Antibiotics and Their Impact on Bacterial Cellular Perturbation

Subjects: Health Care Sciences & Services | Agriculture, Dairy & Animal Science

Contributor: DEBPRASAD DUTTA

Antibiotics belong to different classes of chemicals—including those of biological, synthetic, or semi-synthetic origin—and have selective modes of action. Based on their mechanisms of action, antimicrobial compounds are classified into two groups: bacteriostatic and bactericidal. Resistance is a natural adaptive tool that offers selection pressure to bacteria, and hence cannot be stopped entirely but rather be slowed down. Antibiotic resistance mutations mostly diminish bacterial reproductive fitness in an environment without antibiotics; however, a fraction of resistant populations 'accidentally' emerge as the fittest and thrive in a specific environmental condition, thus favouring the origin of a successful resistant clone.

antibiotic resistance bacteriostatic Evolutionary Microbial Genetics

1. Introduction

The discovery of antibiotics has drastically changed modern medicine and extended the human lifespan. The first naturally occurring antibiotic, namely penicillin, was discovered by Alexander Fleming from *Penicillium notatum* in 1928, which was introduced into clinical practice in 1941 [1][2]. Most of the antibiotics that are used today were discovered and introduced into the market before 1987, and this period is often termed as the golden decade [3]. Particularly, the cessation of new antimicrobial classes was apparent from 1987 until today [4]; during this period, only a few (~9) new antimicrobial classes were discovered and launched into the markets (**Figure 1**). With this slow rate of new antibiotic discovery and the rapid emergence of resistant bacteria, we are in the post-antibiotic era [5].

