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Optimization of Antibiotic Chemotherapy: A Review

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The antibiotics field was initiated when Paul EHRLICH first coined the term 'magic bullet', or chemotherapy, to designate the use of antimicrobial compounds to treat microbial infections. The Center for Disease Control and Prevention in USA has estimated that some 50 millions of the 150 million prescriptions every year are unnecessary. This is true, but the real wonder is the rise of antibiotic resistance in hospitals, communities, and the environment concomitant with their use. The extraordinary genetic capacities of microbes have benefitted from man's overuse of antibiotics to exploit every source of resistance genes and every means of horizontal gene transmission to develop multiple mechanisms of resistance. This review presents the historical overview of antibiotics, magnitude of the problem, current status of antibiotic usage, antibiotic resistance and mechanisms, problems with the use of antibiotics, new era of antibiotic therapy and the role of pharmacist in prevention of antibiotic resistance.

Keyword: Antibiotic therapy, Antibiotic resistance, Resistance Mechanisms, problems with the use of Antibiotics, Role of pharmacist, Combating Antibiotic Resistance

1. Introduction

1.1 Historical Overview of antibiotics

The antibiotics field was initiated when Paul EHRLICH first coined the term 'magic bullet', or chemotherapy, to designate the use of antimicrobial compounds to treat microbial infections. In 1910, EHRLICH discovered the first antibiotic drug, Salvarsan, which was used against syphilis. EHRLICH was followed by Alexander FLEMING, who discovered penicillin by accient in 1928. Then, in the 1935, Gerhard DOMAGK discovered the sulfa drugs, thereby paving the way to the discovery of the anti-TB drug Isoniazid. Then, in 1939, René DUBOS became the first scientist to discover an antibiotic after purposely looking for it in soil microbes. DUBOS discovered Gramicidin, which is still used today to treat skin infections. Finally, in 1943, the first TB drug, Streptomycin, was discovered by Selman WAKSMAN and Albert SCHATZ. WAKSMAN was also the one who coined the term 'antibiotics'. Thus,antibiotics have been used to treat bacterial infections since the 1940s.

The discovery of antibiotics was a leap in modern medicine. They have been able to stop the growth or kill many different kinds of microorganisms. However, bacteria have proven to be much more innovative and adaptive than we imagined and have developed resistance to antibiotics at an ever

increasing pace. Bad practices and mismanagement have only exacerbated the situation.

We could soon return to a state of medical health that was as dire as that which occurred prior to antibiotic use. However, with more research, education of the public, and well thought out regulations, the problems can be solved. Several strategies are currently used to find new antibacterial compounds and new strategies are in development and trial.

Not only is there a problem in finding new antibiotics to fight old diseases (because resistant strains of bacteria have emerged), there is a parallel problem to find new antibiotics to fight new diseases. In the past three decades, many "new" bacterial diseases have been discovered (*E. coli* O157:H7 gastric ulcers, Lyme disease, toxic shock syndrome, "skin-eating" streptococci). Already broad patterns of resistance exist in these pathogens, and it seems likely that we will soon need new antibiotics to replace the handful that are effective now against these bacteria, especially as resistance begins to emerge among them in the selective environment antibiotic chemotherapy. Antibiotics are g given to human for treatment and prophylaxis of infectious diseases, 80% to 90% of antibiotics are used in outpatients and the remainder in hospitals. Antibiotics are appearing to be used not only in excess but also inappropriately and these accounts for 20% to 50 % of all antibiotics used. The Centre for Disease Control and Prevention in USA has estimated that some 50 millions of the 150 millions prescriptions every year are unnecessary.

