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Antimicrobial resistant: A glance on emergence, spread and combat

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Abstract
The discovery of antibiotic in middle of nineteenth century was revolutionized era for mankind suffering. Antibiotic was considered as magic bullet for untreatable infection after its use in therapeutic purpose. Lamentably, the use or rather the indiscriminate use of antibiotics has been accompanied by the rapid emergence of antibiotic resistance. The antibiotic resistance in hospital settings has become a inevitable and even become major problem for treatable infection. Leading outcome of antibiotic resistance in public health are morbidity, mortality, substantial economic loss. Beside use of alternate therapy antibiotic resistance can be managed by many ways; proper hygienic policy, rational use of antibiotics in hospitals or antibiotic stewardship, public health awareness, globally collaborative action plan.

Keywords: Antibiotic, indiscriminate, antibiotic resistance, public health

Introduction

The discovery of antibiotics, the ever time arsenal of modern medicine is considered to be one among the revolutionary discovery of last century. These wonder drugs have saved millions of lives, not only by treating infections but also by preventing bacterial infections among those individuals with weakened immune system such as those undergoing chemotherapeutic treatments against cancer or organ transplantation. Lamentably, the use or rather the indiscriminate use of antibiotics has been accompanied by the rapid emergence of antibiotic resistance. Furthermore, the use of antibiotics in the food animals as feed additives and growth promoters has significantly fueled the acclivity of antibiotic resistant pathogens (Van Boeckel *et al.*, 2015) [25]. Though the antibiotics are primarily used for treating infections, bacteria in turn may develop mechanisms to counterattack the noxious effect of these antimicrobial agents as an adaptive strategy to survive by out-competing their microbial neighbors in the adjacent environment. This biological phenomenon rather, selection pressure imposed by the continuous exposure towards an array of antibiotics during its clinical application has led to the cumulative acquisition of resistant traits in major zoonotic pathogens resulting in multidrug-resistant (MDR) bacteria, which are practically impossible to treat (Medina and Pieper, 2016) [17].

The term multi-drug resistant (MDR) refers to a group of bacterium which carries several resistance genes, it is called informally, a *superbug* or super bacterium this fact is a core challenge for both the medical and animal health communities, since the use of antibiotics has formed the cornerstone of modern medicine for treating bacterial infections. WHO's new Global Antimicrobial Surveillance System (GLASS) reveals widespread occurrence of antibiotic resistance among 5,00,000 people with suspected bacterial infections across 22 countries (WHO, 2018) [30]. The most commonly reported resistant bacteria were *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*, followed by *Salmonella* spp (WHO, 2018) [30].

The emergence of resistance

The management of microbial infections in ancient Egypt, Greece and China is well-documented. The modern era of antibiotics started with the discovery of penicillin by Sir Alexander Fleming in 1928. Since then, antibiotics have transformed modern medicine and saved millions of lives. Antibiotics were first prescribed to treat and cure serious infections in the 1940s. Penicillin was evidently successful in controlling bacterial infections among World War II soldiers. However, shortly thereafter, penicillin resistance became a substantial clinical problem, so that, by 1950s, many of the advances of the prior decade were threatened. In response, new beta-lactam antibiotics were discovered, developed and restoring confidence. From the late 1960s, through the early 1980s, pharmaceutical industry introduced many new

