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Review

History of antimicrobial drug discovery: Major classes and health impact

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A B S T R A C T

The introduction of antibiotics into clinical practice revolutionized the treatment and management of infectious diseases. Before the introduction of antibiotics, these diseases were the leading cause of morbidity and mortality in human populations. This review presents a brief history of discovery of the main antimicrobial classes (arsphenamines, β-lactams, sulphonamides, polypeptides, aminoglycosides, tetracyclines, amphenicols, lipopeptides, macrolides, oxazolidinones, glycopeptides, streptogramins, ansamycins, quinolones, and lincosamides) that have changed the landscape of contemporary medicine. Given within a historical timeline context, the review discusses how the introduction of certain antimicrobial classes affected the morbidity and mortality rates due to bacterial infectious diseases in human populations. Problems of resistance to antibiotics of different classes are also extensively discussed.

Contents

1. Introduction

The highest rate of decline in infectious disease mortality in the USA was recorded for a period of 15 years, from 1938 to 1952, when the annual mortality rate due to infectious diseases was rapidly decreasing, by 8.2% per year [16]. Infectious diseases that mostly contributed to this sharp decline were pneumonia, influenza, and tuberculosis. These declines corresponded to the introduction into clinical practice of sulphonamides in 1935, penicillin in 1941, and streptomycin in 1943, with a number of other

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combination drugs, such as para-aminosalicylic acid in 1944 and isoniazid in 1952, introduced for tuberculosis treatment in addition to streptomycin [21]. This correlation clearly indicates the importance of antimicrobials in the control of infectious diseases. A recent statistics also reflects our success in dealing with infectious diseases that now cause much less mortality compared to many other diseases of a non-infectious nature. In the most recent National Vital Statistics Reports, among the 15 leading causes of death in the USA, infectious diseases, such as influenza and pneumonia, are superseded by heart disease, cancer, chronic lower respiratory diseases, accidents, stroke, Alzheimer's disease, and diabetes [245]. The foundation for this success in confronting death from infectious diseases was built by formidable scientists, who made important antimicrobial drug discoveries and are greatly acknowledged for saving numerous lives.

2. Arsphenamines and the foundation of modern antimicrobial chemotherapy

Paul Ehrlich's idea of a "magic bullet", which is highly selective and targets only the disease-causing microorganisms, came to him while he was working with an extensive range of aniline and other synthetic dyes that became available as a result of the rapidly developing German chemical industry. He noticed that some stains could be specific for certain microbes but not to others. Ehrlich reasoned that chemical compounds could be synthesized in a way that it would be possible "to exert their full action exclusively on the parasite harboured within the organism" (http://pubs.acs.org/cen/coverstory/83/8325/8325salvarsan.html). Based on this idea, in 1904, he initiated a large-scale and systematic screening program for a drug active against syphilis, the disease that had grown to the epidemic levels in the USA and Europe and was hardly curable at the time. The mainstream treatment for this sexually transmitted disease, which is caused by the spirochete *Treponema pallidium*, involved administration of mercury chloride along with other inorganic mercury salts. Due to the extreme toxicity of mercury compounds, the treatment had severe side effects and, yet, poor efficacy. Another type of treatment included arsenic and inorganic arsenical compounds, but the toxicity and low efficiency remained an issue with this treatment as well.