1.2 The Basic Characteristics of Antibiotics

Today, there are about 4 000 compounds with antibiotic properties. Antibiotics are used to treat and prevent infections, and to promote growth in animals. Antibiotics are derived from three sources: moulds or fungi; bacteria; or synthetic or semi-synthetic compounds. They can be used either internally or topically, and their function is to either inhibit the growth of pathogens or to kill them. Antibiotics can thus be divided into Bacteriostatic drugs, which merely inhibit the growth of the pathogen, and Bacteriocidal drugs, which actually kill the bacteria. However, the distinction is not absolute, and depends on the drug concentration, the bacterial species, and the phase of growth.

Antibiotics are more effective against actively growing bacteria, than against non-growing persisters or spores. When two antibiotics are used in combination, the effect could be additive, synergistic, or antagonistic. Antibiotics can also be divided into broad-spectrum and narrow spectrum antibiotics. For example, Tetracycline, a broad spectrum antibiotic, is active against G+ bacteria, Gbacteria, and even against mycobacteria; whereas penicillin, which has a relatively narrow spectrum, can be used mainly against G+ bacteria. Other antibiotics, such as Pyrazinamide, have an even narrower spectrum, and can be used merely against *Mycobacterium tuberculosis*.Antibiotics fight against bacteria by inhibiting certain vital processes of bacterial cells ormetabolism. Based on these processes, we can divide antibiotics into five major classes:

1. Cell wall inhibitors, such as Penicillin and Vancomycin.
2. Inhibitors of nucleic acid synthesis, such as Fluoroquinolones, which inhibits DNA synthesis, and Rifampin, which inhibits RNA synthesis.
3. Protein synthesis inhibitors, such as Aminoglycoside.
4. Anti-metabolites, such as the sulfa drugs.
5. Antibiotics that can damage the membrane of the cell, such as Polymyxin B,Gramicidin and Daptomycin.

1.3 Magnitude of the Problem

- Infections caused by resistant microorganisms often fail to respond to conventional treatment, resulting in prolonged illness and greater risk of death.
- About 440 000 new cases of multidrug-resistant tuberculosis (MDR-TB) emerge annually, causing at least 150 000 deaths.
- Resistance to earlier generation antimalarial medicines such as chloroquine and sulfadoxine-

pyrimethamine is widespread in most malaria-endemic countries.

- A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA).
- Inappropriate and irrational use of antimicrobial medicines provides favourable conditions for resistant microorganisms to emerge, spread and persist.

1.4 Problems with Antibiotics

1. They contribute to cancer
2. Allergic Reactions
3. Destruction Of Beneficial Bowel Flora
4. Development Of Resistant Species Of Micro-organisms
5. Immune Suppression
6. Overgrowth of Candida Albicans And Other More Dangerous Intestinal Infections
7. Chronic Fatigue Syndrome
8. Nutrient Loss And Resulting Deficiency States
9. Treating Effects, Not Causes
10. High Cost.

1.5 Current Status

There is an alarming rise in the occurrence of antimicrobial resistance. For example:

- *Staphylococcus aureus* is a prevalent bacterium carried by humans that can cause a number of problems, from mild skin infections to serious diseases including food poisoning, wound infections, pneumonia, and toxic shock syndrome. The World Health Organization (WHO) recently reported that more than 95% of *S. aureus* worldwide is resistant to penicillin, and 60% to its derivative methicillin.
- Today in the U.S. more than 20% of all enterococcal infections, that is, infections caused by intestinal colonizing bacteria in the genus *Enterococcus*, are resistant to vancomycin, once considered the antibiotic of last resort
- Antibiotics are the third largest selling class of drugs, with an annual market between $7 billion and $22 billion. Current estimates suggest that of this expenditure $4 billion to $5 billion results from antibiotic-resistant bacteria. Although the resistance problem continues to mount, pharmaceutical companies have made little progress in the development of new bactericidal drugs. Consequently, surveillance programs for early detection of multi-drug-resistant bacteria, such as Sentry, have been implemented. Supported by the University of Iowa and private donations, Sentry conducts microbial surveys in 33 nations on 5 continents, gathering over 50,000 samples of various infectious bacteria. Other programs include England's Alexander Project and programs directed by the Centers for Disease Control and Prevention (CDC) and WHO. Their goal is to explore short- and long-term strategies to combat antibiotic resistance.

