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Rise of The Super-Resistant Bugs – Advances in Therapeutics for Drug Resistant Bacteria

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Abstract

Points to be included:

a) Antibiotics have been used for centuries now – among the first discoveries in medicine.

b) Over usage and non-regulation of antibiotics in developing nations – primary reason for resistance

c) Drug resistance is a real problem

d) Most antibiotics in pre-clinical development are for gram positive, because it was easier target than gram negative bacteria

e) Most drug resistance in gram negatives without any cures

f) New antibiotics are newer versions of the old antibiotics. Paucity of new antibiotics

g) Here we discuss the recent advances in the field, in the past 10 years and where it is headed

Keywords: Multi-drug resistant bacteria; Antibiotics; MRSA; Anti-microbials; VRE; ESKAPE; Therapeutics

Abbreviations: MRSA: Methicillin Resistant Staphylococcus Aureus; VRE: Vancomycin Resistant Enterococcus; ESKAPE: Enterobacteria, Staphylococcus, Klebsiella, Acinetobacter, Pseudomonas, Enterococcus; GNB: Gram Negative Bacteria; GPB: Gram Positive Bacteria; ESBL: Extended Spectrum Beta Lactamases; MIC: Minimum Inhibitory Concentration; MDR: Multi Drug Resistant

Introduction

Earliest reference about antibiotics in text

Edward Jenner – Penicillin

We have come a long way in the past century. The future is going to be difficult and challenging.Infections caused by drug-resistant gram-negative bacteria (GNB) are a major health problem and have the potential to cause a global health crisis if new antibiotics are not developed. Developing new antibiotics against GNBs has been challenging because of their large repertoire of drug-resistance mechanisms and their low membrane permeability. No new classes of antibiotics have been clinically approved in the last 25 years, which is problematic, because resistance to all existing GNB antibiotics will likely occur within the next 10-20 years, creating the possibility of a post-antibiotic era. There is, therefore, a great need for the development of new pharmacophores that can act as scaffolds upon which new GNB antibiotics can be developed.

Antibiotics are losing efficacy at an alarming rate, due to the rapid spread of drug-resistant bacteria and the slow rate at which new antibiotics are being developed. In the United States alone, at least 2 million people per year become infected with drug-resistant bacterial pathogens[1], and this number is much higher in developing nations such as China, Russia, Brazil, and India[2-4]. Drug-resistant GNBs have the potential to cause a public health care crisis if immediate action is not taken. In 2013, the CDC, NIH, and WHO issued a report, on "Antibiotic resistance threats in the United States, 2013", in which they grouped bacterial pathogens according to "urgent", "serious",and "concerning" threats[1, 5-7]. The "urgent threat" pathogens included many drug-resistant GNB such as Carbapenem-resistant Enterobacteriaceae (CRE), which include *E. coli* and *Klebsiella pneumoniae*. In addition, outof the "serious threats" pathogens, 7 of the 12 species belonged to GNB. The most important of these are theextended spectrum

β-lactamase producing Enterobacteriaceae as well as the glucose non-fermenting healthcare-associated pathogens *P. aeruginosa* and *A. baumannii* [1]. Additionally, the CDC has highlighted "Four Core Actionsto Prevent Antibiotic Resistance", with one action being the need for alternative drug development. New drugs or new approaches to treating GNB infections are therefore urgently needed.

A key challenge limiting the development of new drugs against GNBs is their low membrane permeability. GNBs have two membranes; an outer membrane (OM) and a cytoplasmic membrane (CM) through which drugs must penetrate, and these two membranes prevent both hydrophilic and hydrophobic molecules from diffusing through GNBs. The two membranes of the GNBs impose severe constraints on the types of molecules that can be pursued as future drugs. Thus, numerous antibiotics have been developed that are active against gram-positive bacteria yet have no efficacy against gram-negative bacteria because of membrane-transport limitations, leading to a great need for effective small molecule scaffolds that can easily permeate GNB.

