The Indian Journal of Pediatrics (January 2020) 87(1):39–42
https://doi.org/10.1007/s12098-019-03087-z

REVIEW ARTICLE

Antibiotics: From the Beginning to the Future: Part 1

Nancy Khardori[1] · Cecilia Stevaux[1] · Kathryn Ripley[1]

Received: 19 September 2019 / Accepted: 20 September 2019 / Published online: 22 November 2019

Abstract
The first written record of intervention against what later came to be known as an infectious disease was in the early seventeenth century by a Buddhist nun. She dried 3 to 4 wk old scabs from patients with mild smallpox and asked well people to inhale the powder. More than a century later in 1796, Edward Jenner described vaccination against smallpox by using cowpox that later was found to be caused by cowpox virus which is non-pathogenic for humans. Another century later in 1890, Robert Koch published the Koch's Postulates allowing the study of pathogenic bacteria and subsequently the study of agents to fight them. The first chemical cure for disease was reported by Paul Erhlich in 1909 in the form of an arsenic compound to treat syphilis. One hundred and ten years since then a lot has happened in the area of preventing and treating infectious diseases with significant contribution to increase in human lifespan. This is the only area of medicine in which treatment (antimicrobial agent) is used to eradicate a replicating biological agent inside the human host. The potential of this second biological agent to mutate under the selection pressure of antibiotics making them resistant was recognized in the 1940s. But the indiscriminate use of antibiotics for over 70 y has led to the present crisis of resistance in major pathogens with increased morbidity and mortality. In this review, we have incorporated all the possible avenues that might be useful in the future. However, none is more important than relearning the judicious use of antibiotics based on microbiology, pharmacology, and genetics.

Keywords Antibiotics · Resistance · Antibiotic stewardship · Bacteriophages · Antimicrobial peptides

Introduction

Human beings have treated their various ailments with extraordinary creativity for more than five millennia. A human body preserved by quick-drying and freezing in the perennial ice was retrieved from beneath a receded glacier in Northern Italy in 1991 [1, 2]. The "Ice Man" was thoroughly studied by many types of scientists, and was found to have lived about 5322 y ago. In addition to highly significant archaeological findings, many medical findings were recorded. A ball made of the fungus, *Piptoporus betulinus*, was found among his belongings, and eggs of the parasite *Trichuris trichura* were found in his rectum. *P. betulinus* contains oils that are toxic to metazoans, have antimicrobial activity against mycobacteria, and contain toxic resins that are powerful laxatives. Prior to the introduction of toxic chenopod oils from the Americas, the toxic oils in the fungus recovered alongside the five-millennia-old preserved human body were the only known remedy known in Europe to treat intestinal ailments. The examination of the preserved nails of this body showed that he had suffered from episodes of anemia likely from intestinal infestation with *T trichura*. The oils contained in the fungus would have resulted in death and expulsion of the worms. Europeans weren't the only ones to search for remedies; "nature's magic bullets" used by Assyrian and Babylonian doctors have been described as early as 2000 BC [3].

As germ theory became established and Koch's postulates became the lay of the land in 1890, more targeted treatments against infectious agents were sought. In the mid-nineteenth century, Louis Pasteur observed that some microorganisms destroy others–the phenomenon that later came to be known as antibiosis. German bacteriologist Paul Erhlich's intense search for a "magic bullet" led to a high-risk arsenic-based treatment for syphilis. Other chemical agents with antimicrobial activity were too toxic for anything but surface use on

✉ Nancy Khardori
nkhardori@gmail.com

[1] Infectious Diseases, Solid Organ Transplant Program at Sentara Norfolk General Hospital, Norfolk, VA, USA

wounds and came to be known as antiseptics. Medicine's accidental hero, Alexander Fleming, was working at St. Mary's Hospital in London when he discovered the antibacterial activity of the enzyme lysozyme; droplets of oral secretions from an accidental sneeze fell onto a petri dish containing bacterial culture. When colonies formed later, none developed in the spots occupied by mucus from the sneeze [4]. This was the first demonstration of a "zone of inhibition" around a bacterial growth However, upon further testing, lysozyme was shown to be active against mostly non-pathogenic organisms. Serendipity visited Fleming's laboratory again in 1928 when he returned from a vacation. He found the culture plate with Staphylococci he had left uncovered had grown mold, and there was a clear space between the staphylococci and the blue-green spotted mold. The mold was identified as *Penicillium notatum* and the culture filtrate able to kill bacteria was named penicillin. The lack of funding and according to some, historian's lack of ambition kept Fleming from immediate success. Fleming's discovery took 12 more years to emerge as the greatest medical advance of the twentieth (or any other century).

The greatest age of anti-infective medicine began in 1934 with the discovery that a dye used to tint cloth was able to cure streptococcal infections in mice and humans. The German pharmacologist Gerhard Domagk treated his own dying daughter with the dye, and she survived. The active compound was later identified by Daniel Bovert, a Swiss-born scientist, as sulfanilamide. In 1939, Domagk was awarded the Nobel Prize in Medicine, which he was not allowed to accept in person by Hitler's orders.