1.6 Antibiotic Resistance

Antibiotic resistance is the term used to describe bacteria no longer being killed by an antibiotic that they would previously have been killed by. Resistance isn't a problem only limited to antibiotics: resistance can be to antibiotics used to treat bacterial infection, to antivirals to treat viruses, or to antifungals to treat fungal infection. So the wider term 'antimicrobial resistance' is also sometimes used to encompass the whole problem, which is where any particular micro-organism is no longer killed by an antimicrobial medicine to which it had previously been susceptible. Antibiotic (or antimicrobial) resistance develops when bacteria (or other organisms) are regularly exposed to the same antimicrobial drug over time. Some organisms will eventually mutate and develop resistance to the action of this drug.

In populations of bacteria exposed to antibiotics, the resistant bacteria survive and replicate in preference to the susceptible bacteria. This means that the favourable 'resistance trait' will be passed on to future generations of bacteria. This is a form of evolutionary selection – Darwin's 'survival of the fittest' at work. Using antibiotics

to treat common, mild illnesses unnecessarily speeds up the problem of antibiotic resistance.This is because the bacteria are being more regularly exposed to these antibiotics than they would be if they were reserved only for the cases when they were really needed.

an example of penicillin resistance reveals the increase in the frequency of antibiotic-resistant organisms since the time when antibiotic use became common. Penicillin is an antibiotic produced by the common bread mold *Penicillium* that was discovered accidentally in 1929 by the British microbiologist, Alexander Fleming. By the 1940s, penicillin was available for medical use and was successfully used to treat infections in soldiers during World War II. Since then, penicillin has been commonly used to treat a wide range of infections. In 1967 the first penicillin-resistant *Streptococcus pneumoniae* was observed in Australia, and seven years later in the U.S. another case of penicillin-resistant *S. pneumoniae* was observed in a patient with pneumococcal meningitis.1 In 1980 it was estimated that 3–5% of *S. pneumoniae* were penicillin-resistant and by 1998, 34% of the *S. pneumoniae* sampled were resistant to penicillin.1 Antibiotic resistance by other organisms reflects the same trend observed between *S. pneumoniae* and penicillin. Tetracycline resistance by normal human intestinal flora has exploded from 2% in the 1950s to 80% in the 1990s.2 Kanamycin, an antibiotic

used in the 1950s, has become clinically useless as a result of the prevalence of kanamycin-resistant bacteria. The increase in resistance among these organisms clearly indicates a change in the frequency of antibiotic resistance genes. Since World War II many more antibiotics isolated from fungi (molds) and bacteria have been used to treat a wide range of human and animal infections. One group of bacteria, the *Streptomyces*, produces most of the medically important antibiotics.3 *Streptomyces* release antibiotics into the soil in a sort of "biochemical warfare" scenario to eliminate competing organisms from their environment. These antibiotics are small molecules that attack different parts of an organism's cellular machinery. *Streptomyces*-produced quinolone and coumarin antibiotics, such as novobiocin, interfere with a protein called gyrase that assists in the normal separation of double-stranded DNA during replication of DNA or transcription of messenger RNA.4 Failure of DNA to properly separate during these processes results in a bacterium not being able to divide normally or produce functional proteins. Ribosomes, the structures where protein synthesis is catalyzed, are the targets of many other *Streptomyces* antibiotics such as spectinomycin, tetracycline, and streptomycin. Spectinomycin and tetracycline prevent proteins from being assembled by the cell and streptomycin induces the assembly of the wrong amino acids into the translated protein.5,6 Without proteins, which are necessary for normal cell function, the cell dies. The slight differences between human ribosomes which are not bound by these antibiotics and bacterial ribosomes make this type of antibiotic ideal for treating many illnesses. Other antibiotics, such as penicillin, block the assembly of the bacterial cell wall causing it to weaken and burst.7 Penicillin is an effective antibiotic for human diseases because it interferes with a biological component in bacteria (cell wall) not found in human cells. The production of antibiotics by these organisms provides them with a competitive advantage over non-resistant bacteria in their environment. Just as large organisms such as plants and animals must compete for living space, food, and water, these microbes use antibiotics to eliminate competition with other microbes for these same resources.

