Strategies to Combat Antimicrobial Resistance

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ABSTRACT

The global burden of antimicrobial resistance is rising and is associated with increased morbidity and mortality in clinical and community setting. Spread of antibiotic resistance to different environmental niches and development of superbugs have further complicated the effective control strategies. International, national and local approaches have been advised for control and prevention of antimicrobial resistance. Rational use of antimicrobials, regulation on over-the-counter availability of antibiotics, improving hand hygiene and improving infection prevention and control are the major recommended approaches. Thorough understanding of resistance mechanism and innovation in new drugs and vaccines is the need. A multidisciplinary, collaborative, regulatory approach is demanded for combating antimicrobial resistance.

Keywords: Antimicrobial resistance, Antibiotic, Control and prevention, Infection, Rational use

INTRODUCTION

Antimicrobial resistance (AMR) including multidrug resistance (MDR), is on the rise among many microorganisms in health-care facilities as well as in community [1]. Reported data suggests that almost 2 million cases of infection with resistant bacteria have been reported in the United States (US) every year leading to $20 billion incremental direct healthcare cost [2]. Estimates of European Medicines Agency (EMA) and European Centre for Disease Prevention and Control (ECDC) reported a toll of 25,000 deaths per year as a direct consequence of a MDR infection with total cost of €1.5 billion [3]. In Canada, hospitalization caused by resistant infections resulted in higher economic burden with excess cost of $9–$14 million [1]. Study by Indian Network for Surveillance of Antimicrobial Resistance (INSAR) group, India reported prevalence of 41% with methicillin resistant *Staphylococcus aureus* (MRSA) [4]. High prevalence of Gram–negative bacterial resistance has also been reported in India [5]. World Health Organization (WHO) estimates that worldwide 3.7% of new cases and 20% of previously treated cases are estimated to have MDR-TB [6].

The path of antibiotic development is challenged at every step by the emerging microbial resistance. Emergence of MRSA, resistant *Pseudomonas aeruginosa* have already compromised the most effective treatments [7]. Recent reports have witnessed changing susceptibility pattern and spreading trend in AMR [8-10]. Development of superbug like New Delhi metallo-β-lactamase 1 (NDM-1) positive Enterobacteriaceae have further complicated the management of such infections [11].

Urgent threats with *Clostridium difficile*, carbapenem-resistant Enterobacteriaceae (CRE) and drug-resistant *Neisseria gonorrhoeae* have been reported by US Centers for Disease Control and Prevention (CDC) [2]. Thus AMR is a major point of concern as it is associated with high death rates and fear of progression to the pre antibiotic era; also has potential to hamper infectious disease control programmes; increase in health care costs and diminish health-care gains achieved so far [6].This review discusses various measures that can be taken to combat AMR with major emphasis on antibiotics resistance.

Call for action

The global threat of AMR calls for the collaborative action for developing effective strategies in combating AMR. CDC recommends 12 steps to prevent antimicrobial resistance in a healthcare setting [12].

We herein discuss the effective strategies for combating AMR. The collaborative approach is required at different levels. Different measures for combating AMR can be directed at international, national, community, hospital, individual and patient level. [Table/Fig-1] summarizes these approaches.
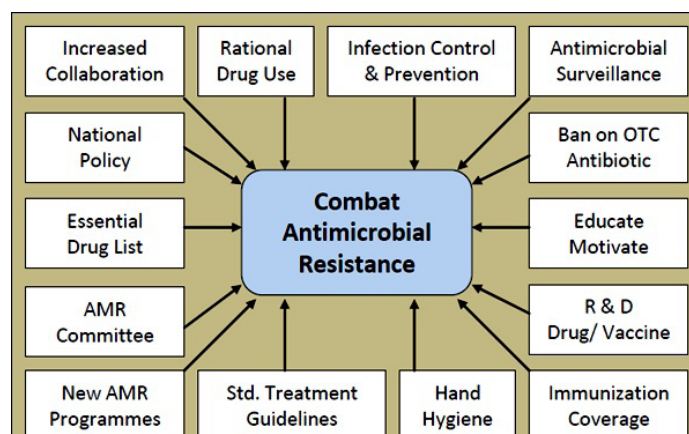
[Table/Fig-1]: Approaches for combating of antimicrobial resistance
Std.: Standard, R & D Research and Development, OTC: Over-the-Counter

1. International Measures

As a global problem, AMR is now well accepted by various stakeholders. In the year 2011, WHO theme was on combating antimicrobial resistance. It was one of the major attempts to draw international attention and need of combined efforts to alleviate the problem of AMR [13]. Some of the WHO recommended approaches are listed below: [14]

- Increased collaboration between governments, nongovernmental organizations, professional groups and international agencies
- New networks that undertake surveillance of antimicrobial use and AMR
- International approach for control of counterfeit antimicrobials
- Incentives for the research and development of new drugs and vaccines
- Forming new, and reinforcing existing programmes to contain AMR.