At Oxford University, Florey and Chain noted that staphylococcus were resistant to sulfanilamide and lysozyme, but susceptible to the extract from *Penicillium notatum* [5]. The much-needed resources and impetus for further study of antimicrobial agents were provided by World War II. In 1940, a small amount of yellowish-brown powder from *Penicillium* was prepared at the Oxford laboratory which was much more potent than the earlier filtrates. The transformation of penicillin into a commercially available drug began in 1941 at the Fermentation Division of the Northern Regional Research Laboratory in the US, in Peoria, Illinois [6, 7].

Starting in 1944, large supplies of the yellow liquid containing penicillin was available to the Allied Forces during World War II, with remarkable increase in survival in the wounded. The name "antibiotics" was given to chemicals (produced by soil-borne fungi and other microbes) that destroy or slow the growth of other microbes, by Selman A. Waksman, a Russian immigrant to the United States. While searching for antibiotic-producing microbes, he found a mold able to kill tubercle bacilli in 1943. Streptomycin, an aminoglycoside, was first used for treatment of pulmonary tuberculosis at the Mayo Clinic in Rochester, Minnesota, in 1944. Waksman received the Nobel Prize for its discovery in 1952.

The challenge of antibiotic resistance was anticipated from the very inception of their use to save human lives. The earliest recorded concern was by Alexander Fleming himself, as reported by New York Times June 26, 1945. Being a microbiologist, he would be expected to be aware of this potential of microbes. The fact that the potential would be recognized by people in medicine in general comes from the warning by Frank L. Meleny, a practicing surgeon in 1947 [8].

Confronting this challenge predicted in 1945 to 1947 has become the present of antimicrobial therapy. Between the decades of 1940 and 1970, the golden era of antibiotic discovery, a large number of antimicrobial agents with a broad spectrum were developed, some with chemical structures that could fight the resistance mechanism of common pathogens. Between 1970 and 2000, very few new classes of antimicrobials for systemic use were introduced, while the resistance of Gram-positive and Gram-negative pathogens continued to grow [9]. The development of resistance in Gram-positive pathogens extended to vancomycin. This led to a fruitful search and commercial availability of a number of agents like streptogramins (Synercid), oxazolidinones (linezolid), lipopeptides (Daptomycin), glycylcycline (Tigecycline), semisynthetic lipopeptides (Telavancin, Dalbavancin, Oritavancin), fifth-generation cephalosporins (Ceftaroline) for treatment of serious infections caused by Gram-positive pathogens resistant to multiple antibiotics including vancomycin. Solithromycin, a novel oral fluoroketolide was shown to be 100% effective for treatment of culture proven gonorrhea at genital, oral and rectal sites of infection. Besides the addition of beta-lactamase inhibitors that antagonize a limited number of beta-lactamases, the discovery of agents to combat highly resistant Gram-negative organisms has lagged behind. This has led us to fall back on the past, as demonstrated by the use of Polymixin B and Colistin (Polymixin E). They had been studied as effective antimicrobial agents in the 1920s. Since their target of antibacterial activity (the cell membrane) is shared by the human cell, their adverse events profile left them on the back burner until much safer choices became ineffective at the turn of the century. The report of resistance to colistin selected by chlorhexidine use, a vey commonly used antiseptic for skin, has added a new dimension to the magnitude of resistance in Gram negative bacteria [10].

Antibiotics: Towards the Future

The development of new antibiotics is the most prominently featured aspect of a multifactorial problem in writings and discussions. We constantly see new drug development changing many diseases. However, the discussion about new antibiotics should focus around the underappreciated core principle that "antibiotics are unique because they are the only

pharmaceutical agents that demonstrate transmissible loss of efficacy over time" [9]. The impact of treatment in infectious diseases is decided by the second living agent that must undergo changes to survive under the threat of any antibiotic–old or new, narrow or broad-spectrum. The imperative not to tolerate any wastage of this life-saving resource was identified by Fleming in 1945. He noted that "microbes are educated to resist penicillin and a host of penicillin fast organisms is bred which can be passed on to other individuals and from there to others until they reach someone who gets a septicemia or pneumonia which penicillin cannot save. In such cases, the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with a penicillin-resistant organism. I hope this evil can be averted" [11].

This report in the New York Times was entitled "Penicillin's finder assays its future." The evil has not been averted and the society has not acted responsibly towards antibiotic misuse. That said, the scientific quest for developing new antibiotics will continue to focus on inhibition of bacterial growth and life cycle as well as interference with microbial attachment to cellular targets. Additionally, the future of antibacterial therapy will be determined by improvement and expediency in antimicrobial susceptibility testing and reporting, upgrading drug delivery systems, reducing side effect profiles, and most importantly, prescribers becoming antibiotic stewards and antibiotic users becoming aware of their role in saving antibiotics for their future generations [12].