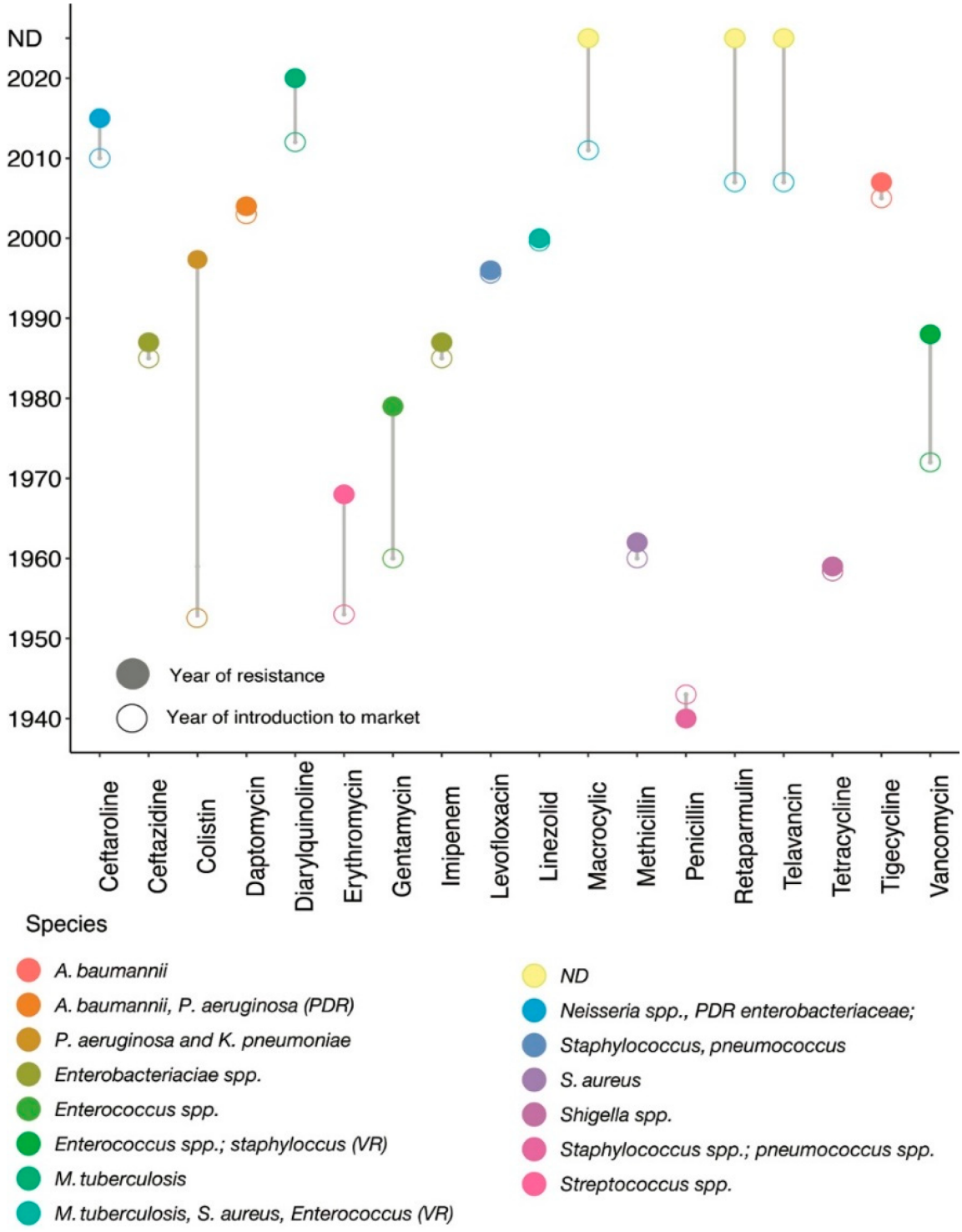


Figure 1. Historical panorama of antibiotic launch and resistance detection. The x-axis indicates different types of antibiotics and the corresponding y-axis shows the year of introduction into clinical practices. Resistance histories to different antibiotics are shown by different circles. Connecting line between empty and filled coloured circles shows the year of introduction of a specific antibiotic into clinical practice and the year of resistance observed for that antibiotic; each coloured circle further represents different bacterial species. For example, colistin was first introduced into clinical practice in 1952 [6], but resistance to colistin was first reported in clinical *P. aeruginosa* and *K. pneumoniae* (shown by a specific coloured circle) in 1998 [7]. Penicillin resistant laboratory *E. coli* was reported

in 1950 [8] before its introduction into clinical practice in 1941, but the first penicillin resistance clinical *S. aureus* was reported in 1942 [9][10]. PDR: pan-drug resistant; VR: vancomycin resistant; spp: species; ND: resistance mechanism not detected.

2. Antibiotics and Their Impact on Bacterial Cellular Perturbation

Antibiotics belong to different classes of chemicals—including those of biological, synthetic, or semi-synthetic origin—and have selective modes of action. Based on their mechanisms of action, antimicrobial compounds are classified into two groups: bacteriostatic (**Table 1**) and bactericidal (**Table 2**). Bacteriostatic drugs are only able to inhibit or hinder growth but cannot kill bacteria. Whereas drugs are called bactericidal when exposure to this group of antibacterial compounds leads to the death of bacteria. Both drugs principally interfere with bacterial cell-wall biosynthesis, DNA synthesis, RNA synthesis, and protein synthesis [11]. Furthermore, antibiotics have been classified based on the cellular components or systems they affect in bacteria. Some of these antimicrobial agents target the synthesis of important cellular components, whereas some other classes of antibiotics interfere with bacterial nucleic acid synthesis or repair [12][13]. The mechanistic actions of the bacteriostatic and bactericidal are featured in **Table 1** and **Table 2**. Furthermore, we have described the mechanistic action of the major bactericidal antibiotics in the following sections.

Table 1. Action and common resistance mechanisms of major bacteriostatic antibiotics.

Bacteriostatic Candidates	Mode of Action	Mechanism of Resistance
Tetracycline	Reversibly inhibits 30S ribosomal subunit of bacteria [14].	Efflux system and protecting ribosomes [15].
Macrolides	Reversibly inhibits 50S ribosomal subunit of bacteria [16].	Methylation of the 23S rRNA, efflux system [17].
Sulphonamides	Inhibits folate synthesizing enzyme dihydropteroate synthase (DHPS) [18].	By horizontal transfer of dihydropteroate synthase gene [19].
Streptogramins	Reversibly inhibits 50S ribosomal subunit of bacteria [20].	Acetyltransferases *vatD* gene expression mediates streptogramin A, wheras *vatE* and