However, not all bacteria are defenseless against the antibiotic producers. Many possess genes that encode proteins to neutralize the affects of antibiotics and prevent attacks on their cell machinery. Efflux pumps, located in the cell membrane, are one method of protection that many bacteria use against the influx of antibiotics. 6 The offensive antibiotic is pumped out of a cell that possesses these pumps before the antibiotic can cause harm to the cellular machinery. Although many efflux pumps may be specific for the substrate they pump out of the cell, they are not uncommon. Ribosomal

protection proteins (RPP) are another source of resistance bacteria use to protect themselves from antibiotics. These proteins protect ribosomes by binding them and changing their shape or conformation . The change in the ribosome shape prevents an antibiotic from binding and interfering with protein synthesis.6 The RPP-bound ribosomes are able to function normally during protein synthesis, an important feature of this method of antibiotic resistance. Some bacteria produce enzymes that neutralize antibiotics by adding acetyl (COCH3) or phosphate (PO32-) groups to a specific site on the antibiotic.8 This modification reduces the ability of the antibiotic to bind to ribosomes, rendering it harmless to the cell.9 Interestingly, all three types of antibiotic-resistant genes that produce efflux pumps, ribosomal protection proteins, and modifying enzymes are found in *Streptomyces* species, the producers of many antibiotics. It appears this is the method *Streptomyces* uses to protect itself from its own antibiotics.

Is it possible to transfer these resistance genes to other bacteria? A unique bacterial characteristic that has not been demonstrated in plant and animal cells is the ability to transfer genes from one bacterium to another, a process called lateral gene transfer. Genes located on a circular strand of DNA called an R-plasmid may contain several antibiotic-resistant genes. Through a process called conjugation an antibiotic-resistant bacterium can transfer the antibiotic resistance genes from an R-plasmid to a non-resistant bacterium.10 Ironically, several antibiotic resistance genes found in other pathogenic bacteria are very similar in DNA sequence to the genes found in *Streptomyces* species.11 The efflux pumps that *Streptomyces* use to pump out antibiotics to eliminate their competitors are likely the same pumps that other species of bacteria are now using to pump out the offensive antibiotic delivered from *Streptomyces!* The antibiotic-resistant bacteria likely have acquired the genes for these efflux pumps through lateral gene transfer. The presence of ribosomal protection proteins and antibiotic modifying enzymes in resistant bacteria has also likely originated from *Streptomyces* or some other antibioticproducing microbe.6 Bacteria don't appear to be evolving new genes; they are acquiring previously existing antibiotic resistance genes through lateral genetransfer. This allows a species of bacteria to possess enough genetic variability to adapt to a changing environment and to compete with its neighbors. The bacterium that acquires the antibiotic resistance genes still has the physical and metabolic qualities that distinguish it from other bacteria kinds and associates it with its own kind of bacteria. The observed increase in the frequency of antibiotic-resistant bacteria has resulted from the increased use of antibiotics in medicine and agriculture, resulting in the reduction of organisms that do not possess antibiotic resistance genes.