Chemical Modification of Known Antimicrobial Agents

The potential of inhibitor of beta-lactamases added to currently available beta-lactam agents continues to be explored. The two combinations most recently added to the armamentarium are ceftazidime plus avibactam and ceftolozane plus tazobactam. A modified tetracycline, Omadacycline, designed to overcome resistance based on active efflux and ribosomal protection has recently become available. Other examples of chemical modification include a glycopeptide in which the vancosamine sugar has been derivatized, resulting in activity against vancomycin-resistant Gram-positive bacteria. This compound is bactericidal against enterococci [13]. The side chain in a carbapenem at the 2 position has been modified to improve affinity of penicillin-binding protein 2a of methicillin-resistant staphylococci and penicillin-binding protein 5 of penicillin-resistant *E. faecium* [14].

Plazomicin is a next generation aminoglycoside (neoglycoside) derived from sisomicin. It has demonstrated in vitro synergistic activity with daptomycin or ceftobiprole, against methicillin resistant *S. aureus* and vancomycin resistant *S. aureus*. It also shows synergistic activity against *Pseudomonas aeruginosa* when combined with cefepime, doripenem, imipenem, or piperacillin-tazobactam. Its activity includes bacteria producing extended spectrum beta lactamases, carbapenemases, and oxacillinases. Plazomicin has potent in vitro activity against carbapenem resistant *Acinetobacter baumanni.*

Most recent antibiotic approved by FDA in July 2019 is Recarbrio. It is a combination of imipenem, cilastatin, and relebactam. Imipenem is a carbapenem antibiotic, cilastatin is an antagonist that prevents inactivation of imipenem by renal dihydropepridase, and relebactam is a betalactamase inhibitor. Relebactam does not have intrinsic antibacterial activity, but protects imipenem from degradation by certain serine beta lactamases (SHV), temoneira (TEM), cefotaximase-munich (CTX-M), *Enterobacter cloacae* (P99), *Pseudomonas* derived cephalosporinase (PDC), and *Klebsiella pneumonae* carbapenemase (KPC).

With resistance to antimicrobial agents a foregone conclusion, the question for scientists, healthcare providers, and the human population at large is: What next? The answer lies in multiple approaches. In the second part of this review, we have categorized various approaches that have the potential of changing what currently seems to be a gloomy prospect for the future of antibiotics. The practical use of antibiotics has always stayed behind the science. It is only when we understand the intense experimentation that is being done currently; it seems possible that we will continue to be able to treat serious infectious diseases including those caused by bacteria that have become resistant to the currently available antibiotics.

The Part 2 of this review discusses the scientific approaches currently being studied based on what we have learned from the experience with antibiotics so far.

Compliance with Ethical Standards

Conflict of Interest None.

References

1. Capasso L. 5300 years ago, the ice man used natural laxatives and antibiotics. Lancet. 1998;352:1864.
2. Khardori N. Antibiotics – past, present and future. Med Clin North Am. 2006;90:1049–76.
3. Hoel D, Williams DN. Antibiotics: past, present, and future. Unearthing nature's magic bullets. Postgrad Med. 1997;101:114–8, 121-2.
4. Alexander Fleming–medicine's accidental hero. US News World Rep. 1998;58–63.
5. Goldsworthy PD, McFarlane AC. Howard Florey, Alexander Fleming and the fairy tale of penicillin. Med J Aust. 2002;176:176–8.

6. Raper K. The penicillin saga remembered. ASM News. 1978;44:645–53.
7. Wright AJ. Symposium on antimicrobial agents. Part VI. The penicillins. Mayo Clin Proc. 1999;74:290–307.
8. Meleney FL. Treatment of surgical infections by chemical and antibiotic agents. Postgrad Med. 1947;1:87–96.
9. Spellberg B, Srinivasan A, Chambers H. New societal approaches to empowering antibiotic stewardship. JAMA. 2016;315:1229–30.
10. Wand ME, Bock LJ, Bonney LC, Sutton JM. Mechanisms of increased resistance to chlorhexidine and cross-resistance to colistin following exposure of *Klebsiella pneumoniae* clinical isolates to chlorhexidine. Antimicrob Agents Chemother. 2016;61:pii: e01162–16.
11. Penicillin's Finder Assays its Future. New York Times. 1945;21.
12. Ellis R, Pillay D. Antimicrobial therapy: toward the future. Br J Hosp Med. 1996;56:145–50.
13. Jones RN, Barrett MS, Erwin ME. In vitro activity and spectrum of LY333328, a novel glycopeptide derivative. Antimicrob Agents Chemother. 1997;41:488–93.
14. Moellering RC Jr. A novel antimicrobial agent joins the battle against resistant bacteria. Ann Intern Med. 1999;130:155–7.