Sometimes, antibiotics are broken down by enzymes of bacteria, as in Beta-lactamases (like ESBL and metallo beta-lactamases) expressed by gram negative bacteria like *Escherichia coli* and *Klebsiella pneumoniae*. Aminoglycoside-modifying enzymes confer resistance to this group of drugs in *Enterococcus* spp.

How to reduce the menace of AMR

Health education is the primary step to reduce the high burden of AMR. Other things like antibiotic stewardship and practising this stewardship will help in reducing the high load of AMR in the community.

Antibiotic ward rounds are also a good way to mitigate the load of AMR. In this, a team of clinicians, laboratory scientists or microbiologist and nurses carry out rounds of patients admitted to the hospital and scrutinize their antibiotic prescriptions for proper dosage and adverse effects keeping in mind their pre-existing health conditions. Pharmacodynamics of a particular drug are also important things to be remembered before prescribing it. India has a National Action Plan on Antimicrobial Resistance. Our national policy for containment of AMR was introduced in 2011. India also saw the Delhi Declaration on AMR, which was endorsed at the Inter-Ministerial Consultation on AMR in April 2017.⁵ India also has National action plan on A3MR (NAP) promulgated in 2021, to counter the challenge of AMR, by 6 key mechanisms which include training, spreading awareness about AMR, Information education communication (IEC) activities and other means. Antivirulence strategies or drugs, and also novel therapeutic options like efflux pump inhibitors, also may play a role in the future to bring down the cases of AMR. Awareness programs about AMR and antibiotic awareness week observation can also play decisive role in promoting safe and judicious use of extant antimicrobials. Global action plan and also GLASS are good initiatives to combat AMR. Most importantly, a concerted effort by medical professionals, veterinarians and environmentalists should generate a holistic or one health view point for managing AMR.

Discussion

AMR is a real public health problem across the world, especially in the developing countries of Asia, South America and Africa. It would

not be wrong to put it as the next pandemic to hit the world very soon. In 2008, about 29% of isolates of *Staphylococcus aureus* were found to be methicillin resistant across the World, and by 2014, this figure rose to a whopping 47%.⁵ All governments must try and collaborate to bring down the burden of AMR. It affects Gross domestic product adversely, and also imparts a substantial financial burden to the patient.⁶ In fact, only AMR can be held responsible for causing loss of about 700000 lives a year.³ Many factors are responsible for such high burden of AMR, like antibiotic misuse and abuse. In fact, antibiotic misuse, overuse, and improper hygiene and sanitation along with poor implementation of infection control policy are the major drivers for AMR across the world. It had been reported that about 70% of medically important antimicrobial compound are approved for use in veterinary practice.⁷ This can lead to a grave situation of antibiotic resistance in most bacterial pathogens. The "ESKAPE" pathogens mentioned earlier cause most of drug resistant nosocomial infections. However now other emergent pathogens are also coming up, like *Clostridium difficile*, carbapenem-resistant *Enterobacteriaceae* (CRE) and drug-resistant *Neisseria gonorrhoeae* which have been reported by US Centers for Disease Control and Prevention (CDC).⁸ Vaccination for infections, wherever applicable, and also proper biomedical waste disposal, may also be pivotal for control of antimicrobial resistance. Maintaining good hygiene and proper handwashing alone can bring reduce infections and usage of antimicrobials by about 40%.³ In this way, pneumococcal vaccination, wherever applicable, can bring down the burden of cases of antibiotic resistant Pneumococcal infections by half or even more.³

Other things like including AMR in medical and paramedical curricula may also be helpful. Nurses and other healthcare providers also need to be educated about AMR and infection control to make control of AMR a success. We also need to publish more and more scientific data on the epidemiology and newer diagnostic methods of AMR. At this moment, the development of an effective in-hospital surveillance and antimicrobial stewardship with unified antimicrobial protocols also seems to be the need of the hour.⁵ This can be carried out by the hospital infection control committee. Surveillance for AMR is also needed very badly. The National policy on AMR in India has recommend 3 types of surveillances, namely comprehensive surveillance, sentinel surveillance and point prevalence.⁹ We must also promote new and rapid diagnostics to allay misdiagnosis of infections and thus enhance proper antibiotic

usage.¹⁰ Clinicians must use broad spectrum antibiotics sparingly, and escalate and deescalate antibiotics judiciously. Overall, we must also act the community level to make more people aware of the perils of AMR. Public should be more aware of antibiotics and the need to use them sparingly and judiciously. The US government performed the AMR Challenge from 2018 to 2019 using a one health approach, to accelerate the fight against AMR. More such efforts are needed. Concordant with the theme of World antibiotic awareness week 2022, people of diverse disciplines must converge and act together in the wake of one health, to bring down the high burden of AMR.

Conclusion

AMR is a real cause for worry and if not tackled now, it is likely to become a major headache for clinicians as well as laboratory people. All must try to bring down AMR to manageable levels by proper diagnostics, spreading awareness and promoting antibiotic stewardship.

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