Antibiotic resistance in bacteria can also be achieved when mutations in a ribosome or protein change the site where an antibiotic binds. For example, four of the antibiotics mentioned earlier, tetracycline, streptomycin, kanamycin, and spectinomycin, bind to a specific region of a ribosome and interfere with protein synthesis. Mutations may prevent an antibiotic from binding to the ribosome (kanamycin)12 or allow the ribosome to function even while the antibiotic is bound (streptomycin and spectinomycin).5 Although it appears these mutations are beneficial and provide an advantage to the bacterium possessing them, they all come with a cost. Ribosomal mutations, while providing antibiotic resistance for the organism, slow the process of protein synthesis, slow growth rates, and reduce the ability of the affected bacterium to compete in an environment devoid of a specific antibiotic.13,14 Furthermore, a mutation that confers resistance to one antibiotic may make the bacterium more susceptible to other antibiotics.15 These deleterious effects are what would be expected from a creationist model for mutations. The mutation may confer a benefit in a particular environment, but the overall fitness of the iv population of one kind of bacterium is decreased as a result of a reduced function of one of the components in its biological pathway. The accumulation of mutations doesn't lead to a new kind of bacterium—it leads to extinction.

1.7 Bacterial Mechanisms of Antibiotic Resistance

Several mechanisms have evolved in bacteria which confer them with antibiotic resistance. These mechanisms can chemically modify the antibiotic, render it inactive through physical removal from the cell, or modify target site so that it is not recognized by the antibiotic. The most common mode is enzymatic inactivation of the antibiotic. An existing cellular enzyme is modified to react with the antibiotic in such a way that it no longer affects the microorganism. An alternative strategy utilized by many bacteria is the alteration of the antibiotic target site. These and other mechanisms are shown in the figure 1 and accompanying table 1.

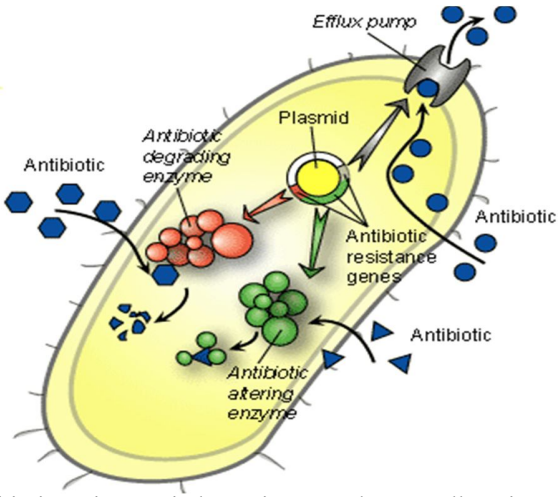

Fig 1: Three mechanisms of antibiotic resistance in bacteria. Most, but not all, resistance mechanisms are encoded by plasmids, which are potentially transmissible to other bacteria. Clockwise. 12 o'clock: Efflux pumps are high-affinity reverse transport systems located in the membrane that transport the antibiotic out of the cell. This is the mechanism of resistance to tetracycline. 4 o'clock: A specific enzyme modifies the antibiotic in a way that it loses its activity. In the case of streptomycin, the antibiotic is chemically modified so that it will no longer bind to the ribosome to block protein synthesis. 9 o'clock: An enzyme is produced that degrades the antibiotic, thereby inactivating it. For example, the penicillinases are a group of beta-lactamase enzymes that cleave the beta lactam ring of the penicillin molecule.

Table 1: Commonly Used Antibiotics and Method of Resistance

Antibiotic	Method of Resistance
Chloramphenicol	Reduced uptake into cell
Tetracycline	Active efflux from the cell
βlLactams,Erythromycin, Lincomycin	Reduces binding of antibiotic to cell target
β-lactams, Aminoglycosides, Chloramphenicol	Enzymatic cleavage or modification to inactivate antibiotic molecule
Sulfonamides,Trimethoprim	Metabolic bypass of inhibited reaction
Sulfonamides, Trimethoprim	Overproduction of antibiotic target (titration)

1.8 Combating Antibiotic Resistance

Antibiotic resistance is a growing public health concern worldwide. When a person is infected with an antibiotic-resistant bacterium, not only is treatment of that patient more difficult, but the antibiotic-resistant bacterium may spread to other people.