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antibiotics to solve the resistance problem, but after that the antibiotic pipeline began to dry up and fewer new drugs were introduced. The decreasing effectiveness of antibiotics in treating common infections has quickened in the recent years and with the arrival of untreatable strains of carbapenem resistant Enterobacteriaceae, we are presently at the dawn of a post antibiotic era. As a result, late in 2015, many decades after the first patients were treated with antibiotics, bacterial infections have again become a threat (Spellberg and Gilbert, 2014) [24]. It could literally be inferred that nearly as quickly as life-saving antibiotics are created, new drug- resistant infections appear. In high-income nations, continued higher rates of antibiotic use in clinical settings, in community and in the agriculture have contributed to the selection pressure, which on the other hand has forced the sustained resistant strains to be more expensive and towards more broad spectrum antibiotics (Laxminarayan and Heymann, 2012) [15]. In low income and middle-income countries, antibiotic use is increasing with rising incomes, high rates of hospitalisation, and high prevalence of hospital infections. Resistance arises as a result of microbial mutation and of course, selection pressure arising from the indiscriminate antibiotic use provides a competitive advantage for mutated strains. Suboptimal doses of antibiotic may help in stepwise selection of resistance. Resistance genes are mainly borne on chromosome and increasingly, on transmissible extra chromosomal elements. The resulting resistant clones, for instance, Methicillin resistant *Staphylococcus aureus* (MRSA) USA 300, *Escherichia coli* ST131, and *Klebsiella* ST258 are disseminated rapidly worldwide. This spread is facilitated by inter species gene transmission, poor sanitation and hygiene in communities and hospitals and the increasing frequency of global, travel, trade, and disease transmission (Laxminarayan *et al*., 2013) [16]. Indian subcontinent is at its stark when it comes to the matter of antibiotic resistance. In 2014, India was the highest consumer of antibiotics, followed by China and the United States. However, the per capita consumption of antibiotics in India is much lower than in several other high-income countries (Laxminarayan *et al.* 2016) [14]. On very serious concern, now days carbapenems which was regarded as last resort drug to treat untreatable infection regrettably has been unsuccessful. Major responsible factors include like high consumption of broad spectrum of antibiotics, Injudicious use of fixed dose combination of antibiotics, access to antibiotics without prescription.

Worldwide spread of antibiotic resistance
The rapid evolution of bacterial resistance is clear in the case of β-lactamases (Davies and Davies, 2010) [5]. The introduction of penicillin in 1941 resulted in a dramatic reduction in the Staphylococcal infection-associated mortality rate and in improved prognosis of infected patients. Unfortunately, *S. aureus* strains resistant to penicillin were reported already one year after this new antimicrobial was introduced (Rammelkamp and Maxon, 1942) [19]. Penicillin was commonly used in the 1950s and 1960s and soon after that, more than 80% of Staphylococcal isolates were resistant to penicillin (Finland, 1955; Barber and Rozwadowska-Dowzenko, 1948) [6, 2]. Penicillin- resistant strains were first emerging in hospitals, spreading later to the community, where they became prevalent (Chambers, 2001) [3]. This prompted a search for β- lactamase-resistant drugs that led to the production of semi-synthetic penicillins, including methicillin and other derivatives such as oxacillin, cloxacillin, dicloxacillin, flucloxacillin and nafcillin. Methicillin was

introduced for clinical use in 1959 and the first MRSA strain was reported in 1961 (Jevons, 1961) [11]. However, the first case of methicillin-resistant *Staphylococcus aureus* (MRSA) was identified during that same decade, in the United Kingdom in 1962 and in the United States in 1968 and spread to rest of the world (Sengupta *et al*., 2013; Ventola, 2015) [23, 26].