The treatment of bacterial infections is a central challenge in medicine. For example, in the United States, in 2010, bacterial infections killed more people than AIDs, breast cancer and prostate cancer combined.1 Moreover, antibiotic resistance is a growing public health concern and there is an urgent need for effective treatments for drug resistant gram negative infections. According to Centers for Disease Control and Prevention (CDC), at least 2 million people in the US suffer from infection by drug resistant micro-organisms (bacteria and fungus combined), and 23,000 people die from it. Colistin is an effective antibiotic within the polymyxin family, and it is consideredto be the "last resort drug" for drug resistant gram negative bacterial infections. For example, colistin is effective against infections caused by multidrugresistant *Pseudomonas aeruginosa, Klebsiella pneumonia*, and many othergram-negative bacteria. However, colistin causes severe nephrotoxicity (kidney toxicity), which limits its clinical use.

Emergence of drug resistant bacteria

Antibiotic resistance is not new, has been happening since the time antibiotics were discovered Horizontal gene transfer–multi drug resistant bacteria. Over use and absence of regulation of broad spectrum antibiotics expedited evolution of the bacterial species(Figure 1 & 2).

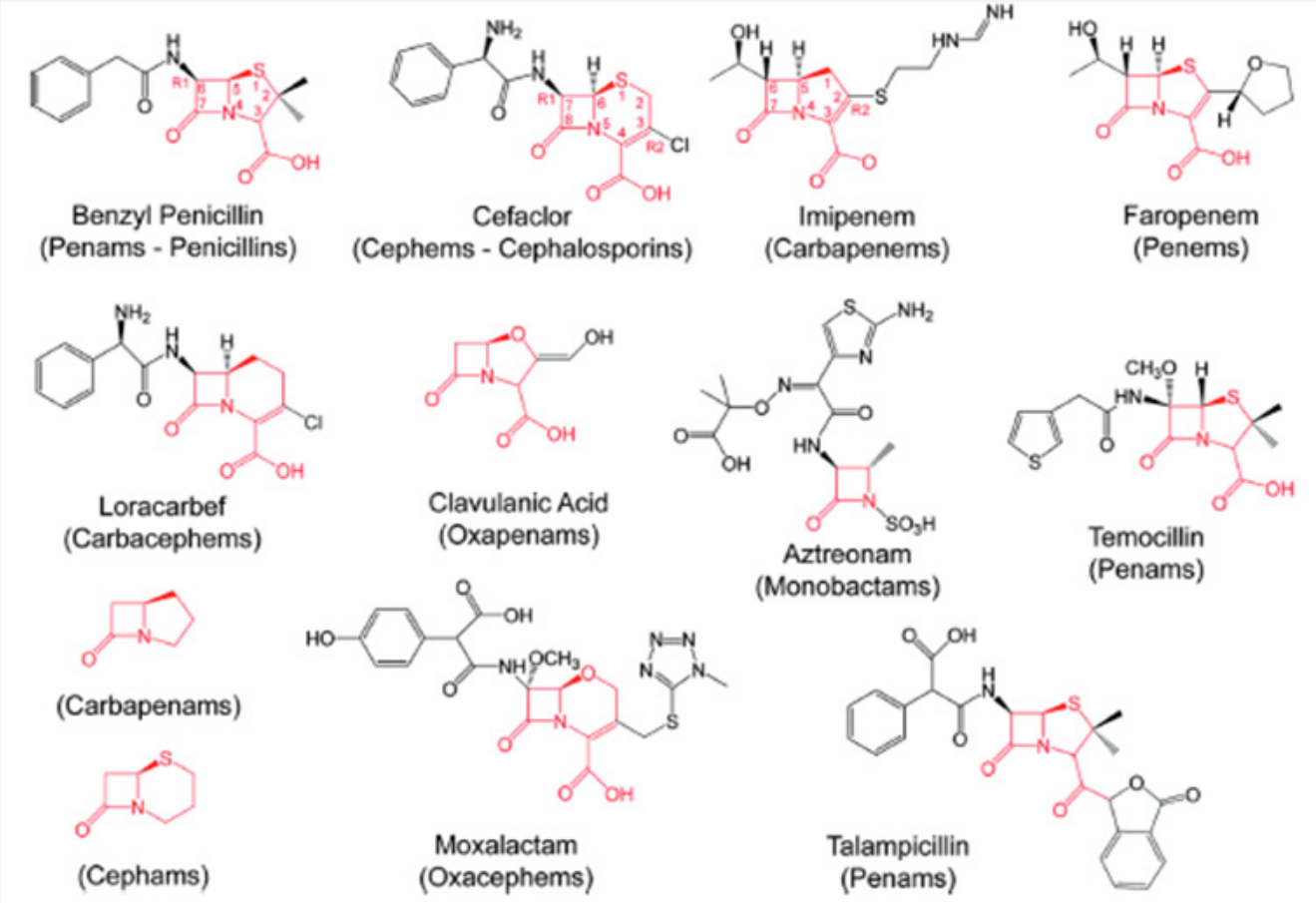

Figure 1: Structure of various antibiotic classes.

