

Rational approaches in combating antibiotic resistance



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Abstract

Antimicrobial resistance, a natural process in which microorganisms evolve in such a way that they resist the action of medications, has unfortunately increased in correlation with the advent of the antibiotic era. Bacterial pathogens have been a significant contributor to disease and mortality throughout human history. To combat this, finding adjuvants that boost the activity of existing AB may lead to an increase in the antibiotic spectrum, broaden its effectiveness against resistant bacteria, and reduce the dose necessary for antibiotics. The current level of investment in their development, particularly in the fields of natural-product-derived and synthetic small molecules, is in stark contrast to the ever-increasing demand for novel antimicrobials to treat life-threatening infections brought on by the global spread of multidrug-resistant bacterial pathogens.

1. Introduction

In every region of the world, antibiotic resistance (ABR) is increasing to dangerously high levels. Our ability to cure widespread infectious diseases is being threatened by the emergence and global dissemination of new mechanisms of resistance (1). As antibiotics (AB) lose their effectiveness, a rising number of infections, including gonorrhoea, blood poisoning, pneumonia, and tuberculosis, have now become difficult to cure and occasionally termed non-curable. Individuals can take a few steps to stop the spread of ABR: infections can be prevented by washing your hands often, cooking your food in a clean manner, avoiding close contact with sick patients, engaging in safer sex, and maintaining a current vaccination schedule (2).

2. Origin, spread, and mechanism of resistance

The emergence of particular mechanisms of resistance hampered the therapeutic use of the first potent antimicrobials, the sulfonamides, since their debut in 1937 (3). The same mechanisms that led to sulfonamide resistance in the late 1930s exist even today; around 70 years later. A bacterial penicillinase was discovered by two members of the penicillin discovery team in 1940, several years before penicillin was made available (4).

AB have been used indiscriminately when necessary. Some instances are for example, when the wrong ABs are taken, when the dosage and duration is inappropriate, when patients skip doses because they feel better quickly after stopping them, and when viral illnesses are treated with AB (3). ABR is on the rise as a result of these misuses (5). Details of the chronological evolution of ABR is mentioned in figure 1.

AB are frequently provided to farm animals to promote growth and prevent sickness in non-medical settings. These medications are exposed to numerous animals and consequently, germs, for a longer time and at lower concentrations (6). Resistance evolves as a result of this. Humans acquire these resistant germs by consuming the animals or coming in close contact with them. Hospitals, poultry farms, and other locations, all have antibiotic-resistant germs that are disseminated via the environment (7).

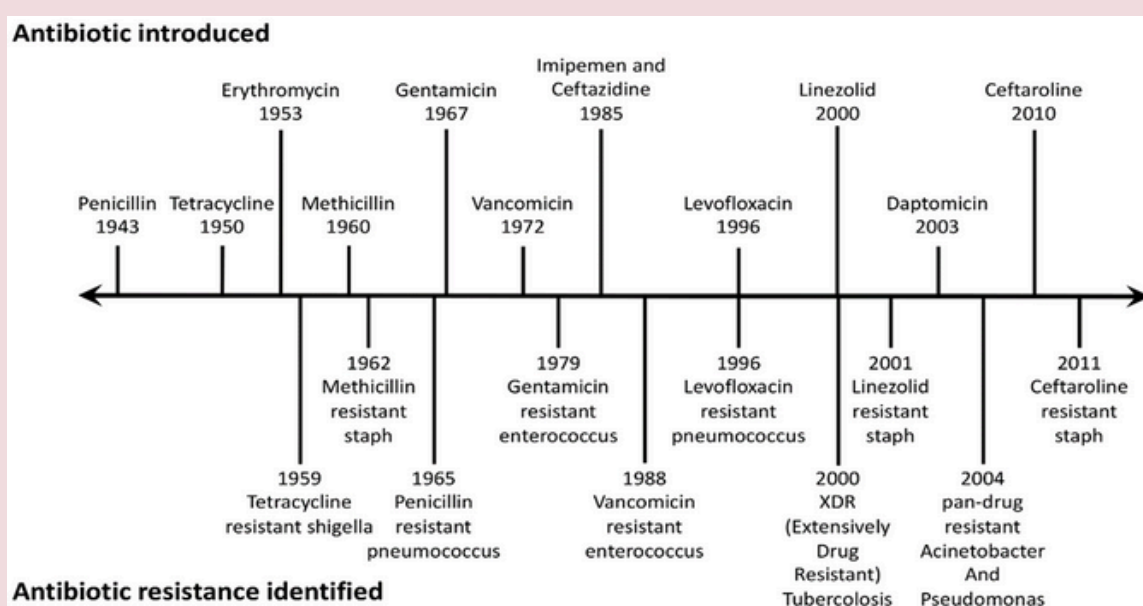


Figure 1. ABR pipeline. On the top, antibiotic introduced and, on the bottom, ABR identified.