2. National Strategies

2.1 National committee with intersectoral coordination and regulatory actions

Establishment of national committee to monitor impact of antibiotic resistance and provide intersectoral co-ordination is required. WHO recommends that such committee would formulate AMR policy; provide guidance on standards, regulations, training and awareness on antibiotic use and AMR. Developing indicators to monitor and evaluate the impact of AMR prevention and control strategies would be amongst priority objectives at national level [15].Further WHO advises that having a registration scheme for all dispensing outlets, making prescription-only availability of antimicrobials, legal binding on all manufacturers to report data on antimicrobial distribution and incentives for rational use of antimicrobials can help contain AMR [15].

Establishing and implementing national standard treatment guidelines, having essential drug list (EDL), enhancing coverage of immunization are other essential strategies desired at national level [14].

2.2 National Antimicrobial Resistance Policy, India

A national policy for containment of AMR was introduced in 2011. The policy aims to understand emergence, spread and factors influencing AMR, to setup antimicrobial program, to rationalize the use of antimicrobials and to encourage the innovation of newer effective antimicrobials. In addition, some major action points identified in national policy were; establishing AMR surveillance system, strengthening infection prevention and control measures and educate, train and motivate all stake holders in rational use of antimicrobials [16]. WHO estimates that less than 50% of all countries are implementing basic policies for appropriate use of medications [17].

3. Action at Community Level

Globally, infectious diseases still continue to be significant cause of morbidity and mortality, affecting more the countries where health services are not sufficiently accessible [18]. Kardas et al., in a review of antibiotic misuse in the community reported that at community level, more than one third of patients were non-compliant to the antibiotic regimen and one quarter kept the unused antibiotics for use in future [19]. This indicates a poor antibiotic-taking behavior [19]. Review on population perspective of AMR by Lipsitch et al., suggests that prevention of AMR in an individual suffering from infection is one of the basic method to prevent further spread of resistance to the wider community [20]. The increasing rate of resistance among community acquired infections like upper and lower respiratory tract infections, bacterial diarrhea, typhoid fever are not matched by development of newer antibiotics [21]. Thus there is urgent need for reforms at community level for curtailing AMR. Different measures directed to control and prevent AMR at community levels are the need of an hour.

3.1 Rational use of antibiotics

Irrational use of medicines is a serious global problem. In developing countries, at primary level, less than 40% patients in public sector and less than 30% patients in private sector are treated in accordance with standard treatment guidelines [17].This mandates public and professional education towards rational use of antibiotics.

3.2 Over-the-counter (OTC) antibiotics

Measures that preserve efficacy of antimicrobials are mainly directed towards the hospitals and drug providers and missing antibiotic use without prescription. In systematic review of non-prescription antimicrobial use, Morgan et al., reported that non-prescription use of antimicrobials varied from as low as 3% in northern Europe studies to 100% in African studies [22]. This implies urgent need for regulatory control on OTC use of antibiotics.

3.3 Guidelines for use of antibiotics at local levels

About use of antibiotics in common situations, Bhagwati A. discussed that an empirical antibiotic therapy should be started considering the clinical condition of the patient and prevalent pathogen and resistance pattern in a locality. Appropriate change in antibiotic is required as per the sensitivity of microbe. Antibiotic guidelines are therefore must to optimize antibiotic selection with their dosing, route of administration and duration of therapy [21].

3.4 Standards of hygiene

Use of alcohol-based hand rubs or washing hands has proven efficacy in prevention of infection [12,23]. This factor can restrict the spread of infection and thereby the AMR. Willingness to put up with high standards of hygiene is the need of an hour.

3.5 Other approaches

These include identifying residents with MDR infections and use of standard treatment regime for their management, vaccination, infection prevention strategies and ban on OTC sale of antimicrobials [12,16].

4. At Hospital or health care setting

A person or a patient in a health care facility is at higher risk of infection with common pathogens. For control and containment of AMR, experts recommend some of the measures as discussed herein.

4.1 Infection prevention and control within health-care facilities [1,24]

Infection prevention and control measures are designed to reduce the spread of pathogens including resistant ones within healthcare facilities and to the wider community. This can prevent further infections and AMR spread [1]. Recommended measures to prevent and control infection in a health-care facility [1,12,16,24-26].

- Establishing an infection prevention and control committee (IPC).
- Good hand hygiene practices.
- Effective diagnosis and treatment of infection.
- Rational antimicrobial use.
- Surveillance of antibiotic resistance and antibiotic use.
- Improving the antimicrobial quality and supply chain.
- Good Microbiology Practices.

Surveillance of Antibiotic resistance and antibiotic use

All over the world, surveillance is considered as strength of the programmes directed towards AMR. The objective of surveillance is to facilitate the containment of antibiotic resistance. It is a useful tool that generates data on antimicrobial use and AMR which is essential in updating national EDLs and formulating infection control policies. It may also help in improving antimicrobial prescribing and development of empirical therapy or standards treatment guidelines [25,26].National policy on AMR in India recommend three types of surveillances which include comprehensive surveillance, sentinel surveillance, and point prevalence [16].

