Antibiotic Resistance: Current Approaches and Future Directions

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***Abstract*- Infections of antibiotic-resistant pathogens pose an ever-increasing threat to mankind. The investigation of novel approaches for tackling the antimicrobial resistance crisis must be part of any global response to this problem if an untimely reversion to the pre-penicillin era of medicine is to be avoided. One such promising avenue of research involves so-called antibiotic resistance breakers (ARBs), capable of resensitising resistant bacteria to antibiotics. Although some ARBs have previously been employed in the clinical setting, such as the β-lactam inhibitors, we posit that the broader field of ARB research can yet yield a greater diversity of more effective therapeutic agents than have been previously achieved. This review introduces the area of ARB research, summarises the current state of ARB development with emphasis on the various major classes of ARBs currently being investigated and their modes of action, and offers a perspective on the future direction of the field.**

***Index terms*- :- Resistance breakers, ESKAPEE, efflux pump inhibitors, membrane permeabilisers, beta-lactamase inhibitors, combination therapy.**

DEFINITION OF ANTIBIOTICS

It can be defined as any of a large group of chemical substances, as penicillin or streptomycin, produced by various microorganisms and fungi, having the capacity in dilute solutions to inhibit the growth of or to destroy bacteria and other microorganisms, used chiefly in the treatment of infectious diseases. In other words, it is a drug used to treat infections caused by bacteria and other microorganisms. Originally, an antibiotic was a substance produced by one microorganism that selectively inhibits the growth of another. Synthetic antibiotics, usually chemically related to natural antibiotics, have since been produced that accomplish comparable tasks.

INTRODUCTION

Since their discovery more than 70 years ago, antibacterial drugs have become an essential part of the modern healthcare landscape, allowing treatment of previously life-threatening bacterial infections. However, ever-increasing levels of antimicrobial resistance (AMR) threaten the health benefits achieved with antibiotics and this phenomenon is recognised as a global crisis (Ventola 2015). Over the period of 2011–2014, the percentage of Klebsiella pneumoniae infections resistant to fluoroquinolones, third-generation cephalosporins or aminoglycosides, as well as combined resistance to all three antibiotic groups, has increased significantly in Europe, with a similar trend also observed for Escherichia coli infections (ECDC 2015). With AMR currently estimated to be responsible for 50 000 deaths annually across the US and Europe, urgent action needs to be taken on an international scale if the modern antibiotic treatment paradigm is to survive (O'Neill 2014). It should be noted that this review will discuss approaches to overcome bacterial resistance, but AMR refers to resistance caused by all microbes against their respective drugs.

While figures vary between different regions, the general trend is that poorer countries are experiencing much higher levels of resistance. This is likely due to several factors, including greater availability of second- and third-line treatments in 'First World' countries compared to their 'Third World' counterparts. Additionally, regional instances of higher resistance levels can have a global effect, with

the advent of rapid intercontinental travel allowing the dissemination of resistant bacterial strains globally. It has been suggested that regional resistance levels could affect international travel and commerce, with people less likely to be willing to travel to areas where they could develop problematic bacterial infections. That AMR levels are only rising, despite implementation of additional healthcare measures in the more economically developed countries of the world, highlights the need for novel approaches to tackling the AMR problem (O'Neill 2014).

The effects of antibacterial resistance are not limited to those patients who develop bacterial infections; wider medical procedures stand to be impacted. Antibiotic prophylaxis is commonly employed to avoid the development of infections, both preoperatively for a variety of surgical procedures and for immunocompromised patients undergoing chemotherapy (Wenzel 1992; Teillant et al. 2015; Crader and Bhimji 2018). Such prophylactic measures will no longer be possible if AMR spreads at its current rate, which could in turn impact the scope of surgical procedures available to clinicians and the quality of patients' lives (O'Neill 2014.).

