DOI: NJLM/2014/8776:2003

Review Article

Internal Medicine Section

Antimicrobial Resistance: An Overview

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ABSTRACT

Antibiotics are one of the greatest discoveries of medical science and have saved millions of lives since their discovery. Antimicrobial resistance is usually of acquired type and is mostly due to mutations in microbes and selection pressure from antibiotic use. Lack of adherence to drug therapies, suboptimal dosing and duration of treatment, ineffective infection control and lack of research on new antibiotics are some of the important factors responsible for development of antimicrobial resistance. Presently antimicrobial resistance is a global problem because of spread of resistant strains across the countries and continents. Economic implications of antimicrobial resistance are huge and enormous money is being spent for treatment various diseases which have become resistant to effective and cheaper older drugs. Here, we describe the epidemiology of antibiotic resistance, its major causes and consequences, and identify critical area which requires urgent action.

Keywords: Antimicrobial resistance, Antibiotic adherence, Rational drug use, Infection

INTRODUCTION

Antimicrobial resistance (AMR) has wreaked havoc in the treatment of common infections leading to delay in effective treatment or inability to provide appropriate therapy. Use of antimicrobial drugs especially antibiotic use has been rising in recent years. A survey on antibiotic use in community reported that the consumption of macrolides was decreased while with cephalosporins increased consumption was seen during the four year period from 2004 to 2008 [1]. This showed preference to particular antibiotics after its introduction into the market, leading to increased consumption of a new antibiotic over the older ones which is possibly because of aggressive marketing strategies [1].

Health and economic consequences of AMR are colossal and costly and it is difficult to quantify the harm caused by AMR. The bacterial disease burden in India is among the highest in the world [2]. As a marker of disease burden, pneumonia is responsible for 24% deaths under 5 years of age [3]. Many of these deaths occur because patients do not have access to life-saving antibiotics [4]. Thus antibiotics play a critical role in limiting morbidity and mortality especially in India. On the contrary, antibiotics are used in situations like common cold and uncomplicated diarrhoea where antibiotics are not expected to improve the patient's condition [3]. Irrational and improper use of antibiotic is one of the most important factors in the evolution of drug resistance in bacteria. Various medical, ecological, epidemiological, cultural, social, and economic factors are also responsible for development of AMR.

Resistance against antibiotics is already at high levels in certain places in the world including India, but the problem has remained largely unnoticed. However this issue got attention with first report of New Delhi metallo-ß-lactamase-1 (NDM-1) in 2009 [4]. The health related consequences of AMR include increased morbidity, prolonged illness, a greater risk of complications, and higher mortality rates whereas economic consequences includes increased cost of diagnosis and treatment to diminished work productivity and loss of income. Thus actions are required to be taken to control AMR. Here we discuss the common mechanisms of antibiotic resistance, factors responsible for its development and spread and ways to control and prevent AMR.

Antimicrobial resistance mechanisms

Natural resistance in an organism is because of the properties specific to the organisms like presence of cell wall. Acquired (non-inherited) resistance is because of a change in genetic composition of a microorganism. Harbouring acquired resistance makes microorganism resistant to the antimicrobial agent that was once effective against the same microorganism. Specific mechanisms of acquired resistance include drug inactivation, cell wall changes, altered targets, efflux pump and bypass targets [5]. Multidrug resistant organisms (MDROs) are those which are resistant to one or more antimicrobial classes. Possibly the most well-known MDRO is methicillin-resistant Staphylococcus aureus (MRSA). Because so much focus has been placed on MRSA during the past decade, we are, thankfully, beginning to see a decline in the incidence

of healthcare-associated MRSA as well as its still eradicable cousin, methicillin-susceptible S. aureus (MSSA) [6].

Resistance in Gram-positive bacteria

Increasing level of drug resistance among Gram positive organisms has been a major concern especially with MRSA. Expression of β-lactamase, cell wall thickening and horizontal transfer of a transposon containing resistant genes has been major mechanisms for resistance to penicillins and vancomycin in S. aureus [7]. Study on 5 MRSA isolates suggests that, "staphylococcal cassette chromosome (SCCmec) acquisition is at least 10-fold more common [8]. In late 1990s, high level of MRSA was reported from most countries and a more virulent community-associated MRSA (CA-MRSA) was also identified [9]. Expression of VanA and VanB genes leading to altered target for vancomycin has been major mechanism of vancomycin resistance in *Enterococci* [7].