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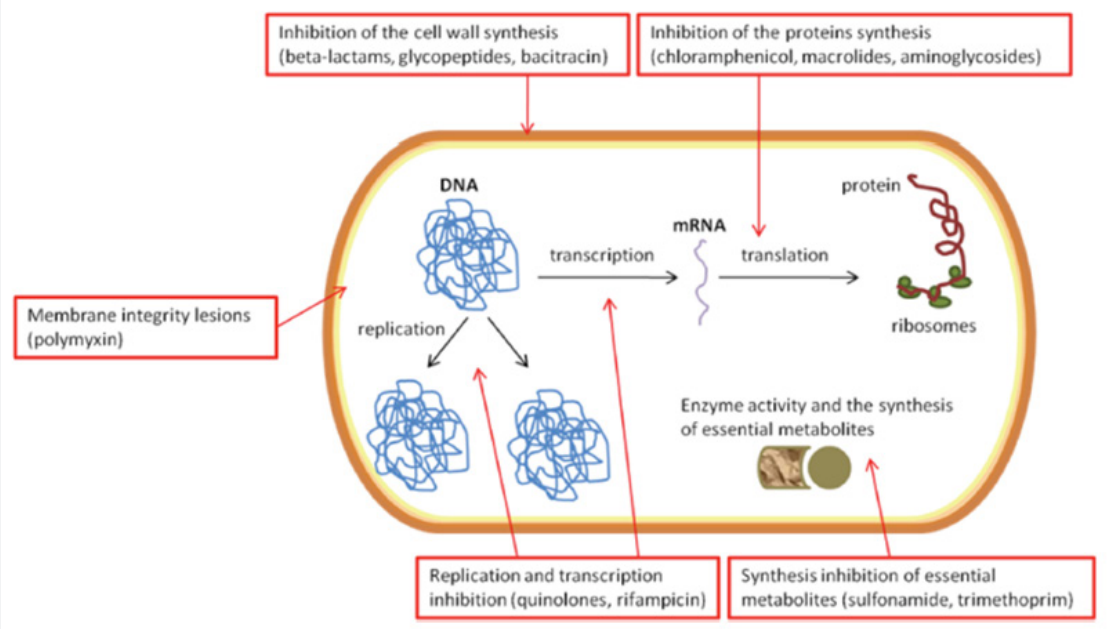

Figure 2: Mechanism of action for the antibiotics.

Common antibiotic targets

I. Cell wall biosynthesis

II. Cell membrane

III. DNA replication

IV. Protein synthesis

V. RNA synthesis

VI. Folate synthesis / Metabolic

VII. Limitations

VIII. New developments

IX. Potential new targets

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Conflict of Interest

The authors declare no conflicts of interest.

References

1. (2013) Centers for Disease Control and Prevention. Antibiotic resistance threats in the united states.

2. Rosenthal VD, Maki DG, Graves N (2008) The international nosocomial infection control consortium (inicc): Goals and objectives, description of surveillance methods, and operational activities. Am J Infect Control 36(9): e1-12.

3. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, et al. (2011) Burden of endemic health-care-associated infection in developing countries: Systematic review and meta-analysis. Lancet 377(9761): 228-241.

4. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, et al. (2013) Antibiotic resistance-the need for global solutions. Lancet Infect Dis 13(12): 1057-1098.

5. (2014) World Health Organization. Antimicrobial resistance: Global report on surveillance.

6. National Institutes of Health (2014) Niaid's antibacterial resistance program: Current status and future directions.

7. Boos W, Shuman H (1998) Maltose/maltodextrin system of *Escherichia coli*: Transport, metabolism, and regulation. Microbiol Mol Biol Rev 62(1): 204-229.

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