Bacteriostatic Candidates	Mode of Action	Mechanism of Resistance
		ermB or *vgbA* gene cluster confers streptogramin B antibiotics [21].
Oxazolidinones	Reversibly inhibits 50S ribosomal subunit of bacteria [22].	High diversity and coselection of *optrA* [23].
Lincosamides	Reversibly inhibits 50S ribosomal subunit of bacteria [24].	Target site modification, efflux system and drug inactivation [25].
	Occupying the active site of bacterial	
Bactericide Candidates	**Mode of Action**	**Mechanism of Resistance**
Penicillins	Competitively inhibits the transpeptidase enzyme resulting cross-linking blockage in cell wall [28].	Beta-lactamase encoded by *blaZ*, altered PBP2a encoded by *mecA* [7][29], extended-spectrum-beta-lactamases (ESBLs), AmpC beta-lactamase (i.e., *blaAmpC*) [30][31][32].
Cephalosporins	Competitively inhibits the transpeptidase enzyme resulting in cross-linking or blockage in cell wall [33].	AmpC beta-lactamase (i.e., *blaAmpC*), ESBLs (i.e., *blaCTX-M*) [30][31].
Carbapenems	Binding with penicillin-binding proteins (PBPs) and inactivation of these proteins leads to cell wall synthesis interruption [34].	Carbapenemases (i.e., class A serine-carbapenemase including KPCs; class B metallo-carbapenemase including New-Delhi-metallo-beta-lactamases or NDM, Verona-integron-encoded beta-lactamases or VIM, Imepenemase IMP-carbapenemase (also a metallo-beta-lactamase); class D serine carbapenemase such oxacillinase (OXA) [35][36], mutation-derived target enzyme modification [37]; preventing the drug entry by modifying outer membrane permeability [38]; pumping carbapenems out by efflux pump systems [39].

Bactericide Candidates	Mode of Action	Mechanism of Resistance
Aminoglycoside	Binding with 30 s ribosomal subunit resulting genetic code misreading followed by interruption of bacterial translation [40].	Mostly through aminoglycosides modifying enzymes encoded by *aac* (aminoacetyl-tranferase) and *aph* (aminophospho-transferase), efflux system, or mutation in *rpsL* and 16S rRNA [32][41].
Fluoroquinolones	Interrupting bacterial DNA replication by inhibiting topoisomerases [42].	Target enzyme mutation (DNA gyrase encoded by *gyrA* and *gyrB*, and topoisomerase IV encoded by *parC* and *parE* genes), efflux system and changing drug entry [43].
Rifamycin	Interrupting transcription by inhibiting bacterial RNA polymerase [44].	Mutation of the target (beta subunit of RNA polymerase encoded by *rpoB*) [45].
Polymyxins	Binding to lipid A of LPS and interfere with outer membrane permeability [46].	The *pmrHFIJKLM* (also known as *arn* operon) and *pmrCAB* operon—both invove in the biosynthesis of LAra4N and modify the lipid A, thus disrupt lipid A charges [10]; mutations in genes encoding the two-component regulatory systems such as *pmrAB* [47], *phoPQ* and plasmid-borne *mcr* genes confer resistance to colistin—the last line of drug [48][49].
Daptomycin	Binding to anionic phospholipids in the cytoplasmic membrane [50].	Mutations in gene *mprF* which encodes the multiple peptide resistance factor [51].
Vancomycin	Binding to the dipeptide terminus d-Ala-d-Ala of peptidoglycan pentapeptide precursors preventing peptidoglycan crosslinking leads to the inhibition of	Replacing d-Ala-d-Ala with d-Ala-d-lac or d-Ala-d-Ser alternatives to which vancomycin has low affinity [53].

ication by interfering with topoisomerase II enzyme—also known as DNA gyrase composed of two subunits encoded by *gyrA* and *gyrB*—leading to cellular death by forming double-strand DNA breaks [54]. Whereas beta-lactam antibiotics—including penicillins, cephalosporins, carbapenems, and monobactams—act by binding to and inhibiting the

Bactericide Candidates	Mode of Action [55]	Mechanism of Resistance
	bacterial cell wall synthesis [52].	[56][57]

cell wall,
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erial RNA

synthesis [58]. During the execution of the normal cellular function, beta-subunit of DNA-dependent RNA polymerase enzyme is involved in the stable channel formation between RNA-polymerase and DNA complex from which newly synthesized RNA strand arises [59][60]. Rifampicin stably binds to the beta-subunit of DNA dependent RNA polymerase (encoded by *rpoB* gene), thus inhibiting the high-fidelity transcription and causing cellular death.