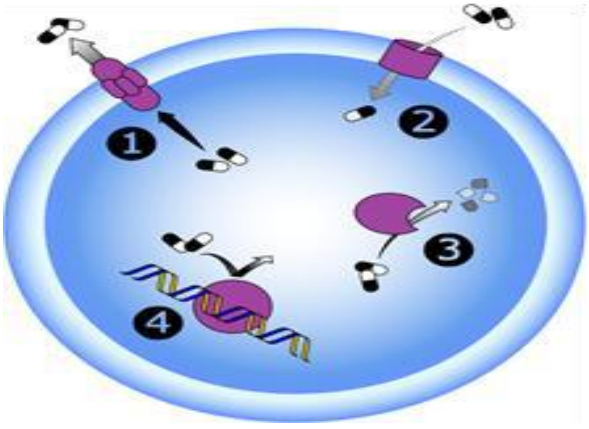
The ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species), whilst not the only problematic pathogens, have been identified as requiring special attention since they are responsible for the majority of hospital-acquired infections per annum and show high incidences of AMR (Rice 2008). With recent observations of strains of Gram-negative ESKAPE bacteria possessing multiple mechanisms of resistance to carbapenems, the drugs of last resort used to treat such infections, the need for new classes of antibiotics with novel modes of action is greater than ever (Limansky et al. 2002; Mena et al. 2006; Rodriguez-Martinez, Poirel and Nordmann 2009; Papp-Wallace et al. 2011). However, since the 1960s only two new antibiotic classes have been released and the scientific community has been unable to keep pace with the emergence of resistance (Coates, Halls and Hu 2011). Investment in antibiotic research by major pharmaceutical companies has declined sharply in recent years, mainly because of the lack of return in investments. Besides a long and difficult regulatory process for new drugs to navigate.

Molecular pumps energetically transfer antibiotics out of the cell:

Active efflux is a mechanism responsible for extrusion of toxic substances and antibiotics outside the cell; this is considered to be a vital part of xenobiotic metabolism [22]. This mechanism is important in medicine as it can contribute to bacterial antibiotic resistance. Efflux systems function via an energy-dependent mechanism (Active transport) to pump out unwanted toxic substances through specific efflux pumps. Some efflux systems are drug-specific, whereas others may accommodate multiple drugs, and thus contribute to bacterial multidrug resistance (MDR) [26].

Antibiotic Resistance by Mutation and Selection:

Typical gastrointestinal bacteria divide and multiply quickly, needing only 15-20 minutes to double by binary fusion. The human large intestine contains about 100 billion bacteria per gram of solid matter and over 100 different species of bacteria. Bacteria grow rapidly and mutate rapidly at a rate of 1 in every 100,000 to 1 in every million [12, 36-38]. Mutations are random events, and typically are not caused by antibiotics. When mutations occur, biochemical changes often occur. A membrane protein, enzyme, or ribosome may be altered. DNA base pair mutations often translate into single, different amino acid changes in the protein with accompanying changes in protein shape, or function, or both. Many potential mutations anywhere along a DNA molecule (the basic hereditary material), resistance mechanisms to antibiotics.



1. Increased drug efflux;
2. decreased drug uptake;
3. drug modification/destruction and
4. Target modification.

Resistance towards antibiotics is acquired by bacteria through either vertical evolution (endogenous) or horizontal evolution (exogenous). Vertical evolution involves the occurrence of a spontaneous mutation within the bacterial genome that confers on the bacterium (and subsequently its progeny) increased resistance to a given compound. The process to achieve high level resistance is often stepwise, wherein the selection pressure of antibiotic treatment causes an initial mutation that allows domination of the pathogen population by the mutant bacteria, followed by subsequent additional mutations that confer an additional survival advantage during further antibiotic therapy. Though mutation frequencies can often be as low as 10−8, this is offset by the vast numbers of cells in bacterial colonies (Drlica and Perlin 2011). Work by Santos Costa et al. into fluoroquinolone resistance in S. aureus showed that, in this case at least, an intermediate resistance phenotype (via upregulation of efflux pump expression) is first to appear and acts as a platform from which higher level resistance mutations can occur by ensuring a sub-lethal intracellular fluoroquinolone concentration.

