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Review Article

A Short Review on Antibiotics and Ever-Changing Microbial Resistance Mechanisms

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ABSTRACT

Antimicrobial resistant organisms are associated with significant morbidity and mortality and have considerable burden on healthcare costs. Antimicrobial discovery was a major breakthrough in the field of infectious diseases and drug discovery until the unexpected rise of antimicrobial resistance which is now a public health threat. Imprudent use of antimicrobials have led to the emergence of microbial resistance strains and favoured microorganisms to successfully exploit every possible resistance mechanisms which includes, but not limited to, genetic mutations, gene pickup, horizontal gene transfer and heterologous expression. They have extended themselves to community settings highlighting the importance of reservoirs of antibiotic resistant microbes in environment. The antimicrobial therapeutic repertoire is also shrinking on a steady pace for present or impossible to treat multidrug resistant infections. This short review briefly discusses the different molecular mechanisms of antibiotic resistance which allow microbes to exhibit multidrug resistance trait. Prompt actions to limit the emergence and dissemination of multi-drug resistant superbugs through novel therapeutic approaches should be designed.

INTRODUCTION

Antibiotics are the class of chemical compounds with a powerful action against disease-causing microorganisms. The advent of first antibiotic discovery by Sir Alexander Fleming in 1928 started the modern era of antibiotics which has essentially transformed the way in which clinical medicine is practiced today (Sengupta et al., 2013; Tan and Tatsumura, 2015). The therapeutic paradigm has been revolutionised by the introduction of antimicrobial compounds. They have been proved extremely useful in preventing infections in patients receiving chemotherapy (Hammond and Baden, 2007) and patients with chronic diseases such as diabetes, renal failure etc. and in patients undergoing complex surgical procedures such as open-heart surgery, total knee replacement and organ transplants (Ventola, 2015). Their beneficial effects extend beyond the health-care field. The antimicrobial compounds are also widely used by the agricultural industry and animal husbandries to promote growth, increase yield and prevent infection

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(Cabello and Godfrey, 2016; Landers et al., 2012; McDermott et al., 2002).

The therapeutic accomplishments of antibiotics have been jeopardised by the development of Antimicrobial Resistance (AMR) in bacteria. The bacteria represent the pinnacle of evolution as they are the most numerous and diverse species on the earth (Michael et al., 2014; Munita and Arias, 2016). The immense genetic plasticity and the natural tendency to adapt in response to the various environmental stressors including antibiotics have shifted the balance in favour of bacteria to become resistant to virtually all classes of antibiotics (Galan et al., 2013; Miller et al., 2014). Several intrinsic and acquired mechanisms are in play to achieve AMR (Cox and Wright, 2013; Malathi et al., 2013). Indeed, World Health Organization (WHO) has stated AMR to be the 3rd major public health issue of this century (2014). This short review will describe the mechanism of antibiotic action and how bacteria develop resistance to their effects. It will also cover different methods of acquiring resistance trait and will give an informed conclusion supporting the notion that the world might, unfortunately, run out of antibiotics unless specific actions are not promptly taken.

PubMed was used to access research articles. "Antibiotics", or "Antibiotic Resistance", or "Antimicrobial Resistance", or "Intrinsic Resistance", or "Extrinsic Resistance", or "Acquired Resistance" were used as the key MeSH-terms in order to scan articles. Boolean operators, AND and OR, were also utilized. Abstracts were reviewed and articles (those with main topic of antimicrobial resistance) were permitted for final manuscript. Articles in language other than English were excluded. In addition, we also reviewed bibliography sections from retrieved articles to identify additional pertinent articles for manuscript.

TUG-OF-WAR BETWEEN ANTIBIOTICS AND MICROBES

Antimicrobial Agents

Antibiotics are selected according to their mechanism of action to treat infectious diseases (Kapoor et al., 2017; Thrum, 1977). Antibiotics are often grouped according to their mechanism of action. It includes inference with the synthesis of cell wall (Beta-lactam and Vancomycin), inhibition of protein synthesis (Aminoglycoside chloramphenicol and Tetracycline), inhibition of nucleic acid synthesis (Quinolone and Rifamycin), interference with metabolic pathways (Trimethoprim-Sulphamethoxazole) and alteration of cell membrane structure (Bacitracin and Polymyxin) (Kapoor et al., 2017; Munita and Arias, 2016; Peach et al., 2013).

