ARCH
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Antibiotic Resistance in 2020

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Abstract

Antibiotic resistance has become a growing issue in the past decade. With more and more bacteria becoming increasingly resistant, healthcare workers are finding it more and more difficult to treat certain bacterial resistant infections. Several factors contribute to this issue which may include a lack of profitability of antibiotics and lack of new mechanisms of action being discovered. The FDA and WHO are attempting to combat this problem, but despite their efforts, there are still too few new novel antibiotics. With COVID-19 emerging in the last year, the uncertainty around increasing antibiotic resistance has grown even more.

In January 2020, the World Health Organization (WHO) published a warning about the global threat of antibiotic-resistant organisms and the lack of new antibiotics being developed.[1] Dr. Tedros Adhanom Ghebreysus, the director-general of WHO said, " Never has the threat of antimicrobial resistance been more immediate and the need for solutions more urgent."[1] Reasons for the lack of new antibiotics entering the market includes declining private investment and lack of innovation.[1] Smaller companies have been leading the research and development of new antibiotics while larger enterprises are exiting the field.[1] Antibiotics are not as desirable to produce to larger companies because unlike chronic conditions which require medications that are taken for years, acute infections last only a few weeks. This means that antibiotics have a low profitability for drug makers. In addition, newer antibiotics entering the market do not differ greatly from existing antibiotics.[1] While new antibiotics on the market may have broader coverage, they have very similar mechanisms of action to antibiotics already on the market. For example, one of the recently approved antibiotics, Zerbaxa ® (ceftolozane/tazobactam) is a combination drug that includes a cephalosporin plus a beta lactamase inhibitor, both of which are not novel mechanisms of action.[2]

Mechanisms of Resistance

Gram-negative bacteria, specifically Gram-negative bacilli, are notorious for developing resistance in the past several years.[1] Gram-negative bacteria have an outer membrane, a thin layer of peptidoglycan, and an inner membrane, all of which are used as a barrier to resist antibiotic penetration and permeability.[2] Another way that Gram-negative bacilli acquire resistance is by horizontal gene transfer. This allows the bacteria to produce drug efflux permeases and antibiotic-modifying enzymes.[2] It also allows the bacteria to bypass targets and mutate or modify ribosomes.[2]

Beta-lactamases are especially known for causing resistance to beta-lactam antibiotics. Extended spectrum beta-lactamases (ESBLs) provide bacteria resistance to penicillins and cephalosporins, and carbapenamases provide resistance to carbapenems.[2] Currently, carbapenems are considered the "last line" of defense against highly resistant organisms.[1] There is high concern for drugs that produce ESBL and carbapenemases. Specifically, there is a gap in activity against a beta-lactamase called NDM-1 (New Delhi metallo-beta-lactamase 1).[1] Bacteria that produce this beta-lactamase are resistant to a broad range of antibiotics, including carbapenems.[1]

WHO has published a list of "priority pathogens" that pose the greatest threat to humans.[3] The list includes organisms that are of critical, high, and medium priority. The ranking is based on which organisms have the most resistance to antibiotics.[3] Pathogens in the critical priority ranking include *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacteriaceae.[4] These gram-negative rods are becoming increasingly resistant to broad-spectrum antibiotics (including carbapenems and third-generation cephalosporins) and are a major threat to

patients who are hospitalized, in nursing homes, or patients who require invasive devices such as a pacemaker, ventilator, or catheter.[3] High priority pathogens include *Enterococcus faecium*, *Helicobacter pylori*, Salmonella species, *Staphylococcus aureus*, Campylobacter species, and *Neisseria gonorrhoeae*.[4] Medium priority pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and Shigella species.[4] The priority pathogens list was created in order to help increase research and development for new antibiotics that target these specific pathogens. Tuberculosis is not included in the list of priority pathogens because it has its own dedicated programs.[4] Tuberculosis resistance has been growing in recent years and is listed as a global priority for research and development.[4] Tuberculosis causes 1.8 million deaths per year, making it the number one infectious disease killer in the world.[4]