ANTIBIOTIC RESISTANCE BREAKERS

To tackle the increasing emergence of AMR, alternative treatment strategies have been designed with the collective aim of reducing the number of antibiotics used and preserving the current classes of antibiotic for further clinical use. This review aims to showcase the potential of one such strategy, the use of antibiotic resistance breakers (ARBs). These are compounds that can increase the effectiveness of current antibiotics by combatting the resistance mechanisms employed against them. ARBs may or may not have direct antibacterial effects and can either be co-administered with or conjugated to failing antibiotics. Though ARBs have previously been referred to as antibiotic adjuvants, the latter also refers to alternative treatments such as drugs which stimulate host defence mechanisms to aid the eradication of bacterial infections (Gill, Franco and Hancock 2015); as such, this review will be restricted to the discussion of compounds that are used to reverse bacterial resistance mechanisms. The major classes of ARBs currently under investigation include modifying-enzyme inhibitors, membrane permeabilisers and efflux pump inhibitors (EPIs).

The idea of co-administering ARBs with conventional antibiotics stems from dual antibiotic therapy, which has enjoyed success in the past through either synergistic or additive effects of the individual antibiotic agents (Kalan and Wright 2011), and several ARBs have enjoyed lengthy clinical use including the β-lactamase inhibitors (BLIs) (Drawz and Bonomo 2010). Successful co-administered ARBs should enhance the effects of antibiotics by combatting the bacterial resistance mechanisms employed against the latter, allowing lower doses of antibiotics to be used. The minimum inhibitory concentration (MIC), the minimal concentration required of a compound to prevent visible growth of the pathogenic species under defined conditions (Wiegand, Hilpert and Hancock 2008), is a useful term in this regard; the more successful ARBs achieve greater reductions in the MICs of antibiotics versus antibiotic monotherapy. Such potentiation is an attractive prospect, both because reduced antibiotic selection pressure could slow the onset of resistance and because widening of the therapeutic window may allow for the alleviation of side effects experienced by patients on antibiotic monotherapy.

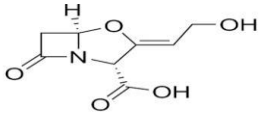
Modifying enzyme inhibitors

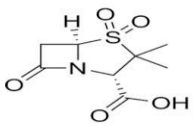
Bacteria employ a diverse range of enzymes to modify or destroy antibiotics in order to render them ineffective and achieve a resistant phenotype. These enzymes can be categorised by both their mechanisms of action and their substrate antibiotics. Hydrolysis of certain susceptible bonds within the antibiotic molecule, transfer of a functional group to the antibiotic and (less commonly) the actions of redox and lyase enzymes are all examples of detoxification mechanisms (Wright 2005). This led to the development of antibiotics that would tolerate their actions, such as the β-lactam flucloxacillin which was designed to tolerate the action of the penicillinases (Sutherland, Croydon and Rolinson 1970). A method which has found more success is the design of modifying enzyme inhibitors, a term which encompasses the wide variety of chemical compounds that target bacterial enzymes involved in antibiotic modification and destruction. Modifying

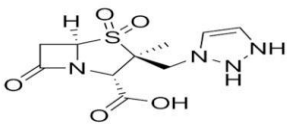
enzyme inhibitors are used to disrupt bacterial detoxification enzymes, increasing the effectiveness of a co-administered antibiotic. Two major classes are the BLIs and aminoglycoside-modifying enzymes.