When antibiotics don't work, the result can be

- Longer illnesses
- More complicated illnesses
- More doctor visits
- The use of stronger and more expensive drugs

More deaths caused by bacterial infections

Table 2: Drug-Resistant Bacteria

Community-Acquired	Hospital-Acquired
Escherichia coli (resistant to extended-spectrum beta-lactamases, may be health care-associated)	Enterobacter species
Haemophilus influenza	Klebsiella species
Methicillin-resistant Staphylococcus aureus	Methicillin-resistant S aureus
Mycobacterium tuberculosis	Pseudomonas species
Neisseria gonorrhoeae	Vancomycin-intermediate S aureus
Penicillin-resistant pneumococci	Vancomycin-resistant enterococci
Salmonella, Shigella	Vancomycin-resistant S aureus

1.9 Development of New Antibiotics

The epidemic of resistant bacteria has spurred renewed interest in finding novel antibiotics. The process of producing a new antibiotic, however, is long and expensive, requiring approximately ten years and $300 million to bring a new antibiotic to market. Many efforts to find novel drugs in fungi and soil result in compounds that are the same or very similar to previously discovered antibiotics. Thus, resistance eventually develops to these new antibiotics. Heavy use of the latest antibiotic can lead to the emergence of resistance in as little as two years. Nonetheless, scientists are still searching for new antibiotics by looking in unusual places such as in bacteria living deep below the earth's surface, in the skin of frogs and in certain insects.

1.10 Can Antibiotic Resistance be Overcome?

One approach taken by scientists to combat antibiotic resistance is to strengthen the action of existing antibiotics by modifying them so the bacterial enzymes that cause resistance cannot attack them. Alternately, "decoy" molecules can be used along with the antibiotic, so that the bacterium's resistance enzyme attacks the decoy molecule rather than the antibiotic. Decoy molecules such as clavulanic acid or sulbactam are already in use for blocking the beta-lactamase enzymes that destroy the penicillin family of

drugs.An alternative approach to the antibiotic resistance problem is to interfere with the mechanisms that promote resistance, rather than to attempt to kill the bacteria. For example, interfering with the duplication or movement of a bacterium's genetic material would eliminate the transfer of resistance genes between bacteria.

1.11 New Era of Antimicrobial Therapeutics

It is a fact that selection of multi-drug-resistant bacteria has occurred throughout history. Unfortunately, however, drug-resistant bacteria have been met with antibiotics that are nothing more than recapitulations of earlier drugs. There has been an urgent need for new avenues of therapeutic treatment, and a new era of prophalytic (preventative) treatment has begun. Here the most plausible approaches are described:

- Bacterial interference
- Bacteriophage therapy
- Bacterial vaccines
- Cationic peptides
- Cyclic D,L-a-peptides

a) Bacterial interference

Bacterial interference, also known as bacteriotherapy, is the practice of deliberately inoculating hosts with nonpathogenic (commensal) bacteria to prevent infection by pathogenic strains. To establish an infection and propagate disease, pathogenic bacteria must find nutrients and attachment sites (adhesion receptors). Infection by pathogenic bacteria is prevented by commensal bacteria, which compete with pathogenic bacteria for nutrients and adhesion receptors or spur attack through secretion of antimicrobial compounds. This treatment has had promising results in infections of the gut, urogenital tract, and wound sites. The major advantage of using bacteria in a positive way to benefit health, known as "probiotic" usage, is that infection is avoided without stimulating the host's immune system and decreases selection for antibiotic resistance. Understanding how bacterial species compete, an essential criterion for research, has been known for at least 20 years but its practical application has yet to be realized.

b) Bacteriophage therapy

Bacteriophages (commonly called "phages") are viruses that infect bacteria and were recognized as early as 1896 as natural killers of bacteria. Bacteriophages take over the host's protein-making machinery, directing the host bacteria to make viral proteins of their own. Therapeutically, bacteriophages were used as a prophylaxis against cholera, typhoid fever, and dysentery from the 1920s to the early 1940s. The practice was abruptly stopped when synthetic antibiotics were introduced after World War II. Now that there is a plethora of multi-drug-resistant bacteria, bacteriophage therapy once again has become of keen interest.