Understanding of antimicrobial resistance rests on the history of how microorganisms have successively evolved overtime and used transgenerational inheritance pattern to prolong their survival (Adam et al., 2008; Hibbing, 2010). Firstly, the concept of antimicrobial resistance belongs to a very distant past and it has been thought to be the consequence of positive microorganism and environmental interaction. Since most of the antimicrobial compounds have their precursor form in the environment, it is likely that microorganisms have developed approaches to neutralize their harmful effects, also termed as intrinsic resistance. In clinical settings, antimicrobial resistance can also be extrinsic or acquired. The extrinsic resistance can be the product of either chromosomal mutations or resistance genes acquired directly from the peer organisms abundantly wandering in environment. Secondly, it is imperative to acknowledge that antimicrobial resistance encountered in clinical setting is a complex phenomenon. The antimicrobial susceptibility patterns, its interpretation and drug of choice might vary from one clinical setting to the other. This could be explained as the effectiveness of antimicrobials through in vitro studies against a range of bacterial population including few pharmacological variables (e.g., antimicrobial concentration in blood and site of infection etc.). Likewise, bacterial inoculum could affect *in vivo* vulnerability of microorganisms to a specific antimicrobial agent. Perhaps evidence has been reported that high inoculum of *Staphylococcus aureus*, despite cephalosporin susceptibility, alters the efficacy of cefazolin (a cepahlosporin) in systemic and deeply rooted infections. Thus, understanding of molecular machinery of antimicrobial resistance holds great promise in clinical practice (2018; Munita and Arias, 2016; Nannini et al., 2013).

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Antimicrobial Resistance

Antimicrobial resistance is a characteristic feature of resistant organisms identifiable when antibiotic loses its efficacy to eradicate susceptible organisms despite therapeutic blood levels; microbial replication persists (Zaman et al., 2017). With the emergence of powerful antimicrobial compounds, a sudden drift in antibiotic resistance was also observed (Levy, 2007). For instance, a study communicated the lost efficacy of ampicillin, tetracycline and trimethoprim-sulphamethoxazole (TMP-SMZ) in treating non-cholera diarrhea in Thailand. *Campylobacter*, Enterotoxigenic *Escherichia coli* (ETEC), non-typhoidal *Salmonella*, and *Shigella* species were investigated for antibiotic resistance. TMP-SMZ resistance was over 90% for *Shigella* and 40% for ETEC and *Salmonella* species. Similarly, nalidixic acid resistance was 97% to 100% for *Shigella dysenteriae* 1 isolates. Interestingly, a drastic change in ciprofloxacin resistance was observed over a period of 4 years (1991-1995) among *Campylobacter* species; from 0 to 84%. About 15% *Campylobacter* and ETEC and 3% of *Salmonella* isolated between 1994 and 1995 were found to be resistant to azithromycin (Hoge et al., 1998).

Sulfonamide antibiotic resistance was initially reported in the 1930s, and the mechanism of resistance, despite after 80 years, is still unaltered (Chopra et al., 2002). Likewise, aminoglycoside also faced the antibiotic resistance challenge by *Staphylococcus aureus* within six years of its development (Gootz, 1990). Methicillin, marketed in 1961, was designed to combat resistant strains of penicillinase-producing *Staphylococcus aureus* could not stand the resistance challenge (Tynecka, 1965). Such resistant features were also observed in fluoroquinolones thereafter which was aimed to treat gram negative organisms (Lowy, 2003).

With the passage of time, injudicious use of antimicrobial compounds in agricultural industry has also increased the severity of antimicrobial resistance (Chang et al., 2015). The fact that similar microbicidal drugs are used in agriculture has led to the emergence of resistant strains (Economou and Gousia, 2015). The food chain is the driving force to transmit a major pool of resistant microorganisms to human population from animals. Similarly, developed countries fed their organisms with food combined with antimicrobial agents which might be acting as a host to resistance organisms and contribute to antimicrobial resistance to that specific antibiotic. The utilization of antibiotics for growth promotion in cattle increases the likelihood of antibiotic resistance, for instance (McEwen and Fedorka-Cray, 2002; Witte, 1998).