Resistance in Gram-negative bacteria

Inactivating enzymes are main causes of resistance used by many serious Gram-negative microbes. These include extended-spectrum beta-lactamases (ESBLs), carbapenemases, and aminoglycoside inactivating enzymes [5]. The ESBLs are plasmid-mediated bacterial enzymes typically found in enteric Gram-negative bacteria. These enzymes are responsible for the drug resistance in various group of antibiotics [10]. ESBL, through horizontal gene transfer causes resistance to oxyimino-cephalosporins. ESBLs are of established plasmid-mediated β-lactamases (e.g. TEM/SHV) or mobilized from environmental bacteria (e.g. CTX-M). CTX-M-15 is the only genotype reported from India and is also very widely distributed across the world [9]. AmpC enzymes (chromosomally encoded β-lactamase) VIM-2 (Metallo-β-lactamases) are common causes of drug resistance in Enterobacteriaceae and *P. aeruginosa* [9,11]. Stepwise mutation in the coding regions of the DNA gyrase subunits (gyrA and gyrB) and DNA topoisomerase IV (parC) have lead to resistance against fluoroquinolones [12].

Prediction of antimicrobial resistance (AMR)

Spread of AMR by mutations occurs at the level of the bacteria (clonal spread), replicons (plasmid epidemics), or of the genes (transposons) which coexist in nature [13]. Therefore it is difficult to predict the AMR. Another way we can predict AMR is by finding the source and evolution of antibiotics whether the antibiotics are natural, synthetic or semi-synthetic. This information tells us that the source of antimicrobial agent may be harbouring the pool of origin of certain resistance genes [13]. Predicting the emergence of resistance by molecular mechanisms to a drug class is nearly impossible. Therefore the only option left is to prevent dissemination of antimicrobial resistance.

Risk Factors for the development of antimicrobial resistance

Adherence to drug therapy: Adherence is one of the most important factors in developing antimicrobial resistance. So patients' compliance to the prescribed treatment is very critical for recovery from the disease. A noncompliance rate of 37.8% was reported in a meta-analysis and better compliance was reported in children compared to adult population [14]. The problem of non-adherence is not only limited for acute ailments, but even for chronic diseases where lifetime treatment is warranted. DiMatteo et al., in a meta- analysis reported an average non-adherence rate of 24.8% with better adherence in patients with HIV-disease, arthritis, gastrointestinal disorders and cancer, as compared to patients with pulmonary disease, diabetes mellitus and sleep-disorders [15]. It is also reported that adherence is very low in patients with chronic conditions, reducing even more after first six months of treatment [16].

India has huge burden of tuberculosis (TB) in the world. Resistance to anti-tubercular drugs has complicated the problem of TB in India. Recent survey in Gujarat State in India reported low to moderate levels of multidrug resistance tuberculosis (MDR-TB). Among new TB cases, the prevalence of resistance was 2.4% and 17.2% among re-treatment cases [17]. Among the variety of causes of drug resistance, non-adherence of patients to the prescribed drug therapy is one of the important causes, even for MDR-TB [18]. Factors like lack of education, poverty and limited or no access to health care also play an important role in adherence to drug therapy.

Suboptimal dosing and duration of treatment: Antimicrobial resistance can be affected by antibiotic dosing regimens. Many *in vitro* and animal experiments have noted that inappropriate and unscientific dose titrations lead to antimicrobial resistance. Marchbanks CR, et al., in an *in vitro* study reported that single high dose of 1200 mg or 300-400 mg of ciprofloxacin 12 hourly did not result in drug resistance in bacteria but 200 mg 12 hourly resulted in bacterial regrowth due to selection of drug resistant bacteria [19]. Evidence indicates that the dose and treatment duration can influence the selection of antibiotic-resistant mutants. Though this is well recognized, there is limited data on the optimal dosing strategies to treat bacterial infections and prevent drug resistance [20].