Bacteriophage therapy is quite attractive for the following reasons:

- phage particles are narrow spectrum agents, which means they possess an inherent mechanism to not only infect bacteria but specific strains
- other pathogens may be targeted through manipulation of phage DNA
- exponential growth and natural mutational ability make bacteriophages great candidates for thwarting bacterial resistance.

c) Bacterial vaccines

- Development of bacterial vaccines has become an increasingly popular idea with the advent of complete genomic sequencing and the understanding of virulence regulatory mechanisms.
- Bacterial genomics allows scientists to scan an entire bacterial genome for specific sequences that may be used to stimulate a protective immune response against specific bacterial strains. This approach expedites the drug discovery process and, more importantly, provides a more rational, target-based approach.
- The best targets are essential bacterial genes that are common to many species of bacteria, which code for proteins with the ability to gain accesses through lipid membranes, and possess no homology to human genes.

- Regulatory genes that control virulence protein production are excellent vaccine candidates for priming the human immune system or inhibiting virulence production.
- Bacterial genomics can also detect conserved sequences from bacterial species and strains worldwide. This technology will inevitably yield superior clinical vaccine candidates.

d) Cationic Peptides

- These diverse peptides are natural compounds that posses both hydrophobic and hydrophilic characteristics, which means portions of the molecule are water avoiding or water loving. Cationic peptides are found throughout nature in the immune systems of bacteria, plants, invertebrates, and vertebrates.
- These peptides are not the usual synthetic drugs encountered in pharmaceutical drug design; however, they do exhibit antibacterial effects. Cationic peptides have several mechanisms of action, all of which involve interaction with the bacterial cell membrane leading to cell death. From a therapeutic standpoint, these proteins have great promise, as they have coevolved with commensal bacteria yet have maintained the ability to target pathogenic bacteria.

c) Cyclic D,L-a-peptides

Unlike cationic peptides, cyclic D,L-a-peptides are synthetic and amphipathic (molecules having both water loving and water hating characteristics) cell membrane disruptors. As the name implies these peptides are cyclic in nature and are composed of alternating D and L amino acids. Cyclic D,L-a-peptides are engineered to target gram-positive and negative membranes (not mammalian cell membranes). In contrast to any other known class of peptides, these peptides can self-assemble into flat ring shaped conformations forming structures known as nanotubes, which specifically target and puncture bacterial cell membranes resulting in rapid cell death.

1.12 Pharmacists Role in Prevention of Antibiotic Resistance

The pharmacist's role in combating and preventing infectious diseases is essential as antibiotic and vaccine regimens become more complex due to the continuously evolving epidemiology of infections. The decrease in drug development makes the preservation of currently available antibiotics paramount, highlighting the roles that pharmacists play in maximizing the utility of available drugs. While further training in infectious diseases may be necessary for some pharmacist roles in preventing antibiotic resistance, many others exist that all pharmacists can embrace.

1.13 Antibiotic Stewardship

Pharmacist-directed antibiotic stewardship programs (ASPs) have proliferated considerably in the past decade. After evidence emerged that these programs improve patient care, the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America published a guideline for the development of ASPs specifying that an infectious diseases–trained clinical pharmacist was an essential core member.As resistance has increased and antibiotic development has lagged, ASPs have become important to improve clinical outcomes, prevent resistance, and decrease adverse events such as *Clostridium difficile* infections.ASPs take many forms, but all utilize a team approach to improve the utilization of antibiotics through means such as interventions on individual patients, guideline development, and system-wide improvement . Over time, ASPs may become a standard for all hospitals and long-term-care facilities across the nation; however, at this time only California has developed a statewide initiative to require ASPs.