Good Microbiology Practices

From accurate collection, handling of specimens to the speedy reporting with standard microbiology practices may help in prevention of AMR spread. Testing with international standards, reporting of resistance pattern to IPC and monitoring the sterilization and disinfection activities underlie the good microbiology practices [16,24].

5. At Personal / Patient level

5.1 Role of Physician

Along with providing direct patient care, complying with local infection control and antibiotic use policies and timely notifying

resistant cases to IPC, the physician can play a major role in combating AMR [24]. Identifying and preventing situations that may act as nidus for infection may help curtail unnecessary infections and thereby AMR [12].

5.2 Role of Nurses/health care providers

Since nurses/health care providers are in direct contact with the patients, they are amongst those related in either spread or control of infection and AMR. Educating nurses and health care providers about the AMR and aseptic practices may help in control of spread of infections. Moongtui et al., have reviewed the role of nurses in preventing AMR and reported the initiatives by Thailand like having Master's programme in infection control nursing with other short training courses and involvement of nurses in AMR prevention and control programme [27].

5.3 Role of Pharmacist

McCoy et al., in their review discussed the Pharmacist-directed antibiotic stewardship programs (ASPs) as an approach to improve the utilization of antibiotics. Pharmacists can counsel patients with viral infections about the ineffectiveness of antibacterials and can recommend appropriate OTC medication for supportive care. Referral to physician is must if a bacterial infection is suspected. Above all, most importantly, addressing patient and clinician concerns related to antimicrobial and understanding of the appropriate use of these agents, pharmacist can be an essential arm in preventing AMR [28]. Pharmacist is the key person to educate patients about antimicrobial use and the importance of complying with the prescribed treatment regime. This may help to reduce the unnecessary use of antibiotics.

5.4 At patient level

(a) Aseptic protocol for any procedures.

Parameswaran et al., reported that MDR microbes caused 30.2% of the catheter-related blood-stream infections and empirical treatment had no role in prevention of such infections [29]. This mandates use of aseptic protocol to minimize local or systemic infections associated with any procedures.

(b) Breaking the chain of infectivity [12].

By simple means like covering mouth while coughing or sneezing, infection spread can be reduced.

(c) Compliance to the antimicrobial regime and antibiotic.

Improved compliance definitely can improve the rate of infection control. Patient education on compliance with antibiotics is must [30]. Using established regimes for prophylactic use of antibiotics in high risk cases and for the shortest duration possible can minimize risk of AMR [31].

6. Other Measures

6.1 Pharmaceutical promotion

WHO recommends that pharmaceutical firms should strictly adhere to the standards of drug promotion, direct-to-consumer advertising and advertising the internet [14]. There is need to identify and prohibit any incentives promoted by pharmaceutical companies that possibly encourage inappropriate antimicrobial use.

6.2 Antibiotic use in animals

Use of antibiotic avoparcin in food of the animals in Europe was the cause of development of vancomycin-Resistant Enterococci (VRE) and consequent colonization in human intestine, thus highlighting its importance [16]. WHO specifically called for stricter legislation to minimize antimicrobial usage in animals. Improved sanitation, provision of probiotics or nutritional supplements in feed and vaccination for common animal diseases can help reduce the antimicrobial use in animals [25].

6.3 Rapid understanding of the AMR mechanisms

In their review, Bergeron and Ouellette suggested that genotyping of bacteria and identification of resistant genes in bacteria can impact

the treatment of infections and contribute to the control of AMR [32].

6.4 Innovation in new drugs and technology

Concerns of increased antibiotic resistance lead to the urgent need of concentrating on the issue of new drugs and vaccines development to combat AMR. Collaborated efforts of national, international, government and academic networks are needed to identify new classes of antibiotics and diagnostic technologies [15]. Providing research funding for development of new antimicrobials to pharmaceutical companies for diseases of public health importance can advance the new drug development.

In summary, it is necessary to enforce essential actions to be taken by government to inspire change by all stakeholders related to AMR as described in WHO policy package for combating AMR [13]. This policy package refers to:

*   Dedicate to a comprehensive, financed national plan with accountability of each one involved and engagement of civil societies

*   Improve and strengthen surveillance and laboratory capacity and facilities

*   Make sure uninterrupted wide access to essential medicines of assured quality

*   Regulate and encourage rational use of medicines, even in animal husbandry, and ensure proper patient care

*   Improvise on infection prevention and control

*   Promote and pursue innovations and research and development for new tools

CONCLUSION

Antimicrobial resistance is a complex problem with many diverse contributing factors. It is major cause of health concerns adding cost to oneself and to the community, directly or indirectly. Prevention is still the best tool to reduce the infection spread and thereby AMR. Along with rational use of existing antimicrobial drugs, development of new effective compounds and new diagnostic technology is the need. Joint efforts from patients, prescribers and individuals to international regulators and policy makers are needed to fight against the globally spreading antimicrobial resistance.

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