According to World Health Organisation (WHO), use of antibiotics has increased enormously at primary care over last two decades. On contrary the compliance of treating doctors to guidelines has become low leading to worrisome situation. In developing countries antibiotic misuse and overuse is common with wide variation in types and volume [21]. Usual practice of prescribing antibiotics in patient of common cold early in its course is an example. Minimizing unnecessary use of antibiotics will help reduce the antibiotic resistance.

Ineffective infection control: Antimicrobial resistance in Hospital Acquired Infections (HAI) is increasing rapidly. These patients are at higher risk of developing drug resistant infection as compared to patients who are treated in outpatient basis. Poor infection control is one of the important factors for drug resistance in the hospitals [22]. Treating such infection is a very difficult task. Therefore many, HAI can be prevented through better hygiene.

Spread of antimicrobial resistance: Role of population mobility and globalisation

Presently antimicrobial resistance has become a global threat as resistant strains have spread all across the countries and continents. The global spread of the international clone 1 of penicillin-resistant *Streptococcus pneumoniae* (PRSP) is a classical example of international spread of antimicrobial resistance [23]. When there is a dramatic rise in drug-resistant infections/diseases in a particular area in which the infection/disease is not common or not a endemic, then there is high chance that the disease may be imported from endemic area [24]. The recent local appearance of novel influenza strains with rapid global distribution raises questions about the role of human mobility in the spread and distribution of drug-resistant viruses [25].

Economic impact of antimicrobial resistance

The impact of antimicrobial resistance on the different stake holders in the diagnosis and treatment of the disease/infection is different because their concerns and priorities are different. The view point of a patient and physician is to achieve disease free state in appropriate and shortest possible time. But the industry view point may be of revenue earned with effective treatment of disease. The health care providers and policymakers are interested in good population health with low level of drug resistance. Although the perspective of everyone involved to achieve healthy life is different, the rational use of drugs is the common thread entwining everybody. Therefore antimicrobial resistance is the major reason for cost escalation of each attribute associated with diagnosis and treatment of the resistant infection compared to infection due to susceptible organisms [26]. Measurement of the actual impact of antimicrobial resistance is difficult because of number of variables and perspectives involved.

New drug discovery and antimicrobial resistance

Since the discovery of first antibiotic to the today's world of variety of antibiotics, we have come a long way in the discovery of new drugs. Though the problem of antibiotic resistance is huge; it is difficult to find development of the new antibiotics with novel mechanism. Pharmaceutical companies which have spearheaded the new drug discovery, have been abandoning the development of anti-infectives [27]. Rising cost of new drug discoveries, delays and hurdles for regulatory approval may be the reason for this trend. This is reflected in such a way that US FDA approval of new antimicrobial agents was decreased by 56% during 1983–2002 [27].

Rational use of already approved antimicrobials and avoidance of unnecessary prescription of antibiotics is the only effective solution to this catastrophic problem. Availability of effective antibiotics has revolutionized public health; it is one of the reasons for major scientific advances in medical field. Rational use of this scarce resource with strict guidelines for its use is the only way ahead in recent future [28]. Rational use of old drugs like ciprofloxacin, cephalosporins and rational combination of two or more drugs can also help us to tide over the crisis of antimicrobial resistance. Fixed dose combination of drugs is one way to prevent drug resistance. It helps to prevent or slow the development of antimicrobial resistance by eliminating monotherapy [28]. This can be an effective alternative to discover new drugs altogether.

CONCLUSION

Prevention of emergence and spread of antimicrobial resistance is difficult and the solution is complex involving many stake holders requiring actions at multiple levels. Only decreasing the overall use of antibiotics may not reverse the bacterial resistance. Rational use of available antibiotic may help decreasing the burden of antimicrobial resistance. Updating the primary care physician about the rational use of antibiotics through continued medical education, learning and workshops may help in reducing the further spread of antibiotic resistance. Use of fixed drug combination can help to prevent or slow the development of drug resistance at both individual and population level. New drugs effective against resistant organisms are needed since the consequences of antimicrobial resistant affect not only the patients but community at large. Effective actions by government, regulators and health care professionals required to control and prevent the antimicrobial resistance.

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FINANCIAL OR OTHER COMPETING INTERESTS:
None.

Date of Submission: **Feb 03, 2014**
Date of Peer Review: **Feb 22, 2014**
Date of Acceptance: **Apr 24, 2014**
Date of Publishing: **Mar 06, 2014**