A less toxic organic arsenical drug, named Atoxyl, was synthesized by Antoine Béchamp in 1859 [47,214], initially for the treatment of African sleeping sickness. This drug attracted the attention of Paul Ehrlich and Alfred Bertheim, an organic chemist working with him. They correctly identified the chemical structure of this compound as aminophenyl arsenic acid, thus opening the possibility of synthetizing various derivatives in the search for a more efficient and less toxic therapeutic agent. They synthesized hundreds of arsenobenzene compounds, and the arsphenamine derivative, the sixth compound in the 600th series (i.e. compound 606), was synthesized in 1907. Although initially aimed at the treatment of African sleeping sickness, the drug appeared to be ineffective at it, but, in 1909, Ehrlich and Bertheim, together with bacteriologist Sahachiro Hata, established the efficiency of this compound in the treatment of syphilis-infected rabbits. In subsequent limited trials in humans, the drug demonstrated significant capacity for the treatment of patients with this venereal disease [72]. This process of systematic synthesis and activity check is considered to be the beginning of the modern chemotherapeutic era (Stefan and [213]. Almost all further developments in modern pharmaceutical research followed this route, with systematic chemical modifications of a lead compound to improve its biological activity and lessen the side effects.

Despite the problems associated with its stability and storage, as well as a rather tedious injection procedure and side effects, the drug, marketed by Hoechst under the trade name Salvarsan, was a great success and, together with a more soluble and less toxic Neosalvarsan, enjoyed the status of the most frequently prescribed drug until its replacement by penicillin in the 1940s [148]. Remarkably, the mode of action of this hundred-year-old drug is still unknown, and the controversy about its chemical structure was solved only in 2005 [142]. Other derivatives of the lead compound, arsanilic acid, however, have been in a much more prolonged use as feed additives in poultry and swine. The U.S. Food and Drug Administration (FDA) announced the complete withdrawal of arsenic-based drugs for use in food-producing animals only by the end of 2015 [83].

Presently, syphilis infections are successfully managed by penicillin drugs, in particular by intramuscular injection of benzathine benzylpenicillin, which allows reaching a prolonged antibiotic exposure over a two- to four-week period after a single dose delivery. Patients with severe allergy to penicillin can be treated with tetracycline or doxycycline. The availability of very efficient therapies resulted in a substantial drop of mortality due to syphilis, from 202,000 in 1990 to 113,000 in 2010 [143]. Still, the number of new infections remains relatively high, with 315,000 cases reported in 2013 [61].

3. β-Lactams

Discovered serendipitously in 1928 by Alexander Fleming [86], penicillin did not immediately take off as a clinically useful antibiotic. This was hindered by many drawbacks, such as low yield, instability, purification and other problems. In fact, military actions in the 1940s helped to develop it into a valuable treatment of infections, with a considerable production for the treatment of sick and wounded soldiers in the U.S. and Allies' military forces. Thereafter, penicillin became a widely used antibiotic for a broad range of previously untreatable infectious diseases, with a wider range of targets and fewer side effects than sulpha drugs (see the next section).

Although the antibacterial properties of mould had been known from ancient times, and researchers before him had come upon similar observations regarding the antimicrobial activity of *Penicillium* fungi from time to time (e.g., Vincenzo Tiberio, see [46]), it was Alexander Fleming's firm faith in the idea and his impressive determination that made the difference. For more than a decade after his initial observation, he tried hard to involve chemists in resolving the problems of purification and stability of the active compound, supplying the producer strain to every request. And finally, in 1940, an Oxford team, led by Howard Florey and Ernest Chain, published a paper describing the purification procedure for penicillin in quantities sufficient for clinical testing [53]. The following refinements and optimizations of the original procedure, isolation of more efficient penicillin producer strains, and optimization of the strain fermentation procedure eventually led to the mass production and distribution of penicillin in 1945 [171].

The screening procedures in the discovery of Salvarsan and Prontosil required testing of many compounds using the animal models of human disease. The screening method of Alexander Fleming used inhibition zones in lawns of pathogenic bacteria on the surface of agar-medium plates and, thus, required much less time and resources. At least in the initial stages of screening, before testing in animal disease models, the approach made it possible to reasonably inexpensively test a much larger range of compounds with a potential antimicrobial activity. This method became widely used in mass screenings for antibiotic-producing microorganisms by many researchers in academia and industry during the antibiotic discovery programmes.

Identification of 6-aminopenicillanic acid as the core of penicillin by scientists of Beecham Research Laboratories in the UK