Antimicrobial Resistant Superbugs

Superbugs are class of microorganisms that have mutantly evolved to withstand the deleterious effects of antimicrobials and conferred the ability to cause significant morbidity and mortality (Gaur, 2017; Ofori-Asenso, 2017). Among them, *Mycobacterium tuberculosis*, a multi-drug resistant (MDR) organism, is the most frequent epidemic pathogen common to both developed and developing countries (Davies and Davies, 2010). Despite ground-breaking anti-tuberculosis drug developments, a surge of genetically modified strains of *M. tuberculosis* is on constant rise. Interestingly, new categories of M. tuberculosis; extremely drug resistant (XDR) and totally drug resistant (TDR) tuberculosis are considered both setback and challenging for scientists. Such superbugs have perhaps dwarfed the therapeutic options for clinicians to treat serious infections, with extended hospital stay and burgeoning healthcare costs (Shah et al., 2007; Sotgiu et al., 2009; Velayati et al., 2009). Undoubtedly, superbugs are present everywhere and their grave consequences are further escalated in turbulent circumstances; for instance violence, natural calamities and poor healthcare practices. They are indeed regarded as the most obvious threat in terms of global morbidity and mortality (Davies and Davies, 2010).

Diverse Resistance Mechanisms

The bacteria have developed sophisticated processes to evade killing by antimicrobial compounds (Cag et al., 2016; Tenover, 2006). The important biochemical routes that are implicated in resistance includes modification and destruction of antibiotic molecule (Garneau-Tsodikova and Labby, 2016; Wright, 2005), limit access of antibiotic to the target site, alteration of the target sites which leads to decrease binding of

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antimicrobial compound (Soares et al., 2012) and development of efflux pump mechanism that extrude antimicrobial compound from the bacterial cell (Blanco et al., 2016; Poole, 2007). Relevant examples include changes in the expression and structure of porins molecules (shift in expression from OmpK35 to OmpK36) in *Klebsiella pneumoniae* which effects intracellular transport of β-lactam antibiotics (Domenech-Sanchez et al., 2003). Likewise, methylation of ribosomes confers macrolide resistance in *staphylococci* and leads to decrease in binding of the drug to the target site (Munita and Arias, 2016). Of note, some bacteria use multiple pathways described above to facilitate their survival in presence of the antibiotics. For example, *Pseudomonas aeruginosa*, a gram-negative bacterium, facilitates drug resistance by restricting uptake, use of efflux pumps and modification of the target site (Lambert, 2002).

The microbes have the upper hand in the tug-of-war against antibiotics. The discoveries of new antimicrobial compounds are soon overcome by the rapid appearance of the resistance mechanisms (Fair and Tor, 2014). The acquired resistance to β-lactam compounds is the classical example (Fuda et al., 2004). After the emergence of resistance against Penicillin, newer β-lactam (ampicillin) were introduced in the market that had wider spectrum and decrease in susceptibility to the action of penicillinase. However, after some time, studies reported new plasmid-encoded β-lactamase that was capable to hydrolyse ampicillin among gram-negative bacteria (Paterson and Bonomo, 2005). Similarly, the discovery of fluoroquinolone which functions by inhibiting bacterial DNA gyrase and topoisomerase IV was cherished as an effective weapon against microorganisms, but the resistant cases were soon identified by the development of chromosomal mutations in the enzymes which decreased the potency of these drugs (Hooper, 2002).

The emergence of resistance against the broad spectrum and powerful antibiotics such as Methicillin (semisynthetic derivative of penicillin stable against the staphylococcal penicillinase) and vancomycin has begun the start of the post-antibiotic era. *Methicillin resistant Staphylococcus aureus (MRSA)* and *vancomycin resistant Enterococci (VRE)* is one of the notorious infections to treat in clinical settings and account for increased morbidity and mortality worldwide (Loomba et al., 2010). These examples highlight the evolution in bacteria which made them immune to the arsenal of antibiotics.