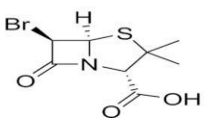
B-lactamase inhibitors

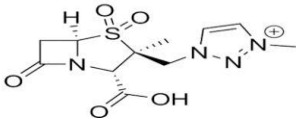
The most successful class of ARBs is arguably the BLIs. β-lactam antibiotics function by interfering with bacterial cell-wall synthesis, binding to and inactivating the C-terminal transpeptidase domain of penicillin-binding proteins which are responsible for the cross-linking of the peptidoglycan chains in the cell wall (Fisher et al. 2005). The β-lactams include several frequently prescribed families of antibiotics such as the penicillins and cephalosporins. They remain the most widely used class of antibiotics, reported to comprise 65% of the global antibiotic market in 2004 (Elander 2003), while broad-spectrum penicillins and cephalosporins were reported to be the two most consumed drug classes globally in 2010 (Van Boeckel et al. 2014). β-lactamases (EC 3.5.2.6) are bacterial enzymes that hydrolyse the β-lactam rings such drugs possess, inactivating them. Modification of β-lactam drugs is the major defence mechanism for Gram-negative pathogenic bacteria, with β-lactamases differing in their mechanisms and their substrate specificities (Wilke, Lovering and Strynadka 2005). Of note, carbapenemases can often act on carbapenem drugs and a wide range of other β-lactams, including penicillins, cephalosporins and monobactams (Queenan and Bush 2007). These enzymes are of special concern, since carbapenems are generally reserved as a last resort for many complicated infections, including those caused by both Gram-positive and Gram-negative bacteria (Papp-Wallace et al. 2011).



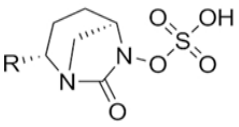








As early as the late 1980s, nosocomial isolates resistant to combination therapies involving the aforementioned β-lactam-based BLIs were being reported (Legrand et al. 1988; Ling et al. 1988; Eliopoulos et al. 1989; Cullmann and Stieglitz 1990). New BLIs were required for the next generation of combination treatments, and to this end classes of structurally divergent compounds with BLI activity were investigated. One such class of newer, non-β-lactam BLIs is the diazabicyclooctanes (DABCOs), based on a (5R)-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl sulphate core (Fig. 3). The strained nature of this core, further activated towards nucleophilic attack through the incorporation of a sulphate group on one nitrogen of the urea functionality, underlies the β-lactamase inhibitory activities of the DABCOs (Mangion et al. 2011). Fig. 3 and Table 1 list the structures of the compounds in this class either approved for clinical use or currently in development.



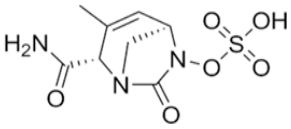
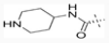
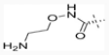


Table 1.
Structures of DABCOs currently in clinical use/in development (Mangion *et al*. 2011; Maiti *et al*. 2013; Garber 2015; Patil *et al*. 2016; Bush and Page 2017; Papp-Wallace *et al*. 2018; Thye 2018).

Name	R group	Name	R group
Bicyclic urea core	H	Zidebactam	
Avibactam		WCK 5153	
Relebactam		WCK 4234	
Nacubactam		GT-055	

Future direction for the research on antimicrobial Based on these information available on antimicrobial compounds and resistance mechanism of the bacteria it is every evident that antimicrobial resistance is biological phenomenon that has existed in the microbes from early evolution and would continue till the existence of the microbial world.

Thus, the most rational approach would be minimizing and optimum use of antimicrobial compounds that would help to control the emergence of resistant bacteria. Alternate approaches like probiotics and vaccine have been effective in prevention of infectious diseases [89, 90]. Likewise, bacteriophages or "phages" that disrupt bacterial metabolism and cause the bacterium to lyse could be another therapeutic option. Several reports on therapeutic use of lytic bacteriophages to treat pathogenic bacterial infections are made available for future research. Phage therapy may prove as an important alternative to antibiotics for treating multidrug resistant pathogens [91-93]. Similarly, researches on antimicrobial peptides have also shown that these components of innate immunity are potent, broad spectrum antibiotics which demonstrate potential as novel therapeutic agents. These peptides can act on both Gram negative and Gram positive bacteria, including mycobacteria, Mycobacterium tuberculosis, enveloped viruses, fungi and even transformed or cancerous cells. It may also be useful in enhancing immunity by functioning as immunomodulators [94, 96]. Development of new drugs by making use of bioactive phytochemicals and plants have an almost limitless ability to synthesize aromatic substances are targets of several ongoing research. Most of these compounds are phenols or their oxygen-substituted derivatives such as tannins. In many cases, these substances serve as plant defense mechanisms against predation by microorganisms, insects, and herbivores.

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