As of late, the selection pressure caused by the use of millions of tonnes of antibiotics over the past 75 years has made almost all disease-causing bacteria recalcitrant to antibiotics which are generally referred to treat them. Bacterial pathogens acquiring resistance has spread worldwide. For example, antibiotic-resistant gonorrhoea emerged in Vietnam in 1967 (Holmes *et al*., 1967) [10] which later spread to the Philippines, and finally to USA (Rasnake *et al*., 2005) [20]. The NDM enzymes, first reported in 2008, are now found worldwide (Nordmann *et al*., 2011). The distribution of resistance genes, such as Enterobacteriaceae- producing extended-spectrum β-lactamase (ESBL), NDM-1 and *Klebsiella pneumonia* carbapenemase (KPC), indicates the ease with which resistance can spread. A study conducted in New Delhi observed the presence of NDM-1- producing bacteria (including, *Shigella boydii* and *Vibrio cholera*) in two (4%) of the 50 drinking water samples and 51 (30%) of 171 seepage samples suggesting the possibility of acquiring resistance outside health-care facilities (Walsh *et al*., 2011) [28], which infers to the significance of hygienic settings in our country. In addition, waste water treatment plants that serve in the antibiotic manufacturing facilities have particularly been implicated in the transfer of resistance genes into human microbiota and eventually pose a serious threat to antibiotic effectiveness in a setting like India (Johnning *et al*., 2013) [12]. Quinolone antibiotics, in particular, are exemplified as an aftermath of misadventure. Even though these drugs are synthetic in origin, and do not arise naturally, the resistance to these agents is epidemic 30 years after their widespread use (Ruiz *et al*., 2012) [21]. More specifically, whole genome studies suggest that quinolone resistance was a crucial factor in the evolution of hospital acquired-MRSA infection (Holden *et al*., 2013) [8]. Such examples of antibiotic-driven evolution go a long way to explain the present epidemics of resistant health-care setting associated infections (Ammerlaan *et al*., 2013) [1]. In health-care settings, especially within intensive care units, the spread of resistant clone can be rapid and have serious far–reaching consequences for the vulnerable hosts (Harris *et al*., 2007) [7]. Resistance is also a problem in early-onset, presumably maternally acquired neonatal infections reported from hospital series in developing countries.

Carbapenem-resistance among common Enterobacteriaceae has increased sharply over the past decade. The epidemiology of ESBLs-producing pathogens is complex and the prevalence of bacteria producing ESBLs varies across the world (WHO, 2014) [29]. As a result of the high rates of ESBL production in *E. coli,* the use of second-line treatment with extended-spectrum cephalosporins has been restricted (Viswanathan *et al*., 2011) [27]. A perturbing emergence of pan– drug resistant untreatable carbapenem-resistant Enterobacteriaceae and *Acinetobacter* spp. infections were explored in a study conducted at Pakistan with high mortality rates in neonatal nurseries (Saleem *et al*., 2010) [22]. Compounding this problem is the emergence of several carbapenemase- resistance mechanisms. In India, *E. coli* (n= 1,815) isolated from the community showed a high overall resistance towards ampicillin, naladixic acid and co-trimoxazole (75%, 73% and 59%, respectively), between 2004 and 2007 (Holloway *et al*.,

2009) [9]; 30% showed resistance to injectable antibiotics, such as aminoglycosides (represented by gentamicin). The proportion of *E. coli* producing ESBLs increased from 40% in 2002 to 61% in 2009, and the proportion of *K. pneumonia* with carbapenem resistance increased from 2.4% to 52% in a study conducted on blood-stream infections (Datta *et al.*, 2012) [4]. This marked increase in antimicrobial resistance among common bacterial pathogens is now threatening the existing therapeutic accomplishment, jeopardizing the successful outcomes of critically ill patients. In fact, the World Health Organization (2014) [29] has named antibiotic resistance as one of the most important public health threats of the 21st century. Concisely, the spread of resistance could be described as 'more than we could have imagined'.

Combat against Antimicrobial resistant

Antibiotic resistant could be managed by many ways; proper hygienic policy, rational use of antibiotics in hospitals or antibiotic stewardship, public health awareness, collaborative action to educate the people to control of infection in community whereas treatable method like antimicrobial resistance testing, targeted research include; Plasmid inhibit replication or resistant mechanism such as efflux pump inhibitors. Moreover the use of bacteriophage, probiotics, endolysins, as well as antimicrobial peptides can serve as an alternative treatment approach for such superbugs (Laximinarayan *et al.*, 2013) [16]. Nevertheless epidemiology tracking data for readily detection resistance mechanism. To ensure the effective response the integration of all local, national and international commitment needed against antimicrobial resistance threat.

Conclusion

Antibiotics have saved countless lives and enabled the development of modern medicine over the past 70 years. However, it is clear that the success of antibiotics might only have been temporary and we now expect a long-term and perhaps never-ending challenge to find new therapies to combat antibiotic-resistant bacteria. Alternative of conventional antibiotics has been considered as potential replacement against antimicrobial resistance catastrophe.

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