1.14 Community Pharmacists as Gateway Practitioners

As gateway practitioners, community pharmacists have some of the most significant opportunities to intervene and prevent unnecessary antibiotic use, which is strongly associated with increased resistance. Patients often go to their community

pharmacy first to seek advice regarding infections and OTC medications to alleviate their symptoms. Pharmacists may counsel patients on viral infections, the futility of antibacterials for them, and recommend appropriate OTC products for supportive care. Avoiding an unnecessary trip to a physician's office can prevent the pressure that physicians may feel to prescribe antibiotics that they do not believe are necessary. Of course, pharmacists should refer a patient to see a physician if a bacterial infection is suspected, the patient is severely ill or complicated by significant comorbidities, the infection is prolonged, or the pharmacist is not comfortable judging that a mild viral infection is present. A useful resource for pharmacists regarding these counseling points is the CDC Web site Get Smart: Know When Antibiotics Work.

1.15 Vaccination

Pharmacists are crucial to promoting currently available vaccines. Vaccines can decrease the use of antibiotics directly by preventing primary infection and indirectly by preventing bacterial superinfection after a primary vaccine-preventable illness, such as influenza. Pharmacists can screen patients and identify those in need of immunizations at various time points and places: admission to a health care facility; visits to community pharmacies; at a specific age; for certain chronic conditions, medical or surgical procedures; and at certain times of the year.Pharmacists can also now administer vaccines in the community setting in every state.

1.16 Education

Perhaps the most important pharmacist role in preventing antibiotic resistance is that of an educator. Due to many misconceptions that exist about antibiotics and vaccines, addressing patient and clinician concerns is vital to increasing the understanding of the appropriate use of these agents. Some parents are hesitant about vaccinating their children because of the concern for side effects, both real and imagined. Pharmacists can help patients to separate fact from fiction regarding immunizations. They may also educate on antibiotic resistance, act as gateway practitioners as mentioned previously, and provide resources for clinical decision making so appropriate choices are made regarding antibiotics. Education regarding infection-control practices is also an important avenue for pharmacist involvement. Pharmacists may be proactive in regard to educating the public about important infection-control practices such as general hygiene, hand hygiene, cough etiquette, immunizations, and staying home when sick.These topics may seem like common sense, but patient understanding of these basic infection-control practices should not be overestimated. Various tools are available online to support pharmacists in these endeavors. Pharmacists can access both print materials and tips on how to communicate with patients about respiratory viral infections, appropriate antibiotic use, and other relevant topics

2. Conclusion

Antibiotic resistance is a continually evolving and dangerous problem that requires immediate attention as well as future planning to impede a global health crisis. The new alternatives, discussed in this article have begun to target the pathogen and not the organism, through this way we can combat the antibiotic resistance. In addition to current research efforts, the world's health organizations, such as WHO, CDC, and the Food and Drug Administration (FDA) are building better monitoring systems to detect rising numbers of multi-drug-resistant bacteria. It is not enough; however, physicians and patients must do their part by understanding the ease with which bacteria develop resistance and the consequences of antibiotic misuse. Antibiotics are a class of medications that can save lives. However, antibiotics are extremely overprescribed and most are quite toxic. They should be used as a last resort, not the first. Very often, simple, inexpensive natural methods described here work better with far fewer adverse effects. Infections are always serious conditions, even seemingly mild ones. Therefore, take care of all infections rapidly, and aggressively. Natural remedies often work superbly. Finally, always ask for help if you are not sure how to use

simple, natural methods or if an infection is not beginning to get a little better, at least, after two or three days, at the most. Pharmacists have a responsibility to assist in the war on antibiotic resistance. They have the knowledge and resources at their fingertips to raise awareness and to act. There are multiple opportunities for pharmacists to assist in this campaign. The recognition of pharmacists as key members of antibiotic stewardship teams in health systems is a milestone in infectious-diseases pharmacy practice. Community pharmacists have a critical role to play in combating antibiotic resistance as front-line practitioners who can educate and vaccinate patients.

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