Notably, numerous biochemical routes can typically be used to establish resistance to a single antimicrobial class, and a single bacterial cell may be able to utilize a variety of resistance mechanisms to fend off an antibiotic's effects (figure 2) (8). For instance, mutations in the genes encoding the target site of fluoroquinolones (FQs; DNA gyrase and topoisomerase IV), overexpression of efflux pumps that extrude the drug from the cell, and protection of the FQ target site by a protein known as Quasi-Newton-Raphson are three different biochemical routes through which resistance to FQs can develop. All three of these biochemical pathways may coexist in the same bacteria at the same time, producing an additive effect and frequently increasing the levels of resistance (9).

3. Techniques/novel methods to combat resistance

A limited availability of a set of ABs in our arsenal has forced us to search for better ways to modify dosing and use a combination of drugs to increase efficacy and decrease resistance. Various techniques that have been employed to combat resistance are sequential regimen, synergistic ABs, optimal dosing regimen, promoting synergy between the immune system and the Abs, and sensitizing the resistant bacteria with antisense technologies (10).

Apart from the above-mentioned techniques, photodynamic therapy in endodontics (11), alternative strategies to develop inhibitors of resistance, development of new ABs (Computer aided drug design/ combinatorial techniques) (12), developing effective vaccines (13), exploring bacteriophage therapy, nano AB (futuristic), single cell pathogen diagnostics (14), and natural compounds quorum sensing are the novel methods used to treat drug resistant pathogens (15).

4. Overcoming ABs challenges in biofilm-associated infections

There is a dire need to adopt alternative treatments for biofilm-associated infections other than ABs. For the biofilm environment, many researchers have proposed a conjugative, mixture of phages, and polymeric nanoparticle-based delivery systems (16). Nanoparticles and nanoantibiotics are the future nanotechnologies that can combat biofilm mediated infections. Nanoparticles of metals like Ag, Au, Zn, Mg, Ca, Cu, CuO₂, Fe₂O₃, TiO₂, Bi, Gd- Fe₂O₃ in combination with ABs have paved a way to address the challenges laid down by multidrug resistance (17).

Natural products/ plant extracts/ secondary metabolites from natural origin like marine alkaloids, and their analogs, polyphenols, and other natural sources including, the plant-based approach – plant-based quorum sensing (QS), can be explored to break the pathways of resistance (18).

5. Modern alternative therapies

5.1. Anti-virulent therapy/ quorum sensing inhibitors (QSI)

Bacteria are the most common pathogen that proliferate within quorum sensing circuits-mediated biofilms. QSI or quorum quenchers can quench the bioactive compounds which can disrupt the biofilms. Acylated homoserine lactones, patulin (isolated from fungus *Pe. coprobium*), halogenated furonones, cyclic disulphur compounds extracted from garlic, crown vetch, soybean, carrot, water lily, tomato, pea seedling (*Pisum sativum*), habanero (Chillies) have been found to be promising QSIs under investigation (19-20).

5.2. Passive immunization/ monoclonal antibodies

Passive immunization through nasal, oral, and topical administration of egg yolk-derived IgY antibodies from immunized chicken have shown to be effective in treating infections caused by resistant pathogens as listed by WHO (21). Anti-glucosaminidase (GMD) monoclonal antibodies can alter the growth habit of *S. aureus* (Methicillin Resistant *Staphylococcus aureus*), and suggest that GMD may be a target for direct growth inhibition and focusing on having an effect on the immune system This study shall be a ray of hope to treat osteomyelitis by crossing the barriers of resistance (22). However, using a cocktail of monoclonal antibodies can be the most promising approach to treat resistance.

5.3. Antimicrobial peptides

The combined application of antimicrobial peptides with ABs or other antimicrobials is another proven but yet to be investigated strategy for the development of antimicrobial peptide-based therapeutics against ABR (23).

5.4. Chemoprophylaxis

Vaccines contain a variety of benefits that make them significant among the available approaches to treat ABR. Few aspects of vaccines like vaccines being less likely to develop

resistance; vaccines and antimicrobial agents working in tandem for postponing the tolerance to a medication; and long-term effects produced with a few doses of vaccines alone, have placed vaccines at the forefront (24).

5.5. Phage therapy

A strategy that harnesses the potency of bacteriophages to drive strong selection on their bacterial host is the phage therapy. It mostly relies on target bacteria resisting the phage. This therapy not only kills bacterial cells but also “steers” survivors towards resistance (25).

5.6. Phytochemicals

Delivery of antimicrobial phytoactives using potential nanocarriers like liposomes, nanoemulsions, Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), and micelles can be strategies developed to face the ABR. Apigenin, capsaicin, carvacrol, thymol, p-cymene, c-terpinene, citral, curcumin, ellagic acid, menthol, oregano, lemon grass, hydroquinone, eugenol, α -tocopherol, theaflavin, quercetin, and thymoquinone are the various natural products used as antimicrobial phytoactives. Few essential oils are also employed for this purpose (26-27).

5.7. Nanoparticles (NPs)

NPs/ nano scale materials/ nanocomposites can be tailored and combined with a variety of antimicrobial agents to overcome antibiotic resistance. It is essential to determine the mechanisms by which these NPs or their complexes inhibit or kill bacteria. Moreover, synergistic effects of NPs with ABs can be a promising regimen to combat bacterial resistance (28).

6. Conclusion

In conclusion, this article helps in providing an overview and the futuristic antimicrobial therapies to combat this resistance.

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