Another class of bactericidal antibiotic such as aminoglycoside causes bacterial cellular death by interfering with cellular energetics, ribosome binding and protein synthesis inhibition [61]. Bacterial protein synthesis through the translation of mRNA occurs in a sequential fashion involving initiation, elongation, and termination. This process is operated in the cytoplasmic space involving the collaborative action of the ribosome (which acts as a factory) and many other important accessory translation factors available in the cytoplasm [62]. The ribosome is composed of two ribonucleoprotein subunits called the 30S (encoded by *rpsL* gene) and 50S. Following the formation of a complex between mRNA-transcript, N-formyl methionine-charged aminoacyl tRNA, several initiation factors and a free 30S subunit (this process is called initiation step of translation), the ribosome is assembled for the next translational step [63]. While translation is a complex process that requires many cellular components and translation factors, drugs can interfere with protein synthesis in various ways. Antibiotics that inhibit protein synthesis are classified into the 50S and 30S inhibitors, respectively. The 50S inhibitors (i.e., erythromycin, clindamycin, streptogramin, chloramphenicol, and linezolid) interfere with protein synthesis by blocking the initiation of protein translation or translocation of peptidyl tRNAs [64][65]. Inhibition of 30S ribosome (i.e., caused by tetracyclines and aminocyclitols) involves blocking of the access of aminoacyl tRNAs to the ribosome. Both spectinomycin and aminoglycosides—including streptomycin, kanamycin, and gentamycin—bind to the 16S rRNA, a component of the 30S ribosomal subunit. Specifically, aminoglycosides bind to the 16S rRNA, which in turn alter the conformation of the complex formed between an mRNA codon and its cognate charged aminoacyl tRNA in the ribosome. This interaction results in defective protein [12][15][66], thus cellular death occurs.

Polymyxins group of antibiotics (polymyxin A–E) are of cationic cyclic polypeptide origin with strong bactericidal effects. Among these, only polymyxin B and polymyxin E—also called colistin—are used in clinical practices [67]. Both antibiotics are commonly prescribed to treat infections caused by Gram-negative bacterial pathogens, particularly against extensively drug resistant (XDR) *P. aeruginosa* and *A. baumannii* [68]. These cyclic antimicrobial peptides have long hydrophobic tails which directly interact with LPS of the outer membrane of Gram-negative bacteria. Particularly, polymyxins destabilize calcium and magnesium bridge by binding to the lipid A component of the LPS. This event causes bacterial outer membrane permeabilization and allows polymyxins to enter the outer membrane, leading to cellular death [49].

Daptomycin is another class of bactericidal antibiotic and is composed of cyclic polypeptides. Daptomycin is used for the treatment of infections caused by Gram-positive bacteria, particularly against methicillin resistance *S. aureus* and *Enterococcus faecium*. Daptomycin interacts with anionic phospholipids in the presence of calcium ions in the cytoplasmic membrane. This interaction helps daptomycin penetrate the membrane, which ultimately causes membrane depolarization and cellular death. However, unlike most other bactericidal antibiotics, the detailed mechanistic basis of cellular death and resistance for daptomycin is not yet fully elucidated [69]. Detailed mechanisms of action of the major classes of bactericidal antibiotics are depicted in **Figure 2**.