The bacteria also have the tremendous potential to transfer resistant traits between each other. It is mainly mediated by three main routes also known as the horizontal method of gene transfer (HGT) and include transduction, transformation, and conjugation (*Figure 1*).

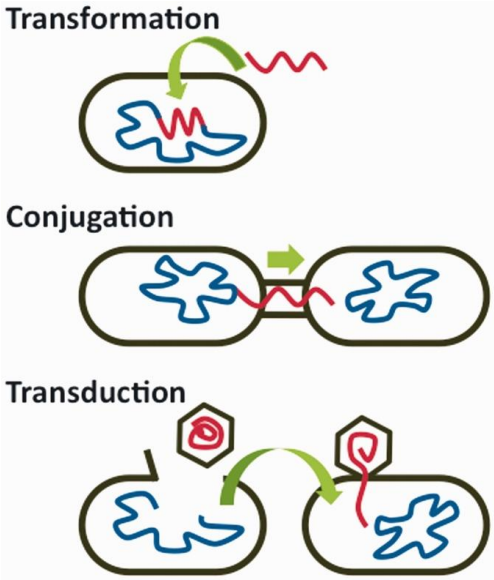

Fig 1: Types of Horizontal Gene Transfer in Bacteria; **1) Transformation:** Ingestion of bacterial DNA from environment; **2) Conjugation:** Transfer of genes directly from one bacteria to another; and **3) Transduction:** Transfer of genes from one bacteria to another facilitated by *Bacteriophages* (bacterial viruses) (Burmeister, 2015).

The former two are mediated by the virus (*bacteriophage*) and incorporation of DNA released by another bacterium following cell lysis, respectively. The later (conjugation) is mediated by elongated processes (pilus) which facilitate joining of the two organisms and mediate the transfer of plasmid containing the genetic material. These HGT methods, in particular conjugation, are responsible for the propagation of the resistant property between bacterium. Conjugation has also been implicated in the dissemination of resistance property from the resistant strain in the environment to the susceptible microorganism (von Wintersdorff et al., 2016). Studies have pointed out that the natural compounds of antibiotics have existed in the environment since the beginning of time (Wright and Poinar, 2012). As pointed above, the bacteria have a great potential to

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thrive under the pressure of different environmental stressors. These naturally occurring compound of antibiotic, therefore, provide the right selection pressure and produce resistant strains. It is highly likely that the newer antibiotics compound under discovery exists in nature in some form with the presence of resistant strain against them which awaits appropriate selection pressure and propagation machinery to spread resistance.

CONCLUSION

Concluding, the bacteria have the intrinsic genomic plasticity that enables them to withstand the 'attack' of antibiotic. Bacteria also acquire resistance and evade different mechanism by which antimicrobials exert their effect. Additionally, the horizontal transfer of resistance help spread the resistant characteristics from one bacterium to another. Based on the evidence provided above, it is inevitable that the world will face an era of antibiotics shortage in terms of efficacy. It is difficult to outsmart microorganisms which have billions of years of experience to live in the hostile environment and adapting to arrays of stress including naturally occurring antimicrobial compounds. Nonetheless, it is highly imperative to further understand the mechanism of bacterial resistance as it will allow discovery of novel therapeutic strategies and targets.

FUTURE RECOMMENDATIONS

Measures that can be adapted to defer the onset of post-antibiotic era include the production of newer classes of antibiotic that are effective against the range of microorganisms and target multiple processes in bacteria. Unfortunately, as indicated by a report, the antibiotic production has been significantly decreased with only two new classes of antibiotics entering the market in the last thirty years (Hogberg et al., 2010). In addition to the production of new antibiotics, judicious use of existing antibiotics in health-care, agricultural and animal husbandry is warranted. Interventions to limit antibiotic overuse in health-care sector should encompass development of rapid and reliable diagnostic tests, improvement of risk stratification for patients receiving prophylactic antibiotics, and alteration in prescribing habits.

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