WHO and the Food and Drug Administration (FDA) have taken measures to attempt to increase the research and development of new antibiotics.[1] WHO, along with the Drugs for Neglected Disease Initiative (DNDi), have formed the Global Antibiotic Research and Development Partnership (GARDP).[1] GARDP is a non-profit research and development organization that aims to accelerate the development of new antibiotics that target drug-resistant bacteria.[1] GARDP's goal is to deliver five new treatments by 2025.[1] The organization is also working with partners in over 20 other countries to grant access and affordability to treatments to those in need.[1] In 2012, the Generating Antibiotics Incentives Now (GAIN) Act was signed into law as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) which aimed to strengthen drug development efforts for bacteria that were growing increasingly resistant.[2] The GAIN Act created a designation for antibiotics called qualified infectious disease products, or QIDP, if it meets certain criteria.[2] Antibiotics qualify for QIDP designation if they treat serious or life-threatening infections caused by emerging pathogens or specific multidrug resistant pathogens specified by the FDA.[2] In the past decade, 12 new antibiotics have been approved using the QIDP designation, treating infections such as complicated urinary tract infections, hospital-acquired pneumonia, ventilator-associated pneumonia, acute bacterial skin and soft tissue infections, traveler's diarrhea, and complicated intra-abdominal infections.[2]

Fortunately, several new antibiotics are currently in the pipeline. Of the 50 antibiotics in the pipeline as of January 2020, 32 target WHO priority pathogens.[1] However, only a few are active against multi-drug resistant Gram-negative bacteria.[1] The preclinical pipeline looks more promising with over 250 agents being researched to treat WHO priority pathogens.[1] However, these drugs still need to show safety and efficacy and will most likely not be available for several years.[1]

Another promising development in research and drug development is the use of artificial intelligence (AI). In February of 2020, a paper was published that described how AI had been used to discover a new potential antibiotic.[5] Researchers collected data of over 2,000 unique compounds and trained a neural network to find molecules

that stop *E. coli* growth.[5] The model then went through over 6,000 molecules to identify compounds that target *E. coli*, and it correctly predicted antibacterial activity in 51 compounds.[5] Specifically, a molecule called c-Jun N-terminal kinase inhibitor SU3327 was identified by the AI and had very promising activity.[5] In mice, *E. coli*, *Clostridium difficile, Mycobacterium tuberculosis,* and pan-resistant *Acinetobacter baumannii* were susceptible to the newly discovered compound.[5] The drug was effective against every organism that it was tested against aside from *Pseudomonas aeruginosa*.[6] Furthermore, after 30 days, *E. coli* had not developed resistance to the compound while the bacteria began to develop resistance to ciprofloxacin within 3 days.[6] Researchers named the compound "halicin" after Hal, the AI system in the movie *Space Odyssey 2001*.[5] Halicin's structure is unlike typical antibiotics, which means that AI could be very important in discovering new classes of antibiotics in the future.[6]

In the age of the COVID-19 pandemic, antibiotic resistance continues to be an issue, and the pandemic brings forth additional resistance and infectious disease issues. Hospitalized COVID-19 patients may be receiving unneeded antibiotics, and for several weeks, azithromycin and hydroxychloroquine were being used, which is now considered by the CDC to be an inappropriate treatment for COVID-19.[7] Antibiotics are not recommended for COVID-19 patients unless evidence suggests that there is an underlying bacterial infection.[7] Using antibiotics when they are not needed can lead to resistance and potentiate the already existing antibiotics resistance issue. Additionally, hospital admissions increase the risk of acquiring and transmitting healthcare-associated infections which tend to be more resistant and may increase antibiotic use.[7] The pandemic has also led to interruptions in care such as patients not receiving vaccinations on time. Furthermore, wide use of biocidal agents can select for more resistant strains and contribute to antibiotics resistance.[7]

Overall, antibiotic resistance is a global issue that needs the attention of medical professionals, especially pharmacists. Pharmacists can have a crucial role in helping to be stewards of antibiotics by using them appropriately and avoiding overuse.

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