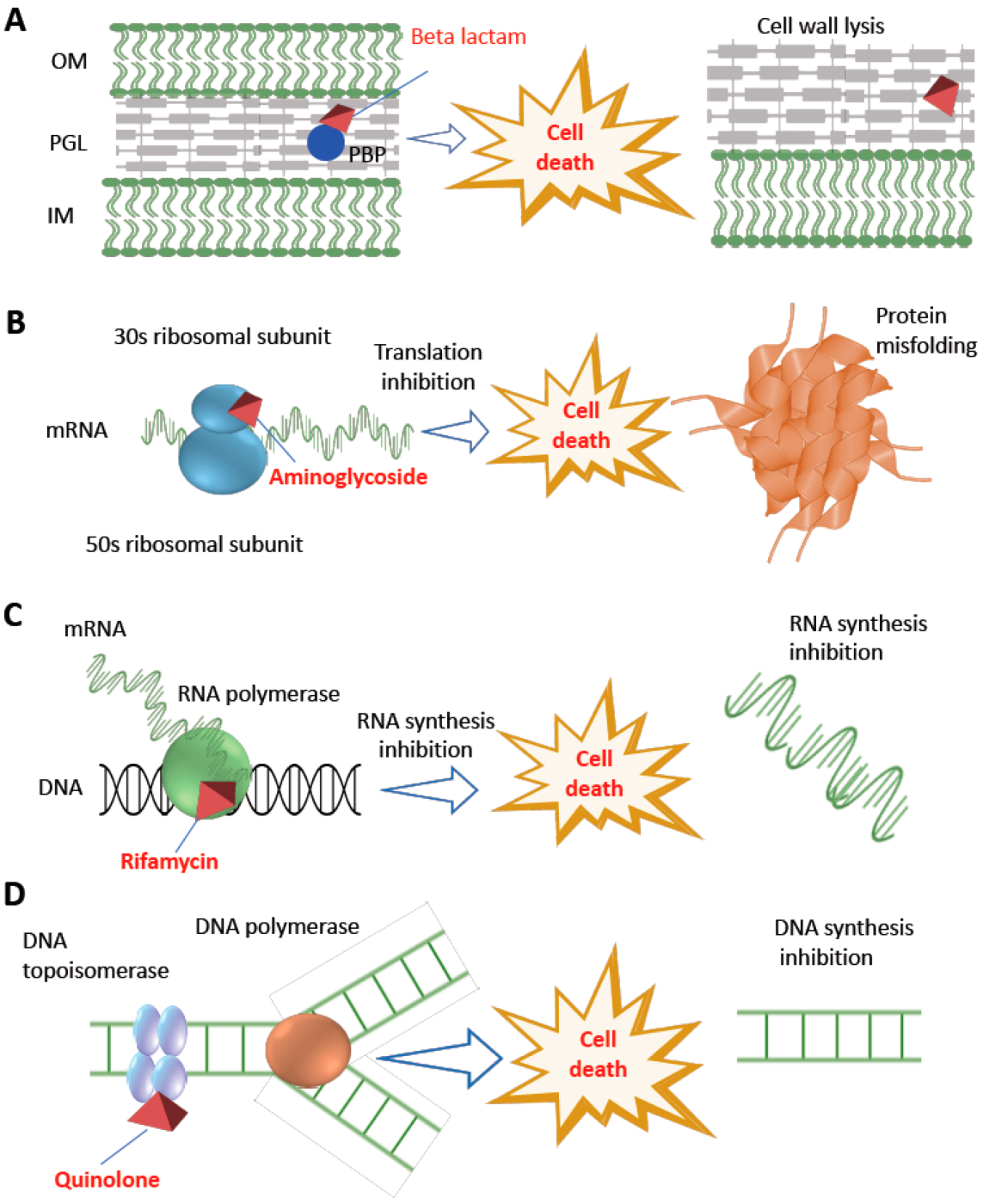


Figure 2. Diversity of antibiotic resistance mechanisms. The figure shows the major bactericidal antibiotics and their different targets. Beta-lactam antibiotics degrade bacterial cell wall by interfering with cross-linking or transpeptidations within the bacterial cell wall by binding with PBP (panel **A**), aminoglycoside interferes with protein synthesis by binding with 30S ribosomal subunit (panel **B**), rifamycin inhibits bacterial transcription by interfering with beta-subunit of DNA dependent RNA polymerase enzyme (panel **C**), whereas quinolone class of antibiotics inhibit DNA synthesis by interfering with DNA topoisomerase (panel **D**). OM: outer membrane; PGL: peptidoglycan layer; IM: inner membrane; PBP: